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Thyroid Function in Patients with Breast Cancer

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Abstract—*Thyroid function was evaluated in 58 patients with breast cancer and compared with data obtained from an age-matched control group of healthy women. Thyroid antibodies at low levels were present in 29 patients (50%): 21 patients (36%) had thyroid stimulating antibodies at low activity. Ten patients (17%) had thyroglobulin antibodies compared with 3 in the control group ($P < 0.05$). Nine of 10 patients with thyroglobulin antibodies had microsomal antibodies as well. Two patients had only microsomal antibodies. Additionally 10 autoimmune antibodies were determined. These were, however, either absent or present in low concentrations in serum. Independent of the stage of disease, no differences were demonstrated between patients and controls in serum levels of triiodothyronine, thyroxine, free T3 index, free T4 index, thyroid stimulating hormone, and thyroglobulin. In conclusion, we found an increased frequency of thyroid autoantibodies in euthyroid patients with breast cancer compared with healthy controls suggesting a possible relation between this disease and autoimmune thyroid disease.*

INTRODUCTION

IT IS controversial whether thyroid dysfunction plays a role in the pathogenesis of breast cancer. The conflicting results may partly be explained by the lack of a control group or difference in the selection of control groups [1–3]. The aim of the present study was to investigate thyroid function and signs of autoimmune disease in patients with breast cancer and compare results with those obtained from age-matched healthy controls, all from the same area without endemic goitre.

METHODS

Sixty-two consecutive patients admitted to the department of oncology, Herlev Hospital, postoperatively after mastectomy for mammary carcinoma, were considered for participation in the study. In the same period 13 patients with recurrent disease more than 6 months after a previous treatment period were considered for the study. Excluded from the study were patients with known present or past thyroid disease, impaired renal function, liver disease, other cancers and patients who received medication known to interfere with thyroid function. A total of 17 patients were excluded from the study becaue of missed blood samples ($n = 12$), pituitary tumor ($n = 1$), medication with β-blockers ($n = 1$), iodide ($n = 1$) and myxoedema ($n = 2$). Thus 58 patients with a median age of 56 years (range 27–80 years) were included after informed consent.

The patients were divided into 3 groups:

Group 1: Twenty-three patients recently operated for local mammary carcinoma without known metastases to lymph nodes, bones, lungs or liver.

Group 2: Twenty-three patients recently operated for mammary carcinoma with metastases to axillary lymph nodes, but with no evidence of further spread.

Group 3: Twelve patients with disseminated disease treated more than 6 months previously with either high-voltage irradiation, endocrine or chemo-therapy.

Blood samples were taken 16–42 days after the operation in group 1 and 2. The control group consisted of 75 healthy age-matched women, selected from hospital staff and their relatives and from an ongoing population study in Copenhagen. None had a goitre or evidence of previous or present thyroid disease. None received any medication known to interfere with thyroid function [4]. Thyroglobulin antibodies (TgAb) were measured by a radiocoprecipitation method [5]. Results were

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Table 1. *Thyroid autoantibodies in* 58 *patients with breast cancer*

TSAb	17
TgAb + MAb	5
TgAb + MAb + TSAb	3
MAb	2
TgAb	1
TgAb + TSAb	1
	29 = 50%

TSAb = thyroid stimulating antibodies.
TgAb = thyroglobulin antibodies.
MAb = microsomal antibodies.

expressed in relation to Medical Research Council research standard A 65/93, which by definition contains 1 mega unit per litre (1 MU/l). The detection limit was 0.002 MU/l. Microsomal antibodies (MAb) were measured by an immunofluorescence method [6]. Serum thyroglobulin (Tg) was quantified by a double antibody radioimmuno-assay [7] due to interference only in TgAb negative sera. The 95% reference interval was 6.2–55.6 μg/l. Thyroid stimulating antibodies (TSAb) were measured by an adenylate cyclase stimulating assay using human thyroid homogenate, the 95% reference interval was 73–108% [8]. Serum T4, T3, TSH and T3 resin uptake (T3RU) were determined as previously described [9]. Free T4 index and free T3 index were calculated as total hormone concentration × T3RU and given in arbitrary units. Autoimmune antibodies against salivary gland, adrenocortex, parietal cell, smooth muscle, mitochondria, extractable nuclear antigen, antinuclear, anti-DNA, IgM rheumatoid factor, granulocyte-specific anti-nuclear were measured by methods previously described [10–13]. Mann–Whitney's rank sum test and the χ^2-test were used for statistical analyses. Probability values < 0.05 were regarded as significant.

RESULTS

Thyroid antibodies were present in 29 patients (50%) (Table 1). Ten patients had TgAb (median: 0.026 MU/l, range 0.008–0.649 MU/l) compared with three controls (median: 0.039 MU/l, range 0.02–1.35 MU/l) ($P < 0.05$). Microsomal antibodies were found in 1/10–1/160 dilution. A total of 21 patients (36%) had TSAb > 108% (median 118%, range 110–156%). The antibodies were equally distributed in the three groups of patients. Of seven patients who had had irradiation of the supraclavicular region including the lateral part of one thyroid lobe 1–12 years before the study, one had thyroid antibodies. No differences could be found between patients and controls regarding serum levels of T3, T4, free T3 index, free T4 index and TSH (Table 2). Serum Tg level in patients without TgAb was not different from that of controls, median: 20.4 μg/l (range; 7·6–185 μg/l) and 22.9 μg/l (range; 2.2–77 μg/l), respectively.

The measurements of other serum autoimmune antibodies (salivary gland, adrenocortex, parietal cell, smooth muscle tissue, mitochondria, extractable nuclear antigen, antinuclear, anti-DNA, IgM rheumatoid factor, granulocyte-specific antinuclear) disclosed these to be either absent or sparsely occurring like in normal controls (data not shown).

DISCUSSION

Illness *per se* may influence thyroid function. Serum T3 and/or T4 concentrations may be low and TSH normal in several acute and chronic diseases [14, 15]. Therefore comparison with a matched control group is mandatory. A relation between thyroid dysfunction and breast cancer is controversial. Some authors have found that approximately one third of breast cancer patients had elevated levels of basal as well as TRH stimulated TSH, compared with healthy controls [1, 16]. But Abe *et al.* [17] comparing patients with breast cancer and patients with benign breast disease found similar values of serum TSH, T3, T4 and iodine-131 uptake in the thyroid gland. However these values were not compared with those obtained from a healthy control group. Lemaire and Baugnet-Mahieu [18] found mean values of serum T3 and T4 in patients with breast cancer significantly higher than those of healthy controls; they did not, however, exclude patients with apparent thyroid disease i.e. 8 of 226 breast cancer patients were hyperthyroid with elevated levels of T3, T4 and free T4. In the present study both patients and controls with overt thyroid disorders were excluded thus probably accounting for some of the difference observed in relation to previous findings. Rose and Davis [19] reported decreased serum levels of T3 and normal levels of T4 in breast cancer patients and patients with advanced colonic cancer, compared with an age-matched control group. This is probably due to the well-known influence of non-thyroidal disease on thyroid function [15] and not a specific interrelation between breast cancer and the thyroid. Kapdi and Wolfe [2] analysed the frequency of breast cancer among 635 women receiving thyroid supplements and found a significantly higher frequency than in a control group of 4870 women not receiving thyroid supplements. The increased risk of breast cancer might be due to the fact that the group of patients with thyroid medication was selected among women who attended a hospital for breast disease. Later investigations of hypothyroid women compared with healthy control groups have not shown an increased risk

Table 2. Thyroid function tests in patient with breast cancer according to stage of disease (median and range)

Patient group	TSH (μU/ml)		T_3 (nmol/l)		T_4 (nmol/l)		Free T_3-index (arb U)		Free T_4-index (arb U)	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
1. n=23	1.2	1.0	2.1	2.1	98	93	2.1	2.1	102	95
	0.3–3.3	0.2–4.0	1.2–2.5	1.4–3.0	81–125	57–125	1.3–2.9	1.5–3.2	70–145	52–116
	NS		NS		NS		NS		NS	
2. n=23	0.9	1.1	2.1	2.1	104	93	2.3	2.2	106	97
	0.3–5.5	0.2–2.8	1.7–2.8	1.0–2.6	87–131	57–108	1.5–3.0	1.4–2.5	87–126	62–119
	NS		NS		NS		NS		NS	
3. n=12	1.0	1.6	2.0	2.0	111	96	1.8	2.0	111	91
	0.3–2.4	0.2–1.8	1.0–2.9	1.7–2.8	75–195	62–100	1.0–2.9	1.6–2.3	79–148	68–120
	NS		NS		NS		NS		NS	

NS = not significant.

of breast cancer, whether thyroid supplements were given for short or long periods [3, 20].

In the present study patients with breast cancer, independent of the stage of disease, had serum T3, T4, TSH and Tg values similar to healthy women. We included an estimate of serum levels of free T3 and free T4 to clarify a possible change in protein-binding in the cancer patients, but these values were the same in the patients and the controls. Serum Tg has not been measured in a large group of breast cancer patients until the present study, in which serum Tg was similar to that in healthy controls. In the present study there was a marked increase in thyroid antibodies in the breast cancer group compared to controls. TSAb has not previously been measured in breast cancer patients. Generally TSAb are regarded as indicative of autoimmune thyroid hyperfunction as in Graves disease. The presence of a high incidence of TSAb at low levels without evidence of thyroid dysfunction has, however, previously been recorded in other diseases of presumable autoimmune origin, e.g. Hashimoto's thyroiditis, rheumatoid arthritis, pernicious anaemia, diabetes mellitus and also in thyroid carcinomas [21–23]. Presence of thyroglobulin and microsomal antibodies without evidence of thyroid dysfunction has been described as asymptomatic autoimmune thyroiditis with an increased risk of spontaneous hypothyroidism [21]. Former irradiation of the thyroid has been suggested to induce a slight transient production of thyroid antibodies in some patients [24]. However, these findings are still controversial [25], and not confirmed in the present study. In 1975 Itoh and Maruchi [26] suggested a relationship between Hashimoto's thyroiditis and breast cancer. Thyroid antibodies, however, were only measured randomly. Mittra *et al.* [27] studied thyroid and other autoantibodies in healthy British and Japanese women and in British and Japanese women with breast cancer. In the healthy groups the circulating TgAb and MAb were significantly higher in British women, who have a high risk of breast cancer compared to Japanese women, whereas the incidence of thyroid autoantibodies were identical in women with breast cancer and healthy women in either race. Adamopoulos *et al.* [28] contrarily found that patients with breast cancer had a significantly higher incidence of MAb than healthy controls 13.4 and 1.7%, respectively. Their study, however, was not quite comparable with our study, because they included patients with overt thyroid dysfunction.

The increased occurrence of low levels of thyroid antibodies in the present study may point towards a common factor in autoimmune thyroid disease and breast cancer of autoimmune or exogenous origin. The latter was suggested by Kieffer *et al.* [29] based on a study of rat mammary carcinogenesis and thyroid disease by use of a potent carcinogen (*N*-nitrosomethylurea). Only long-time follow up may clarify if the present patients are more exposed to develop overt thyroid dysfunction.

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