Relationship between Breast Cancer and Thyroid Disease: Relevance of Autoimmune Thyroid Disorders in Breast Malignancy*

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ABSTRACT

The relationship between thyroid dysfunction and breast cancer (BC) is debated. To clarify this controversial issue, a prospective study on thyroid function in BC was performed. The prevalence of thyroid disease was examined in 102 consecutive BC patients with ductal infiltrating carcinoma after surgery and before starting any chemohormonal or x-ray therapy and in 100 age-matched control healthy women living in the same borderline iodine-sufficient geographic area. All subjects were submitted to clinical ultrasound thyroid evaluation and serum free T_4 , free T_3 , TSH, thyroperoxidase antibody, and thyroglobulin antibody determination. Fine needle aspiration was performed in all thyroid nodules. Estrogen and progesterone receptors (ER and PR, respectively) were assayed in 92 and 55 BC specimens, respectively. The overall prevalence of thyroid disease was 47 in 102 (46%) in BC patients and 14 in 100 (14%) in controls (P <0.0001). The prevalence of nontoxic goiter was 27.4% in BC patients and 11% in controls (P = 0.003). Hashimoto's thyroiditis was found in 13.7% of BC patients and in only 2% of the controls (P < 0.005). Other thyroid disorders found in the BC group included 2 cases of Graves' disease, 2 of thyroid carcinoma, and 1 of subacute thyroiditis, whereas in the control group only 1 case of Graves' disease and none of the other disorders were found. Mean free T_3 , free T_4 , and TSH concentrations showed no difference between BC patients and controls. The prevalence of thyroperoxidase antibody was higher in BC patients than in controls (23.5% *vs*. 8%; P < 0.005), whereas the prevalence of thyroglobulin antibody was not different. In BC patients the presence of thyroid antibodies was more frequently associated with clinically detectable autoimmune thyroiditis (14 of 26, 51.8%; P = 0.03) and was more common in the younger group. The positivity of ER was found in 51 of 92 (55.43%) and that of PR was found in 26 of 55 (47.27%) BC specimens. No relationship was found among ER, PR status, and the presence of serum thyroid antibodies.

In conclusion, 1) the present study provides evidence that the overall prevalence of thyroid disorders is increased in patients with breast cancer; and 2) thyroid autoimmune disorders, especially Hashimoto's thyroiditis, account to a large extent for the increased prevalence of thyroid disease in patients with breast cancer. This feature is independent from the ER and PR status of the primary tumor. The present findings call attention to the usefulness of screening for thyroid disease in any patient with breast cancer. (*J Clin Endocrinol Metab* 81: 990-994, 1996)

THE RELATIONSHIP between thyroid dysfunction and breast cancer (BC) is controversial. An association between BC and thyroid diseases has been reported in several epidemiological studies [1] [2] [3] [4] [5] [6] . Interestingly, a high incidence of BC in patients with Hashimoto's thyroiditis and clinical hypothyroidism has been observed by some [6] [7] [8] [9] [10] , but not other [11] , [12] , researchers. Similarly, an association between BC and hyperthyroidism has been observed in some [13] , but not all [14] , studies. Most of these studies were retrospective, and the use of different diagnostic criteria for thyroid disease may account for the discrepancy described above. The possible role of iodine deficiency in breast disease has been examined by various researchers [15] [16] [17] . The experimental studies in rats [15] and epidemiological studies in humans [16] , [17] indicated that iodine deficiency may be relevant to the development of fibrocystic disease. However, no data are available on the relevance of iodine deficiency in the development of BC, and no change in BC incidence was found after iodine prophylaxis [13] , [18] .

The aim of the present study was to evaluate the prevalence of thyroid disorders in a prospective study carried out in a large number of consecutive BC patients using well defined diagnostic criteria. A higher prevalence of thyroid disease and a highly significant association with thyroid autoimmunity was found in BC patients with no relationship to the estrogen and progesterone receptor (ER and PR, respectively) status of primary breast tumor.

Materials and Methods

Our series included 102 consecutive women, aged 26-88 yr (mean ± SD, 54.3 ± 11.25), submitted to modified radical mastectomy for infiltrating ductal carcinoma of the breast, who gave formal consensus for participation in the study. In 81 (79.4%) patients, an involvement of axillary nodes was demonstrated; no cases of visceral, bone, or lung metastasis were documented. All patients were living in Pisa and its surroundings, a borderline iodine-sufficient area with previous exposure to mild iodine deficiency. The patients were evaluated 20 days or more after surgery and before starting any chemo-hormonal or x-ray therapy. A family history of BC and thyroid disease was found in 5 (4.9%) and 12 (11.7%) BC patients, respectively. Six patients had a known diagnosis of thyroid diseases: 2 with nontoxic goiter, 1 with differentiated

thyroid carcinoma under L-T_4 suppressive therapy, 1 with Hashimoto's thyroiditis, and 2 with treated Graves' disease.

The control group consisted of 100 healthy age-matched women living in the same geographic area with well definite socioeconomic and cultural status. A family history of breast malignancy and thyroid disease was found in 5 and 3 control subjects, respectively. The body size of BC patients and controls, calculated as the body mass index (weight/height^2 ratio), was similar (medians, 21 and 19, respectively).

All subjects were submitted to clinical and sonographic thyroid evaluation; blood samples were drawn for free T_4 (FT_4), free T_3 (FT_3), TSH, thyroglobulin antibody (TgAb), and thyroperoxidase antibody (TPOAb) determination. The immunocytochemical assay of ER and PR on BC tissue was carried out in 92 of 102 and 55 of 102 patients, respectively.

FT_3 and FT_4 were measured by RIA using Liso-phase Kits from TecnoGenetics (Milan, Italy). The sensitivity was 0.5 pg/mL for FT_3 and 0.8 pg/mL for FT_4. TSH was measured by a solid phase, two-site, fluoroimmunometric assay using a commercially available Kit (Delfia hTSH, Pharmacia, Turku, Finland). The detection limit was 0.03 muU/mL. The normal ranges, defined as the mean ± 2 SD of values for healthy controls, were 2.5-5.5 pg/mL for FT_3, 6.5-16.5 pg/mL for FT_4, and 0.4-3.7 muU/mL for TSH.

TgAb were determined by a sandwich enzyme immunoassay using a Melisa Kit (Cambridge Life Sciences, Cambridgeshire, UK), and TPOAb by RIA using a commercial kit (Sorin Biomedica, Vercelli, Italy). Subjects with TgAb values greater than 110 U/mL and/or TPOAb values greater than 15 U/mL were considered positive for the presence of thyroid antibodies (TAb). Ultrasonographic evaluation of the thyroid gland was carried out using a commercially available real-time instrument (Aloka SSD 121, Aloka Co., Tokyo, Japan) using a 7.5-megahertz linear transducer. The examiner did not know which group the subject represented. Thyroid volume was calculated according to the method of Aghini-Lombardi *et al.* [19] ; 12 mL was considered the upper limit for normal thyroid volume in adult females. The presence of thyroid nodules, solid or mixed, and thyroid cysts was recorded if they were greater than 5.0 mm. The echo density of the thyroid was also examined, and the level of echogenicity was evaluated according to the method of Marcocci *et al.* [20] .

The diagnosis of thyroid disease was performed according to clinical, hormonal, and instrumental parameters, including fine needle aspiration of any nodular thyroid lesion. Nontoxic goiter was defined as any thyroid enlargement not associated with hyper-or hypothyroidism and not resulting from an inflammatory or malignant neoplastic process. The presence of goiter, serum TAb, and diffuse thyroid hypoechogenicity was indicative of Hashimoto's thyroiditis. The diagnosis of Graves' disease was established by the presence of diffuse goiter and thyrotoxicosis; the presence of infiltrative ophtalmopathy was also evaluated. Focal thyroiditis was characterized by nontoxic goiter, serum TAb, and a scattered or nonscattered hypoechogenicity pattern of the thyroid gland. Thyroid carcinoma was confirmed by pathological features, and subacute thyroiditis was determined by clinical findings and low thyroid radioiodine uptake.

ER and PR were determined by immunocytochemical method on tissue frozen sections of breast cancer. Immunostaining was performed according to the procedure of King *et al.* [21] and the manufacturer's instructions, using anti-ER and anti-PR monoclonal antibodies commercially available in kit form (Abbott Laboratories, Chicago, IL).

Statistical analysis

Results were analyzed by chi^2 test and *t* test for unpaired data.

Results

The distribution of the various thyroid disorders is shown in Fig. 1 . Nontoxic goiter was found in 28 patients (27.4%) and 11 (11%) controls ($P = 0.003$). The mean thyroid volume value, as assessed by ultrasound, was 14 ± 6 and 10 ± 2 mL in BC patients and controls, respectively. Fourteen BC patients had Hashimoto's thyroiditis, including 7 with subclinical hypothyroidism. The prevalence of Hashimoto's thyroiditis was significantly higher in BC patients than in

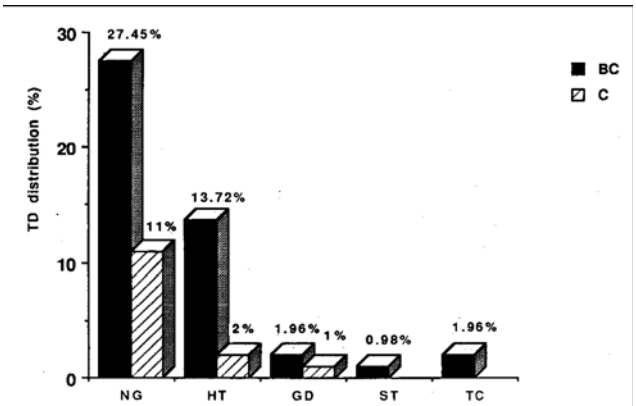

FIG. 1. Distribution of thyroid disease (TD) in BC patients and controls (C). NG, Nodular goiter; HT, Hashimoto's thyroiditis; GD, Graves' disease; ST, subacute thyroiditis; TC, thyroid carcinoma. The frequency of NG and HT in BC was significantly higher than that in C ($P = 0.003$ and $P < 0.005$, respectively).

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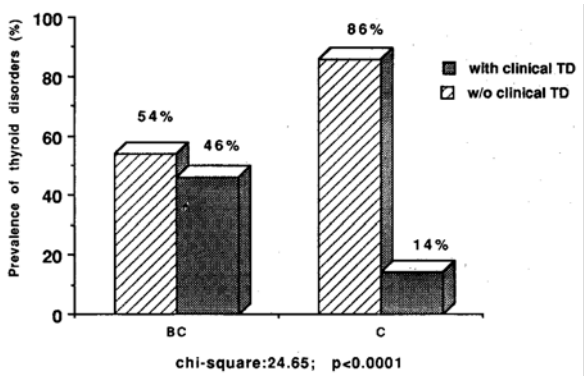

FIG. 2. Frequency of thyroid disease (TD) in BC patients and controls.

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controls (13.7% *vs*. 2%; $P < 0.005$). Graves' disease was found in 2 BC patients and 1 control subject. One BC patient (0.9%) had subacute thyroiditis, and 2 (1.9%) had thyroid carcinoma (1 papillary and 1 medullary). No case of thyroid malignancy or subacute thyroiditis was found in controls. Generally, 47 of 102 patients (46%) and 14% of control subjects had clinical thyroid diseases ($P < 0.0001$; Fig. 2). The frequency of family history of breast malignancy and thyroid disease in BC patients and controls was 4.9% *vs*. 3% and 11.7% *vs*. 5%, respectively. The mean values (± SD) of FT_4 , FT_3 and TSH in BC patients were 9.0 ± 2.27 pg/mL, 3.4 ± 0.2 pg/mL, and 1.7 ± 3.2 muU/mL, respectively, with no significant difference from control values (9.9 ± 2.4 pg/mL, 3.2 ± 0.6 pg/mL, and 1.8 ± 1.4 mu U/mL, respectively). The overall prevalence of TAb was significantly higher in patients than in controls (26.5% *vs*. 12%; $P < 0.005$). The frequency of TPOAb was significantly higher in BC patients (23.5%) than in control subjects (8%; $P < 0.002$; Fig. 3). Instead, the frequencies of TgAb in the 2 groups were similar (16.6% and 12%, respectively). The frequencies of TAb in BC patients and controls with or without autoimmune thyroid disorders are reported in Fig. 4 ; in the BC group, a higher prevalence of antibody-positive patients

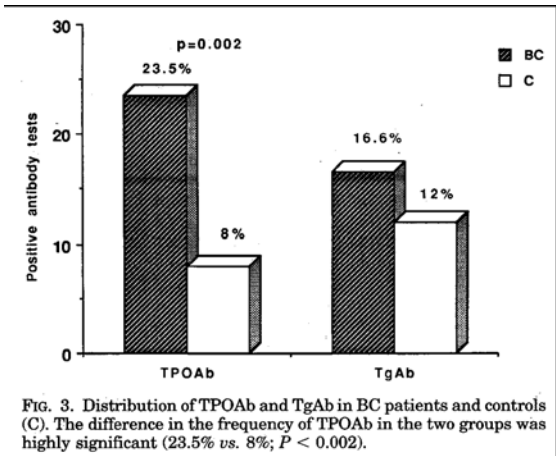

FIG. 3. Distribution of TPOAb and TgAb in BC patients and controls (C). The difference in the frequency of TPOAb in the two groups was highly significant (23.5% *vs.* 8%; $P < 0.002$).

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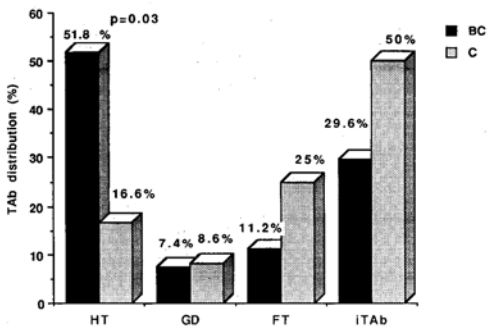

FIG. 4. The percent TAb distribution according to the presence or absence of clinically detectable autoimmune thyroid disorders (HT, Hashimoto's thyroiditis; GD, Graves' disease; FT, focal thyroiditis; iTAb, absence of thyroid disease). Compared to the control group (C), in BC patients the percent distribution of TAb was significantly higher in those with HT ($P = 0.03$).

Figure 4. The percent TAb distribution according to the presence or absence of clinically detectable autoimmune thyroid disorders (HT, Hashimoto's thyroiditis; GD, Graves' disease; FT, focal thyroiditis; iTAb, absence of thyroid disease). Compared to the control group (C), in BC patients the percent distribution of TAb was significantly higher in those with HT ($P = 0.03$).

had clinical evidence of Hashimoto's thyroiditis (14 of 26, 51.8%; $P = 0.03$). In contrast, the control group had a higher incidence of TAb (50%) in the absence of detectable thyroid disease. The presence of serum TAb according to the age of the patients and controls is reported in Fig. 5 . The BC patients and controls were divided into three groups: less than 45, 45-59, and 60 or more yr of age. In BC patients, the highest prevalence of TAb was found in the less than 45 yr and the lowest in the 60 or more yr group. In the less than 45 and 45-59 yr groups, the difference in TAb frequency between BC patients and controls was highly significant ($P = 0.005$ and $P < 0.02$, respectively). No significant difference between TgAb and TPOAb frequency in each age group considered was found. Immunocytochemical evaluation of ER and PR was carried out on 92 and 55 breast cancer specimens, respectively. The positivity for ER and PR was

found in 51 of 92 (55.43%) and 26 of 55 (47.27%) cases, respectively, with no difference between premenopausal and menopausal

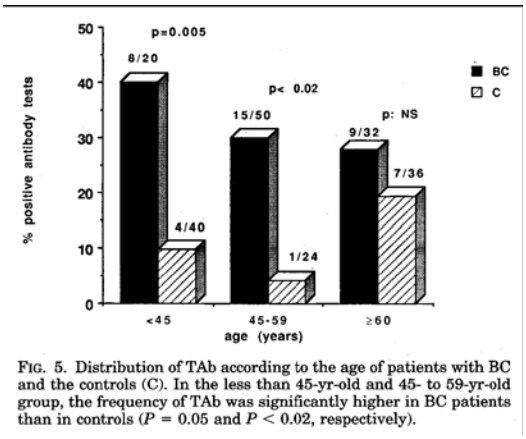

FIG. 5. Distribution of TAb according to the age of patients with BC and the controls (C). In the less than 45-yr-old and 45- to 59-yr-old group, the frequency of TAb was significantly higher in BC patients than in controls ($P = 0.05$ and $P < 0.02$, respectively).

Figure 5. Distribution of TAb according to the age of patients with BC and the controls (C). In the less than 45-yr-old and 45- to 59-yr-old group, the frequency of TAb was significantly higher in BC patients than in controls ($P = 0.05$ and $P < 0.02$, respectively).

women. The presence of TAb was slightly higher in ER-positive than ER-negative patients [18 of 51 (35.28%) and 10 of 41 (24.39%), respectively]; however, this difference was not significant. Similarly, no relationship was found between PR-positive and the presence of circulating TAb.

Discussion

The relationship between BC and thyroid disease is a matter of controversy. Thyroid function, thyroid antibodies, and clinically relevant thyroid diseases were investigated in several series of patients with breast carcinoma [2] ,[3] ,[9] ,[10] ,[14] ,[15] ,[22] ,[23] . Discrepant results were reported on thyroid function in earlier studies based on the measurement of total thyroid hormone concentrations. Data indicating normal [10] ,[24] , reduced [3] , or increased [14] serum thyroid hormone concentrations have been reported. In general, most of these studies were carried out retrospectively in patients with different stages of malignant breast disease and submitted to various treatment procedures. This may account for the discrepant results. More recently, free thyroid hormones have been reported in BC patients [10] . Our data are in agreement with those from the study of Rasmusson *et al.* [10] , which, similarly to the present investigation, was carried out in patients in good general health who were examined shortly after surgery and before beginning any other therapeutic measure.

Our results indicate an increased prevalence of nontoxic goiter in patients with BC. The presence of goiter was assessed by ultrasound thyroid examination, which provides an objective means for the evaluation of thyroid size. Our data are in agreement with previous observations reported for iodine deficiency [15] ,[23] ,[25] showing a higher frequency of thyroid disease in patients with breast neoplasia. Our study was carried out in a population previously exposed to iodine deficiency, and it is of interest that the controls living in the same area and exposed to the same environmental factors had a relatively high prevalence of goiter, but this was significantly lower than that of the BC patients. A possible pathogenic role for iodine deficiency in the development of

mammary disorders has been proposed on the basis of epidemiological evidence [16] ,[17] indicating an increased prevalence of fibrocystic diseases in women living in iodine-deficient areas and of experimental data showing the appearance of mammary fibroblast changes in rats subjected to an iodine-deficient diet [15] . It is worth mentioning that the mammary gland epithelium shares with the thyroid epithelial cells the property of concentrating iodine by a membrane active transport mechanism [26] ,[27] . The question to what extent this accounts for the relationship between iodine deficiency and fibrocystic disease is unclear. Epidemiological studies are demanded to this purpose. As yet, no data are available on the frequency of BC in iodine-deficient populations. The fact that in the present study a higher prevalence of nontoxic goiter was found in BC patients compared to that in control women living in the same area and previously experiencing iodine deficiency is consistent with the fact that a common, albeit unknown, factor may be responsible for both the increased susceptibility to goiter and the mammary gland disorders. A high frequency of BC in thyroid cancer patients has been reported in a retrospective study by Chalstrey and Benjamin [1] . In our series, two patients had thyroid carcinoma, and no thyroid malignancy was detected in controls; these data are not sufficient to clarify this point, and further prospective studies on a larger series of BC patients and controls are demanded.

Mittra *et al.* [7] reported a higher frequency of circulating TAb in British women, a population with a high risk of BC, than in Japanese, a population with a low risk: however, there was no difference in the prevalence of TAb between women with BC and healthy women in either race. Maruchi *et al.* [11] examined a possible association between Hashimoto's thyroiditis and BC, evaluating autopsy series and a cohort of patients with Hashimoto's thyroiditis, and found no significant increase in BC. In all of these epidemiological and clinical studies, the diagnosis of Hashimoto's thyroiditis was made using clinical parameters, and no sonographic evaluation of thyroid gland was carried out. Furthermore, no information concerning the staging of BC and the possible relevance of chemo-hormonal or local x-ray therapy for control of malignant disease was obtained. In our study, using well defined diagnostic criteria, we found that the prevalence of Hashimoto's thyroiditis was significantly greater in BC patients than in control subjects. In addition, the overall prevalence of TAb was significantly higher in the BC group than in the controls. This is in agreement with the report of Rasmusson *et al.* [10] showing an increased frequency of TAb in 58 euthyroid patients with BC; these women, similarly to our BC patients, were examined shortly after surgery and before the beginning of systemic adjuvant therapy or local x-ray therapy. In addition, we demonstrated that only the positivity of TPOAb was higher in BC patients, whereas the prevalence of TgAb was not. The possible role of TPOAb in producing thyroid damage and hypothyroidism in autoimmune thyroiditis has been widely studied [28] [29] [30] [31] . In our BC group, the TAb positivity was more frequently found in patients with autoimmune disorders, in particular Hashimoto's thyroiditis; this suggests a prevalence of cytotoxic antibodies in breast malignancy. In fact, the fre- quency of circulating TAb without detectable autoimmune disorders was significantly greater in healthy controls. Interestingly, in the BC group, a higher frequency of TAb was found in the youngest patients, in contrast to that demonstrated in controls and generally found in normal population [32] . This original observation further supports the hypothesis concerning the prevalence of cytotoxic TAb in BC.

ER and PR in BC tissue are generally considered important substrates for the activity of steroid hormone at the cellular level [33] ; our results exclude a direct relationship between circulating TAb and the expression of steroid receptors in BC tissue.

In conclusion, the present study indicates that 1) the overall prevalence of thyroid disease is increased in patients with BC; 2) Hashimoto's thyroiditis accounts to a large extent for the increased prevalence of thyroid disorders in patients with BC; 3) in the BC group, the level of TAb was significantly greater in the youngest patients and in clinically detectable autoimmune thyroid disease; and 4) the relationship

between autoimmune thyroid disorders and BC is independent of the ER and PR status of the breast tumor. The present findings indicate the usefulness of evaluating thyroid function in any patient with BC.

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