

Research article

## Breast cancer in association with thyroid disorders

Orhan Turken<sup>1</sup>, Yavuz Narn<sup>2</sup>, Sezai Demirbas<sup>3</sup>, M Emin Onde<sup>4</sup>, Ozkan Sayan<sup>5</sup>,  
E Gokhan Kandemir<sup>1</sup>, Mustafa Yaylacı<sup>1</sup> and Ahmet Ozturk<sup>5</sup>

<sup>1</sup>GATA Haydarpaşa Training Hospital, Medical Oncology Department, Kadıköy, Istanbul, Turkey

<sup>2</sup>GATA Haydarpaşa Training Hospital, Nuclear Medicine Department, Kadıköy, Istanbul, Turkey

<sup>3</sup>GATA Haydarpaşa Training Hospital, General Surgery Department, Kadıköy, Istanbul, Turkey

<sup>4</sup>GATA Haydarpaşa Training Hospital, Endocrinology Department, Kadıköy, Istanbul, Turkey

<sup>5</sup>GATA Haydarpaşa Training Hospital, Hematology Department, Kadıköy, Istanbul, Turkey

Corresponding author: Orhan Turken (e-mail: [oturken@hotmail.com](mailto:oturken@hotmail.com))

Received: 21 Feb 2003 Revisions requested: 1 Apr 2003 Revisions received: 14 Apr 2003 Accepted: 24 Apr 2003 Published: 5 Jun 2003

*Breast Cancer Res* 2003, **5**:R110-R113 (DOI 10.1186/bcr609)

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### Abstract

**Background:** The relationship between breast cancer and thyroid diseases is controversial. Discrepant results have been reported in the literature. The incidences of autoimmune and nonautoimmune thyroid diseases were investigated in patients with breast cancer and age-matched control individuals without breast or thyroid disease.

**Methods:** Clinical and ultrasound evaluation of thyroid gland, determination of serum thyroid hormone and antibody levels, and fine-needle aspiration of thyroid gland were performed in 150 breast cancer patients and 100 control individuals.

**Keywords:** breast, cancer, thyroid

**Results:** The mean values for anti-thyroid peroxidase antibodies were significantly higher in breast cancer patients than in control individuals ( $P=0.030$ ). The incidences of autoimmune and nonautoimmune thyroid diseases were higher in breast cancer patients than in control individuals (38% versus 17%,  $P=0.001$ ; 26% versus 9%,  $P=0.001$ , respectively).

**Conclusion:** Our results indicate an increased prevalence of autoimmune and nonautoimmune thyroid diseases in breast cancer patients.

### Introduction

Breast cancer is a hormone-dependent neoplasm. Conflicting results regarding the clinical correlation between breast cancer and thyroid diseases have been reported in the literature. Many studies showed that thyroid diseases are common among women with breast cancer [1–6], whereas other reports did not confirm such an association of breast cancer with thyroid diseases [7–11]. Almost every form of thyroid disease, including nodular hyperplasia [12], hyperthyroidism [13] and thyroid cancer [14,15], has been identified in association with breast cancer. These findings have led to the investigation of the relationship between breast cancer and autoimmune thyroid diseases (AITDs).

Such a relationship is not a new observation, and some authors have reported a higher prevalence of AITDs among breast cancer patients than in age-matched control individuals [16–18]. The precise significance of this association remains elusive, and some reports have shown that the presence of thyroid peroxidase (TPO) antibodies is associated with a significant improvement in outcome among breast cancer patients [19] and is of similar importance to other prognostic indices such as axillary nodal status and tumour size [20]. The aim of the present prospective study was to determine the prevalence of thyroid diseases in patients with breast cancer as compared with that in the general female population.

AITD = autoimmune thyroid disease; ER = oestrogen receptor; FNA = fine-needle aspiration; T<sub>3</sub> = triiodothyronine; T<sub>4</sub> = thyroxine; TSH = thyroid-stimulating hormone; TPO = thyroid peroxidase.

## Materials and methods

### Patient selection

A total of 150 consecutive women with breast cancer and 100 age-matched control women were included in the present study, during the period from May 1998 to December 2002. Breast cancer patients were 38–80 years old (median age 63 years) and were without any known thyroid disease. Three or four weeks after surgical procedure, the patients were evaluated before starting chemotherapy, hormone therapy or radiotherapy.

### Examinations

All patients underwent the following five examinations.

First, each patient underwent palpation of the thyroid gland.

Second, ultrasonographic evaluation of the thyroid gland was conducted by the same radiologist using an ultrasound scan fitted with a hand-held 6.6–11 MHz linear transducer. The volume of each lobe was calculated using the following formula: volume = length × width × height × 0.479 [19]. Upper and lower normal lobe volume limits were 18 ml and 10 ml, respectively.

Third, serum free triiodothyronine (T<sub>3</sub>) and free thyroxine (T<sub>4</sub>) levels were determined, based on a solid-phase I<sup>125</sup> radioimmunoassay designed for the quantitative measurement of free T<sub>3</sub> and free T<sub>4</sub> levels in serum using Coat-A-Count kit containing radioactive I<sup>125</sup>-T<sub>3</sub> or -T<sub>4</sub> analogue (DPC, Los Angeles, CA, USA). Also, serum thyroid-stimulating hormone (TSH) levels were measured using an immunoradiometric assay designed for quantitative measurement of TSH in serum using Coat-A-Count kit containing radioactive I<sup>125</sup>-polyclonal anti-TSH (Diagnostics Products Corporation, Los Angeles, CA, USA). The normal ranges were 2.2–6.8 pmol/l (1.4–4.4 pg/ml) for free T<sub>3</sub>, 0.8–2.0 ng/dl for free T<sub>4</sub> and 0.3–5.0 μIU/ml for TSH.

Fourth, all patients underwent serological determination of thyroid autoantibodies based on a direct Anti-TPO radioimmunoassay kit for quantitative determination of anti-TPO autoantibodies (Immunotech, Prague, Czech Republic). Also, autoantibodies specific for thyroglobulin were measured using a quantitative indirect enzyme immunoassay based on the sandwich method (antithyroglobulin immunoradiometric assay kit; Immunotech, Prague, Czech Republic). The normal ranges were 0–60 IU/ml for antithyroglobulin antibodies and 0–20 IU/ml for anti-TPO antibodies.

Finally, after informed consent had been obtained from each patient, fine-needle aspiration (FNA) of the thyroid gland was performed in breast cancer patients who had a palpable thyroid nodule. The aspiration was performed using a 22 gauge needle and the smears were air dried

**Table 1**

### Patient distribution according to clinical and ultrasound evaluation of thyroid gland

	Patients (n [%])	Control (n [%])	P
Normal gland	63 (42)	70 (70)	0.001
Diffuse goitre	12 (8)	4 (4)	0.29
Nodular goitre	75 (50)	26 (26)	0.001

and dyed with May–Gruenwald–Giemsa dye. FNA smears were considered diagnostic for autoimmune thyroiditis if there was an abundance of lymphocytes and plasmacytes in a diffuse pattern and/or coexistence of many lymphocytes and oxyphilic epithelial cells.

Patients were separated into three groups according to clinical and ultrasound findings: normal gland, diffuse goitre and nodular goitre. Those women without any breast or thyroid disease were the control group. Patients were also classified into the following subgroups according to menopausal and oestrogen receptor (ER) status: premenopausal and postmenopausal; and ER negative and ER positive.

### Statistics

Results are expressed as the mean ± standard deviation. Clinical and other data were analyzed using Mann–Whitney U and student *t*-test, as applied by the computerized statistical program SPSS (SPSS Inc., Chicago, IL, USA).

### Results

The separation of patients into groups on the basis of histopathological diagnosis is shown in Table 1. A total of 118 (79%) patients had invasive ductal carcinoma, 15 (10%) had invasive lobular carcinoma and 17 (11%) had mixed (invasive ductal and lobular) carcinoma. In breast cancer patients, diffuse goitre was identified in 12 cases (8%) and nodular goitre in 75 cases (50%). In the remaining (42%) patients, thyroid glands were totally normal by ultrasound and physical examination. In the control group, diffuse goitre was identified in four (4%) and nodular goitre in 26 (26%). Thus, the prevalence of nodular goitre in the cancer group was higher, and this finding was statistically significant (50% versus 26%; *P*=0.001; Table 1). With respect to thyroid volumes, measured ultrasonographically, the mean volumes of diffuse thyroid gland were 23.1 ml (range 17–26 ml) in the breast cancer patients and 21.9 ml (range 16–27 ml) in the control group. The mean volumes of nodular goitre in breast cancer patients and in the control group were 19.2 ml (range 13–21 ml) and 18.7 ml (range 11–21 ml), respectively.

**Table 2**

Serum thyroid hormone and antibody levels			
	Patients	Control	<i>P</i>
Free T <sub>3</sub> (pmol/l)	8.47 ± 0.75	4.48 ± 0.75	0.48
Free T <sub>4</sub> (ng/dl)	2.64 ± 0.91	1.42 ± 0.31	0.51
TSH (μIU/ml)	3.12 ± 1.40	1.46 ± 0.82	0.27
TPO antibodies (IU/ml)	105.82 ± 21.46	23.08 ± 4.16	0.030
Tyroglobulin antibodies (IU/ml)	140.92 ± 21.52	27.75 ± 7.60	0.094

T<sub>3</sub>, triiodothyronine; T<sub>4</sub>, thyroxine; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

Evaluation of thyroid function was based on serum thyroid hormones. The mean values for serum thyroid hormones were 8.47 ± 0.75 pmol/l for free T<sub>3</sub>, 2.64 ± 0.91 ng/dl for free T<sub>4</sub> and 3.12 ± 1.40 μIU/ml for TSH in breast cancer patients, and 4.48 ± 0.75 pmol/l, 1.42 ± 0.31 ng/dl and 1.46 ± 0.82 μIU/ml, respectively, in the control group. The differences between breast cancer patients and the control group in mean serum free T<sub>3</sub>, free T<sub>4</sub> and TSH levels were not statistically significant (Table 2). Nontoxic goitre was found in 77 (51%) of the breast cancer patients and in 29 (29%) of the control individuals (*P* = 0.001; Table 3).

The mean values for serum thyroid autoantibodies were 105.82 ± 21.46 IU/ml for anti-TPO antibodies and 140.92 ± 21.52 IU/ml for antityroglobulin antibodies in breast cancer patients, and 23.08 ± 4.16 IU/ml and 27.75 ± 7.60 IU/ml, respectively, in the control group. Thus, the mean value for serum anti-TPO antibodies was higher in breast cancer patients than in the control group (*P* = 0.030), whereas the difference between the groups in mean values for serum antityroglobulin antibodies was not statistically significant (*P* = 0.094). Autoimmune thyroiditis was defined by increased serum levels of at least one thyroid autoantibody or diagnostic FNA findings, or both. Among the breast cancer patients, autoimmune thyroiditis was diagnosed by autoantibodies in 42 (28%), by FNA in four (2%) and by both in 11 (7%). The difference in the frequency of autoimmune thyroiditis between breast cancer patients and control group was statistically significant (*P* = 0.001; Table 4). On the other hand, non-AITD was identified, with neither thyroid autoantibody in plasma nor FNA findings specific to autoimmune thyroiditis, in the patients with nodular or diffuse goitre.

The mean thyroid hormone and autoantibody values were compared between breast cancer patients and the control group, according to menopausal and ER status. The differences between two groups according to both menopausal status and ER status were not significant.

**Table 3**

Classification of patients in relation to functional thyroid diseases			
	Patients ( <i>n</i> [%])	Control ( <i>n</i> [%])	<i>P</i>
Hyperthyroidism	6 (4)	1 (1)	0.24
Hypothyroidism	4 (3)	–	0.152
Nontoxic goitre	77 (51)	29 (29)	0.001

**Table 4**

Classification of patients based on autoimmune and non-autoimmune thyroid disorders			
	Patients ( <i>n</i> [%])	Controls ( <i>n</i> [%])	<i>P</i>
Normal	54 (36)	74 (74)	0.0001
Non-AITD	39 (26)	9 (9)	0.001
Autoimmune thyroiditis	57 (38)	17 (17)	0.001

AITD, autoimmune thyroid disease.

## Discussion

The coincidence of thyroid disease and breast cancer has long been a subject of debate. Although associations with hyperthyroidism, hypothyroidism, thyroiditis and nontoxic goitre have been reported in the literature, no convincing evidence exists of a causal role for overt thyroid disease in breast cancer. Geographical variations in the incidence of breast cancer have been attributed to differences in dietary iodine intake, and an effect of iodine on the breast has been postulated [1]. The possible interactions between thyroid gland and breast tissue are based on the common property of the mammary and thyroid epithelial cell to concentrate iodine by a membrane active transport mechanism [18] as well as on the presence of TSH receptors in fatty tissue, which is abundant in mammary gland [21]. Additionally, some endocrine stimuli identified in thyroid products that exert a simultaneous action on the breast and the various thyroid antibodies, which could also interact with receptors on breast tumours, have been postulated to be responsible for the coincidence of mammary and thyroid gland disorders [15,22].

The present study found a high prevalence of goitre as well as a high prevalence of autoimmune thyroiditis, confirmed mainly by antibody positivity, in breast cancer patients. An association of autoimmune thyroid disease with breast cancer has been reported in the literature [1,16]. In those studies, increased serum levels of thyroid antibodies were identified. Although Mittra and coworkers [1] found the levels of thyroid antibodies in British women to be lower than those in Japanese women, they found no differences between incidences in breast cancer among

women of either race. With the use of specific immunoassays for TPO and thyroglobulin antibodies, an increased level of TPO has been demonstrated in breast cancer.

It has been proposed that the presence of thyroid abnormalities may influence breast cancer progression [19]. A recent report suggested a better prognosis for breast cancer among patients with increased levels of TPO [19]. It has been proposed that the immune response might be directed both by tumour and by thyroid tissue [20], or that the tumour and thyroid tissue share common properties, as they both express TPO and the sodium iodide symporter gene [23,24]. Although high TPO level has been shown to be a very important factor in antibody-dependent cell cytotoxicity in the thyroid, and there may be a possible association between autoimmune thyroiditis and the immune system, there is no agreement on the significance of its association with breast cancer.

The relationship between thyroiditis and prognostic factors for breast cancer such as ER and stage has been investigated. In one study [1], a higher frequency of thyroiditis was described in more advanced stages of breast cancer. In another study reported by Giani and coworkers [18] no relationship was found between ER status and the presence of serum thyroid antibodies. We found no correlations among ER status, menopausal status and thyroid antibody levels.

In addition to the reported high prevalence of autoimmune thyroiditis among breast cancer patients, the incidence of breast cancer among patients with chronic thyroiditis has been investigated. In a study conducted by Ito and Maruchi [2], those investigators reported that there was an increase in risk for breast cancer among patients with Hashimoto's thyroiditis.

## Conclusion

In this paper, we have studied thyroid autoantibody levels and thyroid function tests in breast cancer patients and controls. Abnormal thyroid gland characteristics were revealed in the breast cancer patients compared with the control group. The incidence of nodular goitre was significantly higher in the patients with breast cancer. Regarding functional thyroid disorders, nontoxic goitre was significantly associated with breast carcinoma. There was a significant difference between the groups in terms of TPO Ab levels; however, no difference was demonstrated for other variables, such as Tg Ab and TFT.

These results indicate a significant association between breast cancer and autoimmune and non-autoimmune thyroid disorders. However, more research on this subject is required to confirm this association.

## Competing interests

None declared.

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## Correspondence

Orhan Turken, GATA Haydarpasa Training Hospital, Medical Oncology Department, Kadikoy, Istanbul, Turkey. Tel: +9 0216 325 7250/1810; fax: +9 0216 325 7257; e-mail: oturken@hotmail.com