



Original Article



Thyroid-stimulating Hormone and Thyroid Hormones in Women with Breast Cancer. Effects of Neoadjuvant Chemotherapy and Menopausal Status

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Abstract

Background and objectives: The development and progression of breast cancer may be influenced by thyroid hormone levels. In this study, we investigated thyroid function in pre- and postmenopausal women with breast cancer, with and without neoadjuvant chemotherapy (NCh).

Methods: The study included 198 women diagnosed with infiltrating ductal carcinoma: 83 did not receive NCh (39 premenopausal and 44 postmenopausal), while 115 underwent NCh before surgery (63 premenopausal and 52 postmenopausal). Additionally, 78 healthy volunteers, aged 28 to 69 years, served as the control group. Serum levels of thyroid-stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) were quantified using chemiluminescent immunoassays.

Results: We observed a significant increase in serum TSH and fT4 levels in both pre- and postmenopausal women with breast cancer, regardless of NCh treatment, compared to control subjects. However, postmenopausal women with breast cancer who received NCh showed lower fT4 levels than their untreated counterparts. Notably, fT3 levels increased only in premenopausal women with breast cancer who underwent NCh, compared to both the premenopausal control group and untreated premenopausal breast cancer patients.

Conclusions: Altered thyroid function was observed in both pre- and postmenopausal women with breast cancer, characterized by increased TSH and fT4 levels. Neoadjuvant chemotherapy appeared to attenuate the rise in fT4 levels in postmenopausal women while elevating fT3 levels in premenopausal women. These findings highlight the importance of monitoring thyroid hormone profiles in women with breast cancer, considering menopausal status, given their potential influence on tumor progression and chemotherapy effectiveness.

Introduction

In addition to their interaction with the pathophysiology of steroid hormones in breast cancer, thyroid hormones participate through

their nuclear receptors TR α and TR β by exerting various genomic and non-genomic effects.^{1–6} Recent studies highlight the tumor-suppressive role of TR β in breast cancer stem cells, suggesting its potential to inhibit self-renewal capacity.⁷ Additionally, the subcellular localization of TR α and its isoforms plays an important role in the carcinogenesis and prognosis of breast cancer. Cytoplasmic TR α 1 expression correlates with more aggressive disease progression, whereas nuclear TR α 2 expression appears to be a protective factor.⁵ Similarly, patients with unifocal breast cancer showed a significantly worse disease-free survival when expressing THR α 1.⁶ In general, thyroid hormones seem to favor tumor cell survival.^{8–11} These tumor growth-promoting effects are similar to those exerted by estrogens.^{11,12} Moreover, non-genomic effects

Keywords: Breast cancer; Thyroid hormones; Neoadjuvant chemotherapy; Thyroid-stimulating hormone; TSH; Free thyroxine; Free triiodothyronine; Premenopausal women; Postmenopausal women; Tumor progression; Menopausal status.

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of thyroid hormones through the cytoplasmic vitronectin receptor $\alpha v\beta 3$ have also been reported.¹³ Thus, thyroid hormones can activate signaling pathways such as the PI3K/Akt/mTOR pathway, a rapid membrane-initiated signaling cascade that activates downstream effectors and transcription factors, leading to changes in gene expression and cell proliferation, which play a crucial role in cancer cell growth and survival. Additionally, thyroid status has been shown to modulate the tumor microenvironment, influencing stromal interactions and immune cell activity, which may delineate breast cancer progression.³

In experimental breast cancer (BC) models,^{14–16} both intracellular and extracellular effects of thyroid hormones have been observed, with differing contributions to the development and progression of the disease, affecting both cancer cells and tumor stroma.¹⁷ Furthermore, thyroid hormones can modulate the behavior of cancer-associated fibroblasts and immune cells, which in turn affect tumor growth and metastasis. Recent studies have also suggested that thyroid hormone signaling is involved in the regulation of epithelial-mesenchymal transition, a process that plays a key role in the acquisition of invasive and metastatic properties by cancer cells.¹⁸

Recent studies have provided further insight into the relationship between thyroid hormones and breast cancer. Tang *et al.*¹¹ demonstrated that thyroxine (T4) can act as a proliferative factor for breast cancer cells, suggesting a potential role for T4 in promoting tumor growth. In women with BC, elevated levels of T4 have been described, regardless of their menopausal status (pre- or postmenopausal). On the other hand, a negative relationship between triiodothyronine (T3) and BC has also been observed.¹⁹ In fact, a decrease in T3 levels and an increase in free T4 (fT4) have been demonstrated in patients with newly diagnosed BC compared with patients with benign breast lesions.²⁰

These findings suggest a potential role for T3 in protecting against breast cancer, while increased levels of fT4 may promote breast cancer growth. It is important to note, however, that the exact mechanisms through which thyroid hormones influence breast cancer development and progression are still not fully understood, and further research is needed to elucidate the underlying molecular pathways. As an example, the co-expression of TR α and estrogen receptor (ER) α in breast tumors with concurrent thyroid cancer underscores the interplay between thyroid and steroid hormone signaling.²¹

The relationship between chemotherapy for breast cancer and thyroid function is a subject of debate. Some studies have suggested that chemotherapy does not significantly affect thyroid function, while others have reported an increased incidence of thyroid dysfunction in breast cancer patients receiving chemotherapy.^{22–24} Interestingly, the development of thyroid dysfunction in breast cancer patients receiving chemotherapy has been suggested as a potential indicator of response to therapy in some reports.^{25,26} Specifically, it has been hypothesized that chemotherapy-induced thyroid dysfunction may result from immune system activation, which could also contribute to an anti-tumor immune response. However, the precise mechanisms underlying the relationship between chemotherapy, thyroid function, and response to therapy remain unclear. Moreover, the impact of neoadjuvant chemotherapy (NCh) on thyroid function remains underexplored despite its clinical relevance due to several factors. First, the primary focus of research on NCh has been on its effects on tumor response and survival outcomes, with less attention paid to systemic effects like thyroid dysfunction. However, these findings are often limited to small cohorts and specific cancer types, leaving gaps in understanding across broader populations or other cancers.²⁷ Addi-

tionally, thyroid dysfunction during NCh may be underdiagnosed because symptoms can overlap with side effects of treatment, such as fatigue or weight changes. Furthermore, the lack of routine monitoring of thyroid hormones in oncology settings contributes to insufficient data.

It is also important to consider the lack of data on how menopausal status modulates thyroid-cancer interactions. This can be attributed to several interconnected factors. The complexity of hormonal changes during menopause, particularly in estrogen and follicle-stimulating hormone levels, makes it challenging to understand their influence on thyroid cancer risk and progression.¹⁹ Research has predominantly focused on other cancer types, especially breast cancer, in relation to menopausal status, leaving thyroid cancer interactions comparatively underexplored. Large-scale cohort studies often include thyroid cancer but tend to examine a broader range of reproductive and hormonal factors, resulting in less specific insights into menopause-thyroid cancer links.²⁸ Diagnostic challenges arise from the overlap between menopausal symptoms and thyroid dysfunction, potentially leading to misclassification or delayed diagnosis in studies.²⁹ Many research designs fail to stratify data by menopausal status or account for differences between natural and surgical menopause, limiting our understanding of specific interactions.²⁹ Additionally, the higher incidence of thyroid cancer in women during reproductive years may overshadow postmenopausal research, while potential biological differences in postmenopausal thyroid tumors remain underexplored.^{30,31}

Given the differential hormonal profiles between pre- and postmenopausal women, particularly concerning estradiol levels, and the established influence of steroid hormones on breast cancer development and progression, this study aimed to investigate the impact of menopausal status on thyroid function in breast cancer patients. Specifically, this research seeks to determine the serum levels of thyroid-stimulating hormone (TSH), fT4, and free triiodothyronine (fT3) in pre- and postmenopausal women diagnosed with breast cancer, regardless of whether they have undergone NCh. By examining these parameters, we intend to evaluate the potential alterations in thyroid function associated with breast cancer, menopausal status, and neoadjuvant chemotherapy, providing insights into their complex interplay. Furthermore, this investigation aimed to assess whether these alterations differ based on menopausal status and chemotherapy treatment.

Materials and methods

Subjects and study design

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital Complex of Jaén (protocol code CEI-110-5-018). Informed consent was obtained from all subjects involved in the study. A total of 198 women with BC participated, all diagnosed with infiltrating ductal carcinoma. Seventy-eight volunteers without BC formed the control group. The control group consisted of healthy women, aged 28 to 69 years, with no previous history of any type of cancer, chemotherapy, hormonal or antioxidant therapy, or chronic diseases. Women were excluded if they were current smokers, regular alcohol consumers, users of antioxidant supplements, pregnant or lactating, had hepatic, cardiac, or renal dysfunction, were undergoing hormonal therapy, used drugs, or had hypertension, diabetes, or other chronic conditions.³²

Menopausal status was considered. The characterization of the patients (shown in Table 1) and the chemotherapy treatment re-

Table 1. Clinicopathological description of the patients involved in this study

Characteristics	Premenopausal		Postmenopausal	
	Untreated	NCh	Untreated	NCh
	n (%)	n (%)	n (%)	n (%)
Age (years)				
Mean	45.2 ± 1.2	45.1 ± 0.8	65.3 ± 0.9	65.3 ± 0.90
Median	48	46	64	63
Range	27–54	29–53	57–78	56–78
Tumor histology				
Ductal	39 (100%)	63 (100%)	44 (100%)	52 (100%)
Lobular	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Molecular subtypes				
Luminal A	23 (59.0%)	34 (54.0%)	27 (61.4%)	27 (51.9%)
Luminal B	10 (25.6%)	7 (11.1%)	6 (13.6%)	12 (23.1%)
Her-2	2 (5.1%)	18 (28.6%)	4 (9.1%)	0 (0%)
Triple negative	4 (10.3%)	4 (6.3%)	7 (15.9%)	13 (25.0%)
Pathologic tumor size (cm)				
Mean ± SEM	1.31 ± 0.09	3.02 ± 0.17	1.52 ± 0.14	3.36 ± 0.15
Median	1.2	3	1.3	3
Range	0.5–3.1	0.8–5.6	0.8–5.0	1.4–5.0
Pathologic T classification				
0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
1	35 (89.7%)	18 (28.6%)	40 (90.9%)	6 (11.5%)
2	4 (10.3%)	40 (63.5%)	4 (9.1%)	43 (82.7%)
3	0 (0%)	5 (7.9%)	0 (0%)	3 (5.8%)
Scaf-Bloom-Richardson grade				
I	19 (48.7%)	8 (12.7%)	10 (22.7%)	13 (25%)
II	20 (51.3%)	55 (87.3%)	34 (77.3%)	39 (75%)
III	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hormonal status				
ER+	33 (84.6%)	41 (65.1%)	33 (75.0%)	36 (69.2%)
ER-	6 (15.4%)	22 (34.9%)	11 (25.0%)	16 (30.8%)
PgR+	25 (64.1%)	41 (65.1%)	27 (61.4%)	33 (63.5%)
PgR-	14 (35.9%)	22 (34.9%)	17 (38.6%)	19 (36.5%)
HER-2/neu status				
Negative	29 (74.4%)	38 (60.3%)	34 (77.3%)	49 (94.2%)
Positive	10 (25.6%)	25 (39.7%)	10 (22.7%)	3 (5.8%)

ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; NCh, neoadjuvant chemotherapy; PgR, progesterone receptor; SEM, standard error of the mean.

ceived by the patients has been previously described.³² Specifically, 83 women with BC (39 premenopausal and 44 postmenopausal) did not receive NCh, whereas 115 women (63 premenopausal and 52 postmenopausal) received NCh before surgery. The treatment comprised an anthracycline/taxane-based regimen, including four

courses of EC (epirubicin 90 mg/m² and cyclophosphamide 600 mg/m², every 21 days), followed by eight courses of 100 mg/m² paclitaxel once a week or four courses of 75 mg/m² docetaxel every 21 days. Patients with a human epidermal growth factor receptor 2(ER2)/neu-overexpressing tumor also received trastuzumab

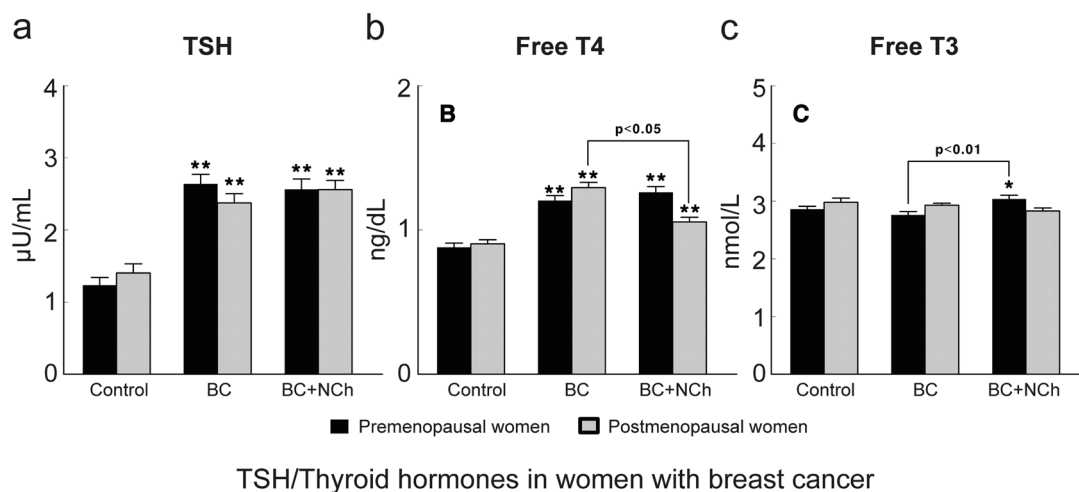


Fig. 1. Circulating levels of thyroid stimulating hormone (TSH) (a), free thyroxine (fT4) (b) and free tri-iodothyronine (fT3) (c) measured in serum of healthy premenopausal and postmenopausal control women, premenopausal and postmenopausal women with breast cancer and premenopausal and postmenopausal women with breast cancer treated with neoadjuvant chemotherapy (NCh) (Mean $\pm$ SEM; * $p < 0.05$, ** $p < 0.01$). BC, breast cancer; SEM, standard error of the mean; T3, triiodothyronine; T4, thyroxine.

(14 courses at 6 mg/kg every 21 days). Women with triple-negative breast cancer received six cycles of 75 mg/m² docetaxel plus carboplatin (area under the curve (AUC) 6).

Sample acquisition

A week after completion of chemotherapy treatment, and in parallel with samples from untreated patients and control volunteers, samples were obtained to be processed under the same conditions.

Blood samples were collected after an overnight fast via venous arm puncture in tubes without anticoagulants (BD Vacutainer® SST™ II Advance), centrifuged at 3,000 g for 10 min at 4°C, and serum rapidly frozen in liquid nitrogen. Samples were stored at -80°C until used for assays.

TSH assay

Clinical TSH levels were measured by a paramagnetic-beads-based chemiluminescence immunoassay from Beckman-Coulter, according to the manufacturer's instructions.³³

fT4 assay

fT4 levels were also measured by a paramagnetic-beads-based chemiluminescence immunoassay from Beckman-Coulter, according to the manufacturer's instructions.³³

fT3 assay

fT3 levels were measured by a paramagnetic-beads-based chemiluminescence immunoassay from Beckman-Coulter, according to the manufacturer's instructions.³³

Statistical analysis

Data were analyzed using one-way ANOVA followed by Newman-Keuls test, using IBM SPSS V.19. All comparisons with p -values below 0.05 were considered significant.

Results

The study comprised 198 women with breast cancer, distributed into four groups based on their menopausal status and the adminis-

tration of NCh. Eighty-three patients did not receive NCh, divided into 39 premenopausal and 44 postmenopausal, while 115 patients received NCh, with 63 premenopausal and 52 postmenopausal (Table 1).

Regarding age, premenopausal women had an approximate mean age of 45 years in both groups (those treated and not treated with NCh), while postmenopausal women showed a mean age close to 65 years in both groups. The total age range of the participants in the study was from 27 to 78 years. The tumor histology was uniformly invasive ductal carcinoma in 100% of the cases in all groups, with no presence of lobular histology or other variants.

Regarding molecular subtypes, a predominance of luminal A and luminal B types was observed, although cases of HER2-positive and triple-negative tumors were also recorded, with a variable distribution among the different groups according to treatment and menopausal status. The average pathological tumor size varied between 1.31 cm and 3.36 cm, depending on the group, and it was noted that patients who received neoadjuvant chemotherapy had a larger tumor size than those who did not receive it. The pathological T classification showed that most tumors were classified as T1 and T2, with some cases of T3; more tumors in stage T2 were observed in the groups treated with neoadjuvant chemotherapy compared to the untreated ones. The Scarff-Bloom-Richardson grade classified most tumors as grade II, with a smaller proportion of grade I and no cases of grade III.

Regarding hormonal status, most tumors were ER+ (estrogen receptor positive) and PgR+ (progesterone receptor positive) in all groups, although a considerable proportion of ER- and PgR- tumors were identified. Regarding HER2/neu status, most tumors were HER2/neu negative, although the presence of HER2/neu positive tumors was observed in all groups.

Figure 1 shows circulating levels of TSH, fT4, and fT3 in pre- and postmenopausal control women and women with BC treated or not with NCh. A significant increase ($p < 0.01$) in TSH levels was found in women with BC, treated or not with NCh (Fig. 1a), when compared with control women, regardless of their hormonal profile.

A significant increase ($p < 0.01$) in fT4 levels was also found in women with BC, treated or not with NCh (Fig. 1b), when com-

pared with control women. Significantly lower levels of free T4 were found in postmenopausal women with BC treated with NCh when compared to postmenopausal untreated patients.

Finally, only premenopausal women with breast cancer treated with NCh increased their fT3 levels when compared with premenopausal control women or untreated premenopausal women with breast cancer (Fig. 1c).

Notably, statistical analyses stratified by molecular subtype, pathological grade, or Scarff-Bloom-Richardson grade revealed no significant differences in TSH, fT4, or fT3 levels among breast cancer patients ($p > 0.05$ for all comparisons).

Discussion

Our results revealed a significant increase in serum TSH levels in both pre- and postmenopausal women with breast cancer, irrespective of NCh treatment, when compared to control subjects. Similarly, a significant increase in fT4 levels was observed in women with breast cancer, treated or not with NCh, relative to controls. However, postmenopausal women with breast cancer who received NCh showed lower fT4 levels than their untreated counterparts. The fT3 levels showed an increase only in premenopausal women with breast cancer who were treated with NCh, compared to both the premenopausal control group and untreated premenopausal women with breast cancer. These findings align with emerging evidence that thyroid hormone dysregulation is a hallmark of breast cancer biology, though the mechanisms remain multifaceted and context-dependent.⁴

Steroid hormones have been the main hormones associated with breast cancer, especially estradiol. In fact, many therapies directed against this disease focus on this hormone.³⁴ A relevant role has also been attributed to progesterone,³⁵ which, in addition to its own effects, participates in many of the processes in which estradiol is involved. Female androgen production also appears to be responsible to some extent for the development of breast cancer, although knowledge about these hormones is more limited.³⁶ Recent advances in receptor tyrosine kinase signaling have further underscored the interplay between steroid and non-steroid hormone pathways in tumor progression.³⁴

There is growing evidence suggesting that alterations in thyroid hormone metabolism can impact the progression and prognosis of breast cancer. Hypothyroidism, in particular, has been widely studied in this context, with several studies reporting an increased incidence of hypothyroidism in breast cancer patients compared to the general population.^{14,15,19,24,33,37–40} Conversely, hyperthyroidism has been associated with a protective effect against the development of breast cancer, as several studies have shown that breast cancer patients with hyperthyroidism have better outcomes compared to those without it.⁴¹ However, it should be noted that treating hyperthyroidism in breast cancer patients may worsen the course of the disease, as some studies suggest that suppressing thyroid function through the use of anti-thyroid medications or radioiodine therapy can lead to a higher incidence of breast cancer recurrence.^{33,42–45}

As also described by other authors,⁴⁶ we have observed an increase in serum TSH and fT4 levels in both pre- and postmenopausal women with BC treated or not with neoadjuvant chemotherapy. However, postmenopausal women treated with NCh showed a lesser increase in their fT4 levels. This attenuation in postmenopausal women may reflect chemotherapy-induced modulation of deiodinase activity, as suggested by recent work demonstrating that taxanes downregulate type 1 deiodinase expression in adipose tis-

sue, thereby reducing T4-to-T3 conversion.²⁵ Similarly, disturbed expression of type 3 deiodinase, the main TH-inactivating enzyme, occurs in several human neoplasms and has been associated with adverse outcomes. Type 3 deiodinase is expressed in both normal and tumor breast tissue, and decreased expression has been linked to poor overall survival in breast cancer patients.⁴⁷ On the contrary, fT3 levels did not change in untreated pre- or postmenopausal women with BC, although premenopausal women treated with NCh showed slightly higher levels of fT3 than premenopausal control women or untreated BC patients. This could be attributed to chemotherapy-induced stress responses, which transiently elevate T3 production via hypothalamic-pituitary-thyroid axis activation.²⁶ However, overall, our results point to an upsurge in thyroid function in women with BC, both pre- and postmenopausal (Fig. 2), consistent with the tumor-promoting role of thyroxine observed in preclinical models.¹¹

Thyroid hormones appear to be involved in breast cancer through several pathways. On one hand, there is a direct pathway through their own nuclear receptors, TR α and TR β , and non-nuclear receptors, such as $\alpha\text{v}\beta3$ or vitronectin, present in the tumor cells themselves.⁴⁸ Cytoplasmic TR β 1 correlates with poor prognosis, suggesting that subcellular localization of thyroid receptors is a critical determinant of breast cancer outcomes.⁴⁹ Similarly, low TR α 2 expression in tumors is associated with aggressive phenotypes and higher mortality, reinforcing the clinical relevance of thyroid receptor profiling.^{5,6,50} Common tumor-suppressive signaling mediated by TR β in both breast and thyroid cancers further supports the therapeutic potential of targeting thyroid hormone pathways in hormone-dependent malignancies.^{51–53}

The role of TR α /TR β expression and PI3K/Akt signaling in breast cancer provides significant insight into cancer progression, influencing cell survival, proliferation, metastasis, and therapy resistance.^{54,55} TR α and TR β may influence breast cancer by modulating cellular proliferation and apoptosis.⁵⁵ Alterations in their expression or localization can disrupt normal hormonal signaling, potentially contributing to tumor growth. Dysregulation of this pathway often occurs through genetic alterations, such as PTEN loss or PIK3CA mutations, which lead to hyperactivation of Akt and downstream effectors.⁵⁶ This signaling cascade can also mediate resistance to therapies like tamoxifen or chemotherapy by promoting cell survival and reducing apoptosis. For instance, studies have shown that miRNAs like miR-548k or lncRNAs like Linc00839 can enhance PI3K/Akt activity by targeting tumor suppressors like PTEN or interacting with transcription factors like Myc.^{56,57} Similarly, TR β has been shown to act as a tumor suppressor in some cancers, and its loss could promote more aggressive phenotypes by exacerbating PI3K/Akt pathway activation while the hyperactivation of PI3K/Akt could further disrupt hormonal receptor functions.⁵⁸

A second pathway involves several systemic factors originating from the action of thyroid hormones, such as altered adipokine secretion in obese patients, which may synergize with T4 to promote tumor growth.⁴⁰ Thirdly, thyroid hormones can regulate the proliferation of mammary tumor cells by ER crosstalk.^{9–11,59} Specifically, T4 induces serine phosphorylation of ER α , triggering transcriptional activation.^{11,12,60} Recent single-cell RNA sequencing studies have further revealed that thyroid hormone-responsive genes are enriched in ER+ luminal cells, suggesting a lineage-specific vulnerability.⁴¹

Furthermore, thyroid hormones also act on tumor promotion through ER signaling.⁸ Synergistic effects of thyroid hormones and estrogen on cell cycle regulation in ER+ breast cancer high-

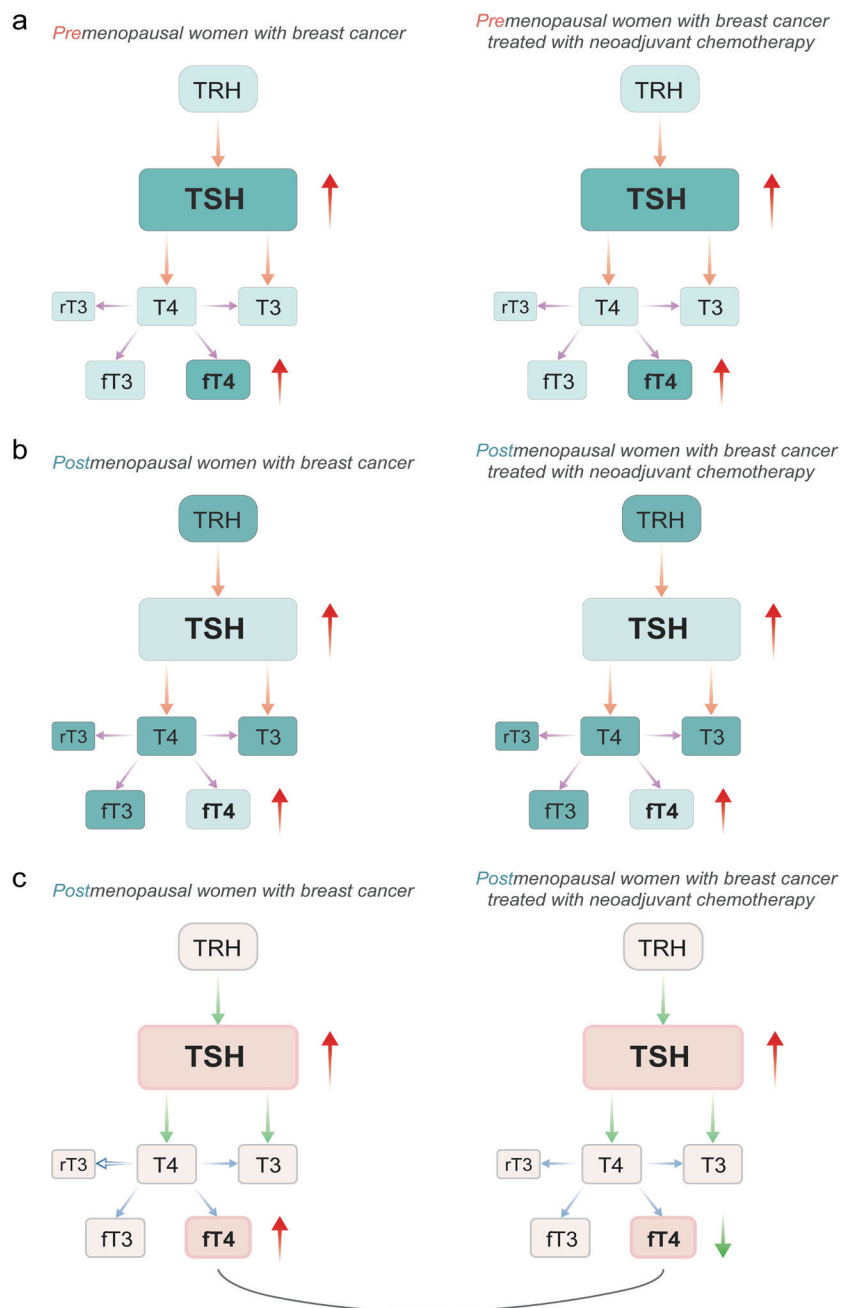


Fig. 2. Changes in thyroid stimulating hormone (TSH) and free thyroxine (fT4) in premenopausal women (a) and postmenopausal women (b) with breast cancer, treated or not with neoadjuvant chemotherapy (NCh), when compared to their corresponding control groups. The effects of neoadjuvant chemotherapy in postmenopausal women on TSH and fT4, when compared with untreated postmenopausal women with breast cancer, are summarized in (c). Panel A highlights that both untreated breast cancer patients and those undergoing NCh exhibit an increase in TSH and fT4 levels compared to healthy premenopausal controls. Notably, premenopausal women receiving NCh display a more pronounced elevation in TSH, suggesting a potential impact of the tumor itself and the chemotherapy treatment on thyroid hormone regulation in this group. Panel B focuses on postmenopausal women, demonstrating that, similar to their premenopausal counterparts, both untreated and NCh-treated breast cancer patients show elevated TSH and fT4 levels compared to control postmenopausal women. However, in contrast to premenopausal women, postmenopausal women treated with NCh exhibit a smaller increase in fT4 compared to untreated postmenopausal breast cancer patients, indicating a difference in the effect of NCh on thyroid hormones based on menopausal status. Finally, the data in panel C underscore that postmenopausal women with breast cancer who received NCh showed a significantly reduced increase in fT4 compared to untreated postmenopausal women with breast cancer. These findings suggest that while breast cancer generally leads to elevated levels of TSH and fT4, neoadjuvant chemotherapy has a distinct modulating effect on fT4 levels, further demonstrating a complex interplay between menopausal status, breast cancer, and thyroid hormone levels. The importance of monitoring thyroid function in breast cancer patients, considering their menopausal status and chemotherapy treatment, in relation to the complex interplay between tumor progression and the effectiveness of oncologic treatment, is emphasized. fT3, free triiodothyronine; rT3, reverse triiodothyronine; T3, triiodothyronine; T4, thyroxine; TRH, thyrotropin-releasing hormone.

light the need to evaluate hormonal crosstalk in therapeutic strategies.⁶⁰ Therefore, given the involvement of thyroid hormones in tumor promotion and progression via ER, the hormonal profile of patients must be considered in relation to the established relationship between thyroid hormones and hormone-dependent pathologies such as BC. Recently, it has been described that thyroid hormone activation regulates crosstalk between breast cancer cells and mesenchymal stem cells, potentially influencing chemosensitivity and tumor-stroma interactions.¹⁸ This stromal reprogramming may explain the differential fT4 responses observed in our postmenopausal cohort, as aging adipose tissue exhibits distinct secretory profiles compared to premenopausal tissue.⁴⁰

Given the complex relationship between thyroid hormones and breast cancer, it is important to consider the hormonal profile of patients when evaluating the role of thyroid hormones in tumor promotion and progression. Furthermore, understanding the mechanisms underlying the interactions between thyroid hormones and ER signaling may lead to the development of new therapeutic strategies for breast cancer that target both pathways. For instance, selective thyroid receptor modulators are now being explored to inhibit TR α -mediated proliferation without inducing systemic hypothyroidism.⁵

In this regard, we have previously described a significant decrease in estradiol levels in premenopausal women with BC, both treated and untreated with chemotherapy, whereas no changes were observed in postmenopausal women with BC, independent of treatment.³² In this context, as a consequence of menopause, where there is a loss of ovarian functionality,⁶¹ the production of estrogens could be reduced, relying on excess adipose tissue in postmenopausal women.^{19,59} Authors such as Ortega-Olvera *et al.*¹⁹ described a strong association between BC and serum concentrations of T3 and T4; the latter differed by body mass index and menopausal status. Our findings extend these observations by demonstrating that chemotherapy exerts menopausal status-dependent effects on thyroid hormone homeostasis.

Furthermore, the effect of thyroid hormones on the cell cycle in mammary tumor cells has also been described. The decrease or absence of thyroid hormones could induce a halt in the cell cycle at the G₀-G₁ phase or decrease mitochondrial metabolism, which hinders the favorable effect of therapies that act on cells with a high metabolic level. Therefore, a high metabolism derived from hyperthyroidism is favorable for the effectiveness of chemotherapy treatment.²⁰ However, the causes of hypothyroidism in cancer patients may be related to a self-protection mechanism, with reduced tissue metabolism to limit tumor growth.²⁰ In this sense, our results agree with those obtained by de Groot *et al.*,²⁷ who described a significant decrease in serum fT4 levels after chemotherapy treatment, compared to baseline, in patients with BC, and an increase in TSH levels.⁶² The decline in fT4 and the increase in TSH levels observed may reflect damage to the thyroid gland inflicted by neoadjuvant chemotherapy. Additionally, the decreased levels of fT4 were more pronounced in BC patients without side effects derived from neoadjuvant therapy. Therefore, we suggest that the difference in menopausal status could impact tumor proliferation through its interaction with thyroid hormones, possibly mediated by chemotherapy-induced shifts in immune cell populations or stromal remodeling.³

Thyroid monitoring during NCh is of great interest because it could optimize treatment outcomes by addressing the observed impact of chemotherapy on thyroid function and its potential predictive value for pathological complete response. Studies such as the NEOZOTAC trial have shown that NCh can significantly alter thy-

roid hormone levels, with decreases in fT4 and increases in TSH, possibly due to thyroid gland damage or adaptive responses like non-thyroidal illness recovery mechanisms. Interestingly, higher baseline TSH levels were associated with pathological complete response in univariate analysis, suggesting that thyroid function may influence treatment efficacy. Additionally, reduced fT4 levels were linked to fewer chemotherapy-related side effects, indicating that thyroid function could also modulate treatment tolerability. These findings highlight the potential utility of routine thyroid function monitoring to identify patients at risk of adverse outcomes or poor response to therapy and to guide personalized interventions that could improve both efficacy and tolerability of NCh.²⁷ Similarly, for patients with pre-existing or chemotherapy-induced hypothyroidism, dose adjustments may be necessary. Hypothyroidism can affect drug metabolism and clearance, potentially altering the efficacy and toxicity of chemotherapy agents. Careful monitoring could guide personalized dose modifications to maintain optimal drug levels while minimizing side effects.²⁷

Limitations and conclusions

While our results indicate a significant alteration in thyroid function in women with breast cancer, irrespective of their menopausal status and NCh treatment, the study is constrained by several limitations. Firstly, the lack of longitudinal data. Our cross-sectional design limits causal inferences and cannot clarify whether thyroid hormone alterations precede breast cancer or result from tumor progression or therapy. Secondly, our study does not account for anti-thyroid antibodies or iodine status, which are important factors in considering autoimmune thyroid diseases (e.g., Hashimoto's thyroiditis) that are common in women and could confound hormone measurements. Thirdly, our cohort exclusively includes patients with infiltrating ductal carcinoma, limiting generalizability to other breast cancer subtypes. Finally, we present a relatively modest sample size, which restricts the generalizability of our conclusions to larger populations and diverse clinical settings. Furthermore, although we have meticulously controlled for several variables, such as smoking, alcohol consumption, and chronic conditions, we recognize that other factors not assessed in this investigation may also influence thyroid hormone levels and their interaction with breast cancer. In fact, the limitations in sample size did not yield statistically significant differences in the studied cohort when stratified by molecular subtype, Scarff-Bloom-Richardson grading, and pathological classification. Future research with larger cohorts and more diverse populations, as well as the incorporation of additional clinical and molecular data, is necessary to corroborate our results and to further elucidate the complex interplay between thyroid hormones and breast cancer. Specifically, the potential impact of other medications, environmental factors, and lifestyle choices on thyroid function in breast cancer patients should be considered. The assessment of long-term effects of chemotherapy on thyroid function also remains an important area for future research. A recent hypothesis-generating review emphasizes the need to explore thyroid hormone receptor isoforms as prognostic biomarkers, aligning with our call for molecular profiling.

We conclude that the observed alterations in thyroid function, specifically the increase in serum TSH and fT4 levels, suggest a potential role for thyroid hormones in breast cancer progression, thereby highlighting the need for closer monitoring of thyroid function in breast cancer patients. This observation takes on special relevance in light of the demonstrated influence of thyroid hor-

mones on tumor proliferation and the effectiveness of chemotherapy treatment. However, these findings cannot be interpreted as definitive conclusions regarding the specific mechanisms driving the observed effects, nor do they imply a direct causal relationship between thyroid function and breast cancer outcomes. Future studies should focus on the clinical utility of thyroid hormone monitoring and potential interventions that could improve outcomes for these patients.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization (MC-G, CC-U, MR-E, JM-M), methodology (MC-G, CC-U), software (MC-G, CC-U), validation (MR-E, JM-M), formal analysis (MC-G), investigation (MC-G, JM-M), resources (JM-M), data curation (MR-E, JM-M), writing - original draft preparation (MC-G, JM-M), writing - review and editing (MC-G, CC-U, MR-E, JM-M), supervision (MC-G, CC-U, MR-E, JM-M). All authors have read and agreed to the published version of the manuscript.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital Complex of Jaén (protocol code CEI-110-5-018). Informed consent was obtained from all subjects involved in the study.

Data sharing statement

Data is unavailable due to privacy or ethical restrictions.

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