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ORIGINAL ARTICLE

Breast cancer in association with thyroid disorders

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Summary

Purpose: *The relationship between breast cancer and thyroid diseases is controversial. Conflicting results have been reported in the literature. The incidence of autoimmune and non-autoimmune thyroid diseases were investigated in patients with breast cancer who had received prior therapy as compared with age-matched control individuals without breast or thyroid disease.*

Patients and methods: *Clinical and ultrasound evaluation of the thyroid gland, and determination of serum thyroid hormones and autoantibody levels were performed in 143 breast cancer patients and 128 healthy control individuals. Patients were classified into subgroups according to estrogen receptor (ER) and progesterone receptor (PR) status and type of oncological treatment.*

Results: *The mean values for serum antibodies against thyroid peroxidase (anti-TPO) were 9 IU/ml and 25 IU/ml for antithyroglobulin antibodies (anti-TGB) in breast cancer patients, and 9.5 IU/ml and 23.5 IU/ml, respectively, in the control group ($p>0.05$. The difference between breast cancer patients and the control group in the incidence of autoimmune and non-autoimmune thyroid diseases was not statistically significant. No significant differences between the groups according to both menopausal status and ER status were seen ($p= 0.67$). Also, no significant influence of hormonal therapy with tamoxifen and chemotherapy on serum levels of thyroid stimulating hormone (TSH), free thyroxin (fT4), TPO and TGB autoantibodies was proved.*

Conclusion: *This study demonstrated a similar incidence of thyroid enlargement and the same frequency of thyroid disturbances in patients with breast cancer and controls. No relationship was found among ER and PR status, and the presence of serum thyroid autoantibodies. Although we have been unable to demonstrate any impact of breast cancer therapy on thyroid function tests, more prolonged studies with larger number of patients may be required to demonstrate significant trends.*

Key words: breast cancer, hormonal therapy, thyroiditis

Introduction

The association between thyroid conditions and breast cancer has been a topic of debate for many years. Almost every form of thyroid disease, including nodular hyperplasia, hyperthyroidism and thyroid autoimmune disorders, has been identified in association with breast cancer [1,2]. Although no convincing evidence exists of a causal role for overt thyroid disease in breast cancer, the preponderance of published works favor an association with hypothyroidism [3,4].

Previous research has shown that autoimmune thyroiditis with hypothyroidism are frequently found in women with breast cancer (in 30% according to several studies). A sonographic enlargement of the thyroid gland and a high percentage of positivity of antibodies to thyroid peroxidase (nearly 34% compared with 18.5% of the controls) have been proved in women with breast cancer in comparison with healthy women [5].

A prospective study conducted by Giustarini et al. confirmed that there is a strong relationship between thyroid autoimmunity and breast cancer. The study included 61 women with nodular breast pathology suspected for malignancy prior to surgery and 100 age-matched controls. Thyroid autoimmunity was deter-

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mined by clinical and ultrasound evaluation of thyroid volume and serologic evaluation of thyroid hormone and antibody levels. This study confirmed the high prevalence of autoimmune thyroid disorders in breast cancer patients and demonstrated that this finding is independent of stressful events such as surgery, treatment, or anaesthetic procedures [6].

Interestingly, several authors have suggested a positive association between thyroiditis and hormonal therapy for breast cancer. While tamoxifen has been shown to alter the concentration of many hormones and their binding globulins, there have been conflicting results regarding its effects on thyroid function tests [7-9].

Irrespective of the conclusions drawn, a weakness of the studies was the lack of appropriate control subjects and high resolution ultrasound techniques that could permit the detection of more subtle changes in thyroid volume. Thus, the significance of the simultaneous occurrence of thyroid diseases and breast cancer remains to be elucidated.

The aim of the present study was to determine the prevalence of thyroid diseases in patients with breast cancer who had received prior therapy for breast cancer as compared with women with non demonstrable breast problems and to explore the possible relationship of thyroid laboratory parameters to the kind of oncological therapy.

Patients and methods

Patient and control groups selection

A total of 143 consecutive women with breast cancer and 128 age-matched control women were included in the present study. Breast cancer patients were 38–75 years old (median 63) and were without any known thyroid disease. One hundred and forty patients had received prior therapy including chemotherapy, hormonal therapy or radiotherapy. The control group consisted of women attending the breast screening outpatient clinic. Both patient and control groups came from the same geographical area and represented a reasonable cross-section of an adult female urban/rural population of varying socioeconomic status.

Examinations

All patients underwent clinical and laboratory examinations. Additionally, ultrasonographic evaluation of the thyroid gland was carried out and the volume of each lobe was assessed using the following formula: volume = length × width × height × 0.5. Serum free triiodothyronine (fT3), fT4 and serum TSH levels were determined with the use of established radioimmunoassay techniques. All patients underwent serological determination of thyroid autoantibodies based on a direct anti-TPO radioimmunoassay kit for quantitative determination of anti-TPO autoantibodies. Also, autoantibodies specific for thyroglobulin were measured using a quantitative indirect enzyme immunoassay based on the sandwich method (antithyroglobulin immunoradiometric assay kit).

In tumor tissue from most of the breast cancer patients ER, PR and c-erbB2 were determined.

Breast cancer patients were separated into two groups (normal gland and thyroiditis) according to clinical and ultrasound findings. Women without any breast or thyroid diseases formed the control group. Patients were also classified into subgroups according to ER status and type of oncological treatment.

Statistics

Results were expressed as the mean ± standard deviation. Clinical and other data were analysed using Student's t-test, and Pearson correlation test using the computerized statistical program SPSS (SPSS Inc., Chicago, IL, USA).

Results

The separation of patients into groups on the basis of pathological diagnosis, hormone receptor status and prior therapy is shown in Table 1. A total of 113 patients (79.5%) had invasive ductal carcinoma, 10 (7%) had invasive lobular carcinoma and 20 (11.8%) had mixed (invasive ductal and lobular) carcinoma.

In breast cancer patients, abnormal thyroid ultrasonography was identified in 54 (38%) cases. In the remaining 89 (62%) patients, the thyroid was normal. The prevalence of abnormal ultrasonography in the cancer group was identical with the control group (n=50, 38.8%; p=0.76).

Mean ultrasonographically measured thyroid volume was 14.5 ml (range 13–17) in the breast cancer patient group and 15 ml (range 14–17) in the control group (p=0.88).

The mean values of serum thyroid hormones were 2.34 ng/ml for fT3, 9.7 ng/dl for fT4 and 1.18 mIU/ml for TSH in breast cancer patients (Table 2). The corresponding values in the control group were 1.29 ng/ml, 9.65 ng/ml and 1.6 mIU/ml. The differences of thyroid hormones levels between breast cancer patients and controls were not statistically significant.

Table 1. Patient characteristics (n=143)

Characteristic	*Patients, n*	*%*
Histology		
Ductal	113	79.5
Lobular	10	7.1
Mixed	17	11.8
In situ	3	2.4
Grade		
I	13	9.3
II	69	48.3
III	61	42.4
Lymph nodes		
Negative	87	61.3
Positive	56	38.7
ER		
Positive	111	78.4
Negative	32	21.6
PR		
Positive	101	70.9
Negative	42	29.1
p53		
Positive	39	27.4
Negative	104	72.6
C-erb-B2		
Positive	54	37.9
Negative	89	62.1
Prior therapy		
CT+hormonal	53	37.3
CT+/-RT	42	28.4
CT+hormonal +RT	48	34.3
Menopausal status		
Premenopausal	58	41
Post menopausal	85	59

CT: chemotherapy, RT: radiotherapy, ER: estrogen receptor, PR: progesterone receptor

Table 2. Comparison of thyroid function test between cancer patients and controls

Thyroid function test	*Breast cancer patients*	*Controls*	*p-value*
fT3	2.34 ng/ml	1.29 ng/ml	0.678
fT4	9.7 ng/dl	9.65 ng/ml	0.780
TSH	1.18 mIU/ml	1.6 mIU/ml	0.973
anti-TPO	9 IU/ml	9.5 IU/ml	0.058
anti-TGB	25 IU/ml	23.5 IU/ml	0.094

The mean values for serum thyroid autoantibodies were 9 IU/ml for anti-TPO antibodies and 25 IU/ml for antithyroglobulin antibodies in breast cancer patients, and 9.5 IU/ml and 23.5 IU/ml, respectively, in the control group ($p > 0.05$ for anti-TPO and $p=0.094$ for antithyroglobulin antibodies).

The mean thyroid hormones and autoantibodies values were compared between breast cancer patients and the control group according to menopausal and ER status. No significant differences between the two groups according to both menopausal status and ER status were seen. Also, no significant influence of hormonal therapy with tamoxifen and chemotherapy on serum levels of TSH, fT4, TPO and TGB autoantibodies was proved. Due to the small number of patients treated with radiotherapy only, its influence on the parameters of thyroid function and thyroid autoimmunity could not be evaluated.

Discussion

Treatment with ER antagonists such as tamoxifen has previously been shown to alter serum concentrations of several hormones and their binding globulin [10,11]. The effect of tamoxifen on TSH secretion is controversial. In our study, we did not find any significant influence of tamoxifen therapy on the serum levels of TSH, fT4, and serum thyroid autoantibodies. This is in accordance with a study that had shown that serum TSH concentrations did not increase in euthyroid women given tamoxifen (20 mg daily) for up to 3 months [7]. However, in another study there was an increase in serum TSH concentrations and a decrease in serum fT4 concentrations in women treated with 30 mg tamoxifen daily for 13 months [8].

Furthermore, in the present study highly sensitive techniques of diagnostic ultrasound to investigate subtle changes in thyroid volume in patients with breast disease were used. Thyroid enlargement has been previously reported in association with breast cancer. In 1993, Smyth used diagnostic thyroid ultrasound to determine thyroid volume and morphology in 184 breast cancer patients and 150 controls. He found a significant increase in thyroid volume in breast cancer patients compared to controls ($p < 0.01$) and a significantly higher number of patients with enlarged thyroid and breast cancer compared to controls ($p < 0.001$) [12]. The study also found that patients with breast cancer had a significantly higher percentage of thyroid abnormalities, defined as nodules and cysts, as compared to controls ($p < 0.001$).

Similarly, in a prospective study of 102 breast cancer patients and 100 healthy age-matched controls, Giani et al. found an increase in the overall prevalence of thyroid disease in breast cancer patients. Both cases and controls underwent clinical and ultrasound evaluation of thyroid volume in addition to having blood samples taken to evaluate thyroid hormones levels. A significantly higher number of breast cancer patients had thyroid disease as compared to controls ($p<0.0001$) [13].

A prospective study conducted by Cengiz et al. with 136 breast cancer patients and 68 controls found

an increased frequency of thyroid pathology in breast cancer patients as compared to controls. Participants underwent thyroid ultrasound and blood sampling for thyroid hormones and antibodies' levels. Breast cancer patients had a significantly higher frequency of thyroid pathology as compared to controls ($p<0.001$) [14].

Gogas et al. studied 600 Greek women to determine whether there is an increased prevalence of autoimmune thyroiditis in women with breast cancer compared to the general Greek female population. They evaluated the thyroid gland volume and performed serologic testing for thyroid autoantibodies on 310 breast cancer patients and two control groups: 100 age-matched women with benign breast disease and 190 age-matched women who were subjected to surgery for other conditions. The findings showed an increase in autoimmune thyroiditis in patients with breast cancer [3].

In contrast to the studies previously described, our study found no association between thyroid dysfunction and breast cancer. By and large, this study demonstrated a similar incidence of thyroid enlargement and the same frequency of thyroid disturbances in patients with breast cancer and controls. Since hormone levels tend to vary day by day, a single TSH or fT4 measurement that is beyond the range of normal may not be sufficient to make a diagnosis of thyroid dysfunction in the individual patient or to make clinical decisions based on that measurement. Both timing of our blood samples and the sensitivity of the assay used for fT4 may explain why we did not detect any differences between the studied groups.

No recommendation can be made at this time because the results of this study are inconclusive for determining if there is an association between thyroid disorders and breast cancer therapy. Further investigation is needed to determine the complete molecular effect of hormonal therapy for breast cancer on thyroid function and how that translates into the final effect *in vivo*.

References

1. Rasmussen B, Rasmussen UF, Hegedus L, Perrild H, Bech K, Hoier-Madsen M. Thyroid function in patients with breast cancer. J Cancer Clin Oncol 1987; 23: 553-556.
2. Shering SG, Zbar AP, Moriatry M. Thyroid disorders and breast cancer. Eur J Cancer Prev 1996; 5: 504-506.
3. Gogas J, Kouskos E, Tseleni-Balafouta S et al. Autoimmune thyroid disease in women with breast carcinoma. Eur J Surg Oncol 2001; 27: 626-630.
4. Lemmarie M, Baugnet-Mahieu L. Thyroid function in women with breast cancer. Eur J Cancer Clin Oncol 1986; 22: 301-307.
5. Smyth PP, Shering SG, Kilbane MT et al. Serum thyroid peroxidase autoantibodies, thyroid volume, and outcome in breast carcinoma. J Clin Endocrinol Metabol 1998; 83: 2711-2716.
6. Giustarini E, Pinchera A, Fierabracci P et al. Thyroid autoimmunity in patients with malignant and benign breast diseases before surgery. Eur J Endocrinol 2006; 154: 645-649.
7. Mamby CC, Love RR, Lee KE. Thyroid function test changes with adjuvant tamoxifen therapy in postmenopausal women with breast cancer. J Clin Oncol 1995; 13: 854-857.
8. Anker GB, Lønning PE, Aakvaag A, Lien EA. Thyroid function in postmenopausal breast cancer patients treated with tamoxifen. Scand J Clin Lab Invest 1998; 58: 103-107.
9. Gordon D, Beastall GH, McArdle CS, Thomson JA. The effect of tamoxifen therapy on thyroid function tests. Cancer 1986; 58: 1422-1425.
10. Fex G, Adielsson G, Mattson W. Oestrogen-like effects of tamoxifen on the concentration of proteins in plasma. Acta Endocrinol 1981; 97: 109-113.
11. Pannuti F, Ciovannini M, Martoni A et al. Tamoxifen-induced effects on T3, T4, TSH, LH, hPRL, 17-O-estradiol, testosterone and aldosterone plasma levels: A preliminary study. IRCS Med Sci 1981; 9: 156.
12. Smyth PP. Thyroid disease and breast cancer. J Endocrinol Invest 1993; 16: 396-401.
13. Giani C, Fierabracci P, Bonacci R et al. Relationship between breast cancer and thyroid disease: Relevance of autoimmune thyroid disorders in breast malignancy. J Clin Endocrinol Metabol 1996; 81: 990-994.
14. Cengiz O, Bozkur B, Unal B et al. The relationship between prognostic factors of breast cancer and thyroid disorders in Turkish women. J Surg Oncol 2004; 87: 19-25.