Research Article

Neoadjuvant chemotherapy modifies thyroid function in postmenopausal but not premenopausal women with breast cancer

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Experimental models have described several intracellular and extracellular effects of thyroid hormones, which contribute differently to the development and progression of breast cancer. In women with breast cancer, an association between elevated levels of thyroxin (T4) has been described, regardless of their pre- or post- menopausal hormonal status.

Aim: Here we determine thyroid function in pre- and postmenopausal women with breast cancer treated or not with neoadjuvant chemotherapy (NCh) by assaying circulating TSH and free T4 (fT4) levels. Comparisons were made with control premenopausal women with regular menstrual periods and postmenopausal women with spontaneous menopause for at least one year.

Material and methods: Samples from patients treated with NCh were obtained after completion of chemotherapy treatment and in parallel to samples from patients not treated with NCh and control volunteers. TSH and fT4 levels TSH levels were measured by paramagnetic-beads based chemiluminescent immunoassay.

Results: We have observed an increase in serum TSH and fT4 levels in both pre- and postmenopausal women with breast cancer treated or not with neoadjuvant chemotherapy. However, postmenopausal women treated with NCh increased to a lesser extent their levels of fT4.

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Nevertheless, as a whole, our results suggest an increased thyroid function in pre- and post-menopausal women with breast cancer.

Conclusion: The monitoring of the thyroid hormone profile takes on special relevance in women with breast cancer, as well as their hormonal status, in relation to tumor progression and the effectiveness of chemotherapy treatment.

Introduction

Thyroid hormones could exert non-genomic and genomic actions in breast cancer (BC) cells[1][2][3][4] through oestrogen receptors (ER), being their tumour growth-promoting effects similar to those exerted by oestrogens[4][5]. In experimental BC models[6][7][8] it has been observed both intracellular and extracellular effects of thyroid hormones but with different contributions to the development and progression of the disease, affecting both cancer cells and tumour stroma[9].

Authors such as Tang et al.,[4] showed that thyroxine (T4), is a proliferative factor in vitro for breast cancer cells. In women with BC, elevated levels of T4 have been described regardless of their hormonal status (pre- or postmenopausal). On the other hand, a negative relationship between triiodothyronine (T3) and BC has been also described[10]. In fact, a decrease in T3 levels as well as an increase in free T4 (fT4) has been demonstrated in patients with newly diagnosed BC compared with patients with benign breast lesions[11].

Nevertheless, the results are debated in patients with BC, since on the one hand chemotherapy does not seem to affect thyroid function, and on the other, the development of thyroid dysfunction may be a sign of an increased likelihood of response to therapy by some reports[12][13][14].

Here we determine thyroid function in pre- and postmenopausal women with BC treated or not with neoadjuvant chemotherapy (NCh), by assaying circulating TSH and fT4 levels.

Material and methods

Subjects and Study design

The present study was approved by the Ethics Committee of the University Hospital of Jaén and all subjects were informed and subsequently gave their informed consent. 198 women with BC participated, all diagnosed with infiltrating ductal carcinoma. Seventy-eight volunteers without BC made up the control group. The control group consisted of healthy women, aged 28 to 69 years old with no previous history of any type of cancer, chemotherapy, hormonal or antioxidant therapy, or chronic diseases.[15].

The characterization of the patients has been previously reported[15]. The hormonal profile was considered. 83 women with BC (39 premenopausal and 44 postmenopausal) did not receive NCh, whereas 115 of them (63 premenopausal and 52 postmenopausal) received NCh before surgery. The chemotherapy treatment received by the patients has been previously described[15]. The treatment comprises an anthracycline/taxane-based regimen including 4 courses of EC (epirubicin 90 mg/m2 and cyclophosphamide 600 mg/m2, every 21 days), followed by 8 courses of 100 mg/m2 paclitaxel once a week or 4 courses of 75 mg/m2 docetaxel every 21 days. Patients with a HER2/neu-overexpressing tumor also received trastuzumab (14 courses at 6 mg/kg every 21 days). Women with triple-negative breast cancer received 6 cycles of 75 mg/m2 docetaxel plus carboplatin (AUC 6).

Sample acquisition

At the end of the chemotherapy treatment, blood samples were obtained and processed under the same conditions, allowed to clot, and centrifuged to obtain the serum, which was quickly frozen in liquid nitrogen and kept at -80°C until used for assays.

Thyroid-stimulating hormone (TSH) assay

TSH levels were measured by paramagnetic-beads based chemiluminescent immunoassay from Beckman-Coulter, according to the manufacturer's instructions[16].

Free thyroxin (fT4) assay

fT4 levels were also measured by paramagnetic-beads based chemiluminescent immunoassay from Beckman-Coulter, according to the manufacturer's instructions[16].

Statistical analysis

Data were analyzed by one-way ANOVA plus Newman–Keul's test, using IBM Pass V.19. All comparisons with p-values below 0.05 were considered significant.

Results

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

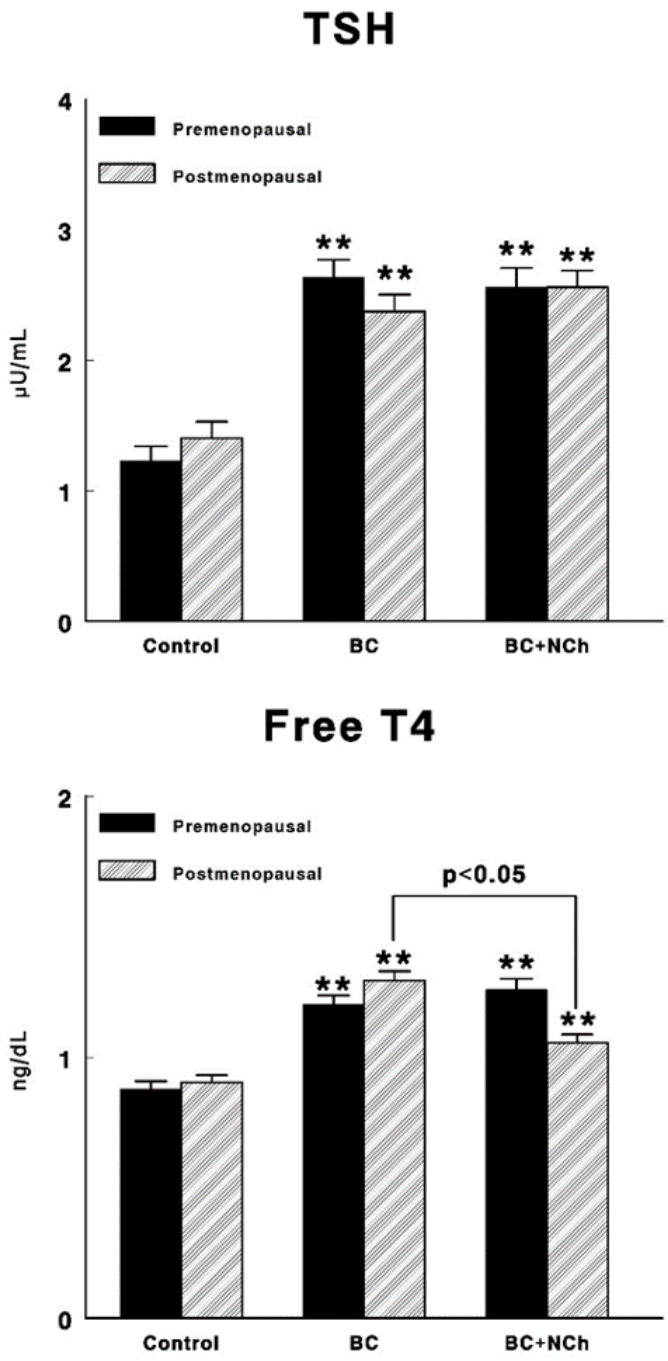

Figure 1. *Circulating levels of TSH (A) and fT4 (B) measured in the serum of healthy premenopausal and postmenopausal control women, premenopausal and postmenopausal women with breast cancer and premenopausal and postmenopausal women with breast cancer treated with neoadjuvant chemotherapy (Mean ± SEM; *p<0.05, **p<0.01).*

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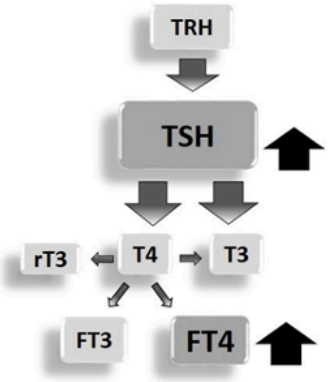
A significant increase ($p<0.01$) in fT4 levels has been also found in women with BC treated or not with NCh (Fig 1B) when compared with control women. Significantly lower levels of free T4 were found in postmenopausal women with BC when treated with NCh when compared to postmenopausal untreated patients.

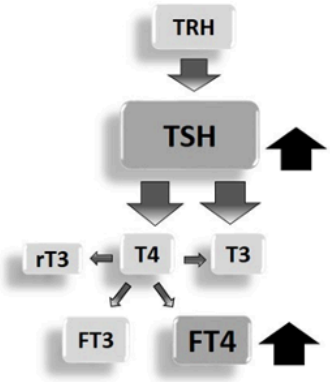
Discussion

Hypothyroidism is considered the most frequently described thyroid disorder related to BC[6][7][10][14][16][17][18]. Conversely, hyperthyroidism would have a protective effect against BC, since the neoplasm pathology worsens when the thyroid disorder is treated[16][19][20][21][22]. 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, as a whole, our results would point to an upsurge in thyroid function in women with BC, both pre and post-menopausal (Figure 2).

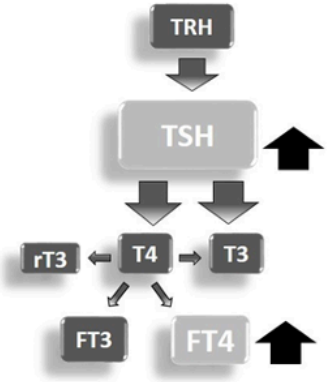
Premenopausal breast cancer women



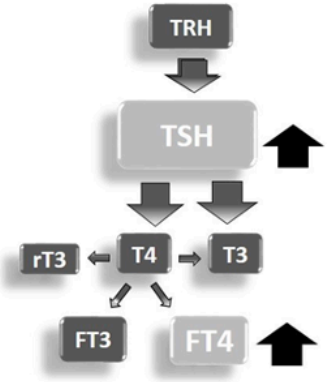
Premenopausal breast cancer women treated with neoadyuvant chemotherapy



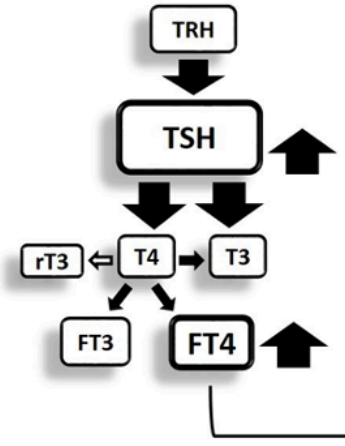
Postmenopausal breast cancer women



Postmenopausal breast cancer women treated with neoadyuvant chemotherapy



Postmenopausal breast cancer women



Postmenopausal breast cancer women treated with neoadyuvant chemotherapy

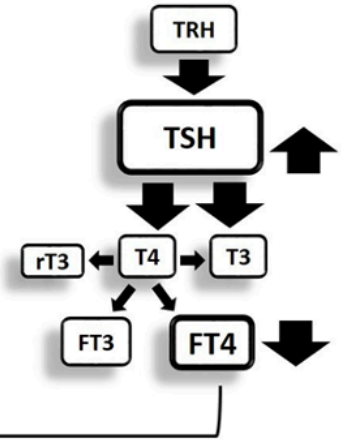


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Figure 2. *Summary of the changes in TSH and fT4 hormonal status in premenopausal women (A) and postmenopausal women (B) with breast cancer, treated or not with neoadjuvant chemotherapy (NCh) when compared to their corresponding control groups. The effects of NCh in postmenopausal women on TSH and fT4 when compared with untreated postmenopausal women with breast cancer are also summarized in (C).*

Thyroid hormones can regulate the proliferation of mammary tumour cells[2][3][4] by oestrogen receptor[23]. Specifically, T4 induces serine phosphorylation of ERα, triggering transcriptional activation[4][5]. Besides, thyroid hormones also act on tumour promotion through ER[1]. Therefore, given the involvement of thyroid hormones in tumour promotion and progression by ER, the hormonal profile of the patients must be relevant to the established relationship between thyroid hormones and hormone-dependent pathologies such as BC.

In this regard, we have previously described a significant decrease in estradiol levels in premenopausal women with BC treated and non-treated with chemotherapy whereas no changes were observed in postmenopausal women with BC independently of the treatment[15]. In this context, as a consequence of menopause, where there is a loss of ovarian functionality[24], the production of estrogens could be reduced to excess adipose tissue, in postmenopausal women[10][23]. Authors such as Ortega-Olvera et al.[10] described a strong association between BC and serum concentrations of T3 and T4; the latter differed by body mass index (BMI) and menopausal status.

Furthermore, the effect of thyroid hormones on the cell cycle in mammary tumour cells has also been described. Thus, the decrease or absence of thyroid hormones could induce a stop of the cell cycle in the G0-G1 phase or decrease mitochondrial metabolism, which hinders a favourable effect of therapies that act on cells with a high metabolic level. Therefore, a high metabolism derived from hyperthyroidism is favourable for the effectiveness of chemotherapy treatment[11]. However, the causes for hypothyroidism in cancer patients may be related to a self-protection mechanism by falling tissue metabolism to reduce tumour growth.[11]. In this sense, our results agree with those obtained by Groot et al.[25] 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. The decline in fT4 and the increase in TSH levels observed may reflect the damage to the thyroid gland inflicted by neoadjuvant chemotherapy by these authors. Also, the decreased levels of fT4 were more pronounced in BC patients without side effects derived from neoadjuvant therapy. Therefore, we could point to the

difference in the hormonal status as a consequence of menopause and ovarian failure could have an impact on the tumour's proliferation through its interaction with thyroid hormones.

Conclusion

We can conclude that the monitoring of the thyroid hormone profile takes on special relevance in women with BC, as well as their hormonal profile, in relation to tumor progression and the effectiveness of chemotherapy treatment.

Conflict of interest statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Declarations

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