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Thyroid Function in Women with Breast Cancer

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Abstract—*The thyroid function was evaluated in a study group of* 226 *breast cancer patients and in control groups, consisting of* 125 *patients with various other malignancies,* 61 *women with benign breast disease and* 166 *healthy blood donors. The mean serum concentrations of total T_3 and T_4 were significantly higher in the breast cancer group than in the controls. The mean TFI (thyroid function index), measured by two indirect techniques (T_3RU, T_4/TBG) or by direct free T_4 measurement, was also significantly higher in this group of patients than in controls. Individual values of TFI exceeding the upper limit of the normal range were related with elevated total T_4 levels and not with abnormal concentrations of total TBG. Eight women with breast cancer* (3.5%) *and one patient with head and neck cancer were clinically hyperthyroid. No case of overt hypothyroidism was observed. There was no relation between thyroid function and spread of the disease (TNM). The control groups, including patients with other-than-breast cancers, did not show any significant modification of the thyroid function tests. In the present study, breast cancer patients, as a group, show a thyroid dysfunction distinct from the non-specific abnormalities (low T_3 syndrome) frequently observed in patients with a variety of acute or chronic non-thyroidal illnesses.*

INTRODUCTION

THERE IS considerable evidence that steroid and polypeptide hormones play important roles in the etiology and pathogenesis of breast cancer, but despite extensive investigation, the possible relationship between thyroid dysfunction and both the incidence and progress of breast cancer has been, for many years, a controversial subject (see reviews [1–3]).

The first reports were based either on the observation of an increased incidence of breast cancer in geographic areas of endemic goitre or on the clinical impression that hypothyroidism frequently occurred in patients with breast cancer.

Early attempts to assess biochemically the thyroid function relied mainly upon the evaluation of basal metabolic rate, serum protein bound iodine (PBI) or ^{131}I uptake and clearance. Although a mild hypothyroidism was repeatedly suggested, a number of studies failed to show unequivocally an altered thyroid function in breast cancer patients.

On the other hand, conflicting data also exist about the incidence of breast cancer in patients receiving thyroid hormone supplements and about the curative and palliative value of thyroid hormone therapy for the treatment of breast cancer. After the publication of a report [4] implying that thyroid hormone administration may play a causal role in breast cancer, the need for new experimental approaches of this problem was again pointed out by the American Thyroid Association [5].

Since then, several retrospective and prospective studies were conducted on large series of thyroid and breast cancer patients [6–11], yet the issue is still not satisfactorily resolved. The development of sensitive radioimmunoassays greatly improved the routine evaluation of the hormonal functions in human patients. Using these techniques, several authors failed to show any significant increase of thyroid abnormalities in patients with breast cancer, compared to patients with benign breast disease or to healthy controls [12–16]. Other studies suggested a tendency to a "mild" or "subclinical" hypothyroidism associated with the mammary disease [17–21].

A rather ancient report of Desaive [22], supported by a large number of clinical observations at the University of Liège Cancer Centre, suggested an association between breast cancer and thyroid hypofunction in this country. The aim of the present work was to re-evaluate, by using a battery of radioimmunological tests, the thyroid function of

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Abbreviations: T_3: 3,5,3'-triiodothyronine; T_4: thyroxine; T_3RU: T_3 Resin Uptake; TSH: thyroid-stimulating hormone; TBG: thyroxine-binding globulin; TRH: thyrotropin-releasing hormone.
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patients attending the University Hospital of Liège for breast cancer. The control groups consisted of patients referred to the hospital for other malignancies and for benign breast diseases and of healthy blood donors originating from the same area.

In the group of breast cancer patients, the mean values of total T_3 and T_4 were significantly higher than the controls. The "thyroid function index" (TFI) [21], obtained either by indirect methods (T_3RU, T_4/TBG) or by direct measurement of the free T_4, was also higher in women with a breast cancer, as a group, than in the other groups of this study. Abnormalities in thyroid function were not correlated with the clinical stage of malignancy.

MATERIALS AND METHODS

The study group consisted of 226 female patients with breast cancer. The mean age was 55 years (range : 28–79). Three other groups of patients and one group of healthy blood donors were used for comparison.

A first group consisted of 78 head and neck cancer patients (63 males, 15 females) ; the mean age was 60 years (range : 33–85). A second group included 47 patients suffering from various other malignancies, listed in Table 1. The mean age was 54 years (range : 20–91). Cancer patients were classified according to the UICC classification (1980).

Blood was drawn from all cancer patients 4 weeks after surgery or biopsy, prior to the initiation of any therapy. A series of non-cancerous patients, consisting of 61 women with benign breast disease were also investigated ; the mean age was 42 years (range : 25–87).

Blood donors (n = 166 ; 38 males and 128 females) served as healthy controls ; the mean age was 46 years (range : 17–65). Patients and controls taking oral contraceptives or any other hormonal therapy during the 3 months preceding our study were excluded.

Table 1. Patients with miscellaneous cancers

Diagnosis	No. of patients
Uterine carcinoma	8
Hodgkin and non-Hodgkin lymphoma	8
Bone and soft tissue sarcoma	8
Astrocytoma	9
Colon carcinoma	3
Lung carcinoma	3
Kidney tumor	3
Melanoma	1
Stomach carcinoma	1
Pancreatic carcinoma	1
Prostatic carcinoma	1
Thyroid carcinoma	1

The radioassay kits for chemical diagnosis from Serono Diagnostics (Italy) and Amersham Radiochemical Centre (U.K.) were used for the determination of T_3, T_4 and T_3 resin uptake (T_3RU). TSH was evaluated by using the radioassay kit from NML laboratories (U.S.A.) and TBG by using the Immophase test from Corning (U.S.A.). Free T_4 serum concentration was measured by the Liso-phase kit from Lepetit (Italy). The limits of normal range, defined as a mean ± 2 S.D. of values for healthy controls were in our laboratory : for T_3 : 0.9–2.1 ng/ml ; for T_4 : 4.6–11.6 μg/100 ml ; for T_3RU : 20–30% ; for TSH : 0–6 μU/ml for TBG : 12–31 ng/ml, and for direct free T_4 measurement : 4.8–19.4 pg/ml. The value for free T_4 index (FT_4I) was calculated by multiplying the value for T_4 with the value for T_3RU divided by 100.

The TRH stimulation test was carried out as follows : after an overnight fast, blood was collected for the estimation of basal TSH level and then 200 μg of TRH (UCB pro diagnostica-Belgium) were injected intravenously ; subsequent blood samples were taken at 20 and 90 min for further TSH estimations. The normal response to TRH stimulation was defined in healthy women, using the 20 min value, as $4 < \Delta$ 20 min < 15 μU/ml.

Every time the clinical examination revealed any thyroid size abnormality (34 breast cancer patients), ^{131}I and ^{99m}Tc scintigrams were taken. Eighteen ^{131}I functional tests were performed.

Comparisons between the group means were carried out using the Student's t-test. The non-parametric Mann–Whitney rank test was used to confirm the significance of the results. Probability values less than 0.05 in both tests were regarded as significant.

RESULTS

In this study, the groups of malignant and benign breast disease patients consisted of women only, whereas male and female subjects were included in the series of patients bearing other malignancies. Blood donors of both sexes were also included as healthy controls. In a preliminary analysis of the results, the possible influence of the sex of the patients on the thyroid function tests was checked by comparing the subgroups of male and female subjects. The mean values of thyroid hormones within a same group of patients were not significantly different and the statistical significance of the comparisons between the different groups of the study was the same, whether men and women were considered separately or together (results not shown).

Table 2 shows the mean serum values of total T_3, T_4 and TSH for the five groups of the study. The serum concentrations of T_3 and T_4 were significantly higher ($P < 0.01$) in breast cancer patients than in the other groups. TSH was of the same

Table 2. Mean thyroid hormones and TSH levels in women with breast cancer and in control groups

Groups		T_3 (ng/ml)	T_4 (μg/100 ml)	TSH (μU/ml)
Breast cancers	A[b]	1.83* ± 1.38[a]	9.68* ± 3.05	2.90 ± 2.00
n = 226	B[b]	1.77 ± 0.57	9.97 ± 2.65	3.13 ± 1.84
Head and neck cancers n = 78		1.54 ± 0.75	7.92 ± 3.49	2.59 ± 1.63
Other cancers n = 47		1.35 ± 0.58	8.26 ± 2.43	2.69 ± 2.15
Benign breast diseases n = 61		1.57 ± 0.38	8.44 ± 2.38	2.58 ± 1.29
Healthy blood donors n = 166		1.50 ± 0.32	8.09 ± 1.73	2.91 ± 1.44

(a) S.D.
(b) A = first blood sample prior to radiotherapy
B = second blood sample after radiotherapy
n = number of subjects in each group.
* = significantly higher ($P < 0.01$) than the other groups.

order of magnitude in all groups. As far as breast cancer patients were concerned, the mean values of thyroid hormones and TSH were not significantly different, when measured before (A) or after (B) postoperative radiotherapy.

According to the TNM classification of UICC, the breast cancer patients were subdivided into 46% of T_1, T_2, T_3 N_0M_0, 52% of more "advanced" cases and 2% not classified. Twenty-one per cent of the "early" and 27% of the "advanced" cases had elevated levels of T_3 and/or T_4. The TNM classification of 57 head and neck cancer patients was also available. Out of 41 patients with T_1, T_2, T_3 N_0M_0, six had an elevated level of T_3 and/or T_4 and eight had a T_3 and/or T_4 level under the lower limit of the normal range. Out of 16 patients with an 'advanced' tumor, five had an elevated level of T_3 and/or T_4 and two had a T_3 and/or T_4 level under the lower limit of the normal range. Statistically, there was no significant correlation between abnormal values of total thyroid hormone concentrations and the clinical stage of malignancy.

Several techniques have been devised in order to measure the proportion of free hormone in blood : *in vitro* T_3 uptake calculated as free T_4 index, T_4/TBG ratio and more recently, the direct radioimmunological measurement of free T_4.

As shown in Table 3, the mean values of T_4/TBG, Free T_4 index and FT_4 (direct measurement) were significantly higher ($P < 0.01$) in the group of breast cancer patients than in the other groups. Elevated values of these parameters in 11% of the breast cancer patients were found to be related with total T_4 levels exceeding the upper limit of the normal range and not to abnormal concentrations of total TBG.

Table 3. Evaluation of free thyroxine by indirect and direct methods, in breast cancer patients and in the control groups

	TBG (ng/ml)	T_4/TBG	T_3RU (%)	FT_4I	FT_4meas. (pg/ml)
Breast cancer	21.15 ± 5.40 n = 52	0.465* ± 0.179	25.33 ± 3.67 n = 166	2.49* ± 0.88	15.87* ± 6.37 n = 40
Head and neck cancer	24.90** ± 5.10 n = 69	0.339 ± 0.184	N.D.	N.D.	10.40 ± 4.59 n = 43
Other cancers	22.90 ± 5.05 n = 41	0.352 ± 0.099	N.D.	N.D.	12.59 ± 5.35 n = 29
Benign breast diseases	N.D.	N.D.	24.92 ± 2.77 n = 61	2.07 ± 0.53	N.D.
Healthy blood donors	21.54 ± 4.78 n = 63	0.371 ± 0.153	25.07 ± 2.48 n = 60	2.03 ± 0.83	12.08 ± 3.66 n = 36

N.D. = No determination.
* significantly higher ($P < 0.01$) than the other groups.
** significantly higher ($P < 0.05$) than the other groups.

No case of overt hypothyroidism was observed in any series of patients included in this study. In the group of breast cancer patients, eight women (3.5%) were clinically hyperthyroid (weight loss, cardiac acceleration at rest, sudation, limbs tremor) and exhibited simultaneously elevated levels of T_3, T_4 and free T_4 and low TSH. Amongst these eight hyperthyroid patients, two toxic thyroid adenomas were diagnosed by scintigraphy. Another case of clinical hyperthyroidism was found in the group of head and neck cancers.

TRH stimulation tests could be carried out on a limited series of 41 breast cancer patients. Twenty patients (50%) had a normal response of TSH to TRH stimulation ($4 < \Delta_{20min} < 15$ μU/ml), 12 patients showed an impaired response ($\Delta_{20min} < 4$ μU/ml) and eight patients showed an exaggerated response ($\Delta_{20\ min} > 15$ μU/ml). There was no significant correlation between the response to the TRH stimulation test and the other parameters of this study : thyroid hormone levels, basal concentration of TSH, clinical stage of the tumor.

DISCUSSION

After attention had been focused again on the possible influence of the thyroid status on the risk of malignant breast disease [4, 5] the incidence of breast cancer was examined in thousands of women registered and followed up during and after the treatment for thyroid dysfunction. Conversely, other investigators collected indications of thyroid disease or use of thyroid supplements among large series of women referred to hospital for mammography, or followed up for breast cancer [6–11]. Most of these prospective or retrospective studies provided no indication of increased occurrence of malignant mammary tumor in association with thyroid disease or thyroid replacement therapy.

The development of radioimmunological techniques for the evaluation of thyroid function provided a useful tool for the biochemical approach of this problem.

Abnormal levels of circulating thyroid hormones have been frequently observed in euthyroid patients with various non-thyroidal illnesses [23–27]. In the present study, it was therefore useful to include in the controls, not only healthy blood donors but also women with benign breast disease and patients with various malignancies other than breast cancer.

Significant differences in thyroid hormones and TSH concentrations have been demonstrated in benign breast disease patients by MacFarlane *et al.* [16]. However, according to these authors, at least 70% of these changes could be ascribed to a recent surgical trauma. Other investigators [28] obtained either abnormal or normal values of the thyroid function tests, depending on the type of benign breast disease (mastodynia, isolated galactorrhea, breast hypertrophy or fibroadenomata).

A few reports appeared in recent years concerning the biochemical evaluation of thyroid function in patients with malignancies other than breast cancer : hepatocellular carcinoma [29], lung cancer [30, 31], malignant lymphoma [32] and leukemia [33], carcinoma of the colon [34]. The characteristic picture of "euthyroid sick syndrome" [26] (low value of T_3, normal T_4, free T_4 normal or slightly elevated) was generally found in patients with weight loss, advanced or metastatic malignant disease.

In our groups of patients with benign breast disease or with miscellaneous malignant tumors (Tables 2 and 3), the mean values of total and free thyroid hormones were not significantly different from those of the healthy controls. The individual values were symmetrically distributed around the mean and most of them were situated within the limits of the normal range. The mean value of TBG was significantly higher in the group of head and neck cancers, without effect on the mean T_4/TBG ratio.

Contradictory results are found in the literature concerning the total thyroid hormone concentrations in breast cancer patients. Serum T_3 and T_4 were considered as normal [13–15] or subnormal [12, 19, 20]. Elevated levels of T_4 were reported by Zumoff [37, 38]. In our series of 226 women with breast cancer, the mean values of T_3 and T_4 were significantly higher than those of all the other groups (Table 2). Individual values of total T_3, T_4 or both exceeded the upper limit of the normal range in 27% of the breast cancer patients ; only 5% were situated under the lower limit of the normal range. Eight patients of this group (3.5%, instead of 0.01% in the normal population of this country) were clinically hyperthyroid. The mean age of breast cancer patients had no influence on this phenomenon. In healthy blood donors (mean age : 46 years) the maximal T_3 and T_4 values were reached at 40 years and thereafter decreased with increasing age, as also found by Bermudez [23]. The maximal T_3 and T_4 values were respectively : in the group of breast cancers : 56 years ; head and neck tumors : 58 years and miscellaneous other tumors : 57 years, corresponding with the age distribution of these groups of patients.

The influence of the stress on the hormonal status of cancer patients cannot be definitely ruled out. Moreover, it is well known that modifications of the thyroid hormone levels may occur during the pre-operative period and the first days following a surgical operation.

In the present study, blood specimens from the cancer patients were generally not available during

the preoperative period. Therefore, the thyroid function tests were routinely performed 4 weeks after biopsy or surgery, prior to the initiation of any other therapy.

Indeed, several authors have demonstrated that the recovery of normal pituitary–thyroid function is complete 7 days after the surgical stress [35, 36].

Another argument in favor of the validity of our conclusion is the observation by Perry *et al.* [18] and Thomas *et al.* [21] that the preoperative levels of the thyroid function index were *higher* than the values obtained 10 days–6 months after mastectomy. In this study, preoperative values eventually higher than our experimental data would confirm and increase the significant difference observed between the breast cancer patients and the control groups.

The concentration of free thyroid hormones in blood is thought to be an important determinant of the thyrometabolic status of the patients. The evaluation of unbound T_4 in the serum is thus considered by several authors as a more reliable index of the thyroid function than the total thyroid hormones, in view of the possible variations of the concentration of thyroxine-binding proteins. In breast cancer patients, free thyroid hormone levels have been reported as normal [12–14, 37] or lower than the controls [18, 21]. In the present study (Table 3) and whatever the technique used for the evaluation of the free thyroid hormone in blood, the group of breast cancer patients was the only one with mean free T_4 levels significantly higher than the other groups: about 10% of the individual values exceeded the upper limit of the normal range, the TBG values remaining in the normal range. Thomas *et al.* [21] have found an index of free T_4 (Thyroid Function Index) significantly lower in early breast cancer, compared with normal controls. The TFI was correlated with histological grade, with the highest values in well differentiated (grade I) and the lowest in anaplastic tumors (grade III) ; the authors suggested that thyroid hormones could play a role in determining the degree of malignancy. The apparent discrepancy between the results obtained by these authors and the present data is probably due to the fact that the greatest part of our 226 breast cancer patients were classified according to Bloom as grade I and grade II, only a few cases being considered as anaplastic tumors.

An elevated basal level of TSH was reported in breast cancer patients by several investigators [12, 14, 17–20]. No significant modification of basal TSH was demonstrated in any group of this study, but abnormal TSH responses to TRH stimulation were observed in 20 out of 41 breast cancer patients. Similar observations were reported by Aldinger *et al.* [14], Mittra and Hayward [17] and Rose and Davis [19], suggesting that, in some cases, alterations in the thyroid hormone regulation could be secondary to dynamic changes at the pituitary level.

A certain correlation between the thyroid hormone patterns and TSH level and the clinical stage of breast cancer (tumor size, spread of the malignant disease) was reported by Rose and Davis [19, 20] but no significant relationship could be demonstrated by other authors [12, 14, 15, 17, 21] and in the present study.

Attempts to follow up women with a malignant mammary tumor with respect to thyroid function led to rather confusing data. Perry *et al.* [18] concluded that patients with breast cancer show more evidence of hypothyroidism as time progresses. Moossa *et al.* [39] failed to demonstrate any statistically significant association between the development of breast cancer and thyroid dysfunction but, when the two diseases coexist, the thyroid abnormality was found to affect the course of breast cancer (shorter 5- and 10-yr survival). Aldinger *et al.* [14] also reported a shorter survival and disease-free interval for patients with elevated TSH and prolactin levels, but in neither case was the difference statistically significant. Adami *et al.* [13] failed to show any significant change in the mean TSH and thyroid hormone levels after 7–28 months follow-up. In the present study (Table 2), the thyroid hormone levels were identical in breast cancer patients, before and after radiotherapy. Further evaluation (2–5 yr follow-up) of the cancer patients taking part in this study is in progress.

The present findings of elevated levels of thyroid hormones in women with breast cancer are most nearly compatible with those of Zumoff *et al.* [38] and MacFarlane (quoted by the latter authors), except that these authors failed to observe any significant increase in plasma T_3 levels. On the other hand, we did not observe any elevation in total and free thyroid hormones in patients with benign breast disease and in patients with various other malignancies, as it was the case in the studies of Zumoff and MacFarlane. Thus, the groups of women with breast cancer, studied by these authors and by ourselves showed a characteristic thyroid dysfunction, clearly distinct from the nonspecific "low T_3 syndrome", but occasionally observed in other groups of cancerous and noncancerous patients.

A specific role of pituitary-thyroid function in the etiology of human breast cancer remains to be unequivocally demonstrated. However, the stimulation of the growth of human breast cancer cells in nude mice by pituitary factors [40] and the presence of nuclear thyroid hormone receptors in human and rat mammary cancer cell lines [41, 42] and in human mammary tumors [43, 44] suggest a direct influence of pituitary and thyroid hormones in breast cancer growth.

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