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Thyroid Function in Breast Cancer Patients before and up to Two Years after Mastectomy

Hans-Olov Adami[1], Jörgen Hansen[2], Åke Rimsten[1] and Leif Wide[3]

From the Departments of Surgery[1], Oncology[2] and Clinical Chemistry[3], University Hospital, Uppsala, Sweden

ABSTRACT

In 41 women newly diagnosed as having breast cancer the thyroid function was assessed by determination of the serum TSH, tririodothyronine (T3), reverse triiodothyronine (rT3), thyroxine (T4), T3-resin uptake and free T4-index. Blood samples were drawn before the primary treatment and at follow-up after 7-28 months. There was no significant change in any of these variables during the period of observation. Nor was there any difference between the values of the patients who developed recurrent disease and of those who did not.

These results contradict previously proposed hypotheses of a progressive decrease in thyroid function after primary treatment and of a relation between the clinical course and the thyroid function in breast cancer patients.

INTRODUCTION

The hypothesis that breast cancer and thyroid function are related to each other has been discussed from different viewpoints ever since Beatson in 1896 (4) suggested thyroid as a treatment in advanced breast cancer.

In a previous study (2) we analyzed the possible role of thyroid disease or dysfunction as an etiologic factor in breast cancer. A comparison with non-hospitalized controls revealed that the patient group had a slightly but significantly higher mean serum concentration of TSH, rT3 and T3-resin uptake and a lower T3 than the control group. These findings were considered inconsistent with a hypothyroidism, which has repeatedly been suggested as increasing the risk for breast cancer (cf 2, 17). The same pattern of changes have, however, recently been reported to be secondary to a number of non-thyroidal diseases (5) and we concluded that the results of our study could not support the concept that a thyroid dysfunction is an etiologic factor in breast cancer.

In a subsequent study (1) further support for this conclusion was obtained when the thyroid function was assessed before, during and at different times after mastectomy in breast cancer patients and compared with that of women undergoing a cholecystectomy. There were no significant differences in TSH or

thyroid hormone levels between the two groups. Both groups showed changes after surgical trauma which were in close agreement with those previously noticed as an unspecific reaction to illness.

The aim of the present study was to find out whether there is a progressive change in thyroid function and if so, whether this is in any way related to the course of the disease as repeatedly reported in earlier (6, 7, 10) and also in some recent (3, 11) studies.

METHODS

Thyrotropin (TSH) in the serum was assayed by a radioimmunosorbent technique using indirectly coupled antibodies (13, 16). The results were expressed in mU/l with the MRC preparation 68/38 used as a reference standard. The incubations were performed overnight at room temperature and the limit of sensitivity was about 0.5 mU/l of serum.

Triiodothyronine (T3) in the serum was measured by solid phase radioimmunoassay with antibodies coupled directly to microcrystalline cellulosa particles activated with cyanogen bromide (15). Incubations were performed at 60°C for two hours and overnight at room temperature in 0.5% polysorbate-20 (Tween-20), in a 0.05 M phosphate-buffered saline, pH 7.4.

Reverse triiodothyronine (rT3) was measured by a radioimmunoassay using polyethylenglycol for separation of bound and free rT3. The reagents were obtained from Biodata (Rome, Italy).

Thyroxine (T4) in the serum was determined according to the Bio-Rad thyroxine column test (Bio-RAD Laboratories, Richmond, California).

The T3-resin uptake test was performed with Sephadex^{R}-G-25 (Pharmacia, Uppsala, Sweden) as a resin and the results were expressed as a percentage of the mean of healthy controls. The value for free T4-index (FT4 I) was calculated by multiplying the value for T4 with the value for T3-resin uptake test divided by 100.

The limits of the reference range, defined as a mean ± 2 S.D. of values for healthy controls, were in this laboratory for TSH 0.5-6 mU/l, for T3 1.3-3.2 nmol/l, for rT3 0.13-0.44 nmol/l, for T4 65-165 nmol/l and for T3-resin uptake 75-115.

MATERIAL

The study comprises 41 women without thyroid substitution therapy. Only one of the patients had a history of thyroid disease. She was operated in 1942 due to a diffuse toxic goitre but euthyroid at the time of this investigation. All patients had a newly diagnosed breast cancer without known distant metastases. They were classified according to a combined clinical and histopathological staging (12). Twentysix patients had no axillary metastases, two had a locally

Table 1. Staging according to a combined clinical and histopathological classification.

Stage	Definition	Number	%
0	In situ carcinoma	2	5
I	No local tumour complications, no axillary metastases	24	59
II	No local tumour complications		
a	Axillary metastases	3	7
b	As IIa but perinodal tumour growth and/or involvement of apical nodes	10	24
III	Locally advanced tumour	2	5
		41	100

advanced tumour but nobody had known distant metastasis at the time of primary treatment (Table 1). The mean age at diagnosis was 60.2 years (range 30-80 years).

All patients were treated by a total mastectomy. An axillary dissection was done in all cases where a peroperative histological examination of axillary node biopsies revealed metastases. Postoperative irradiation was given against the supraclavicular and parasternal region to patients with medially or centrally located cancers in stage I or IIa. All 12 patients with cancers in stage IIb or III in addition got postoperative irradiation against the axilla.

The first serum sample was obtained after the initial hospital admission but before surgery. All patients were postoperatively followed regularly at the Department of Oncology where a second serum sample was drawn after an observation time varying between 7 and 27 months with a mean of 18 months. The period of observation was for one group of 12 women 7-13 months (mean 9.4) and for another of 29 women 19-27 months (mean 22.2). All sera were stored at $-20^{\circ}C$ until they were concomitantly analyzed.

RESULTS

The mean values before treatment and at follow-up are shown in Table 2 for the whole group and after subdivision into one group with a shorter (n = 12) and one with a longer (n = 29) observation time. The differences between the first and the second sample were very small, were not more pronounced in those followed for a longer period and were all insignificant ($p > 0.05$, t-test). Five patients had developed distant metastases during the observation period. There were no significant differences ($p > 0.05$, t-test) between any of the mean values for this group and for the whole group, neither before treatment nor at the follow-up (Table 2).

Table 2. Thyroid function before treatment (I) and at follow-up (II) in the whole material, in subgroups with a shorter and a longer observation time and in patients with recurrent disease.

	Mean ± S.D.							
Test	All patients n = 41		Patients with observation time 7-13 months n = 12		Patients with observation time 19-27 months n = 29		Patients with metastatic disease n = 5	
	I	II	I	II	I	II	I	II
TSH mU/l	2.45±1.34	3.99±8.40[1)]	2.75±1.06	2.95±1.19	2.32±1.44	4.42±10.00[2)]	2.16±0.40	2.56±0.42
T3 nmol/l	1.79±0.35	1.93±0.34	1.87±0.32	1.97±0.24	1.76±0.36	1.92±0.38	1.83±0.11	1.92±0.22
rT3 nmol/l	0.34±0.10	0.32±0.11	0.37±0.08	0.37±0.12	0.30±0.10	0.34±0.10	0.34±0.06	0.25±0.04
T4 nmol/l	108±31	111±27	126±28	124±22	106±29	108±31	108±14	111±13
T3-resin uptake %	95±14	91±9	88±9	92±8	91±9	95±14	94±7	97±13
FT4I	9.6±2.7	10.3±2.4	11.0±1.9	11.3±2.0	9.9±2.4	9.6±2.7	11.1±2.1	10.4±0.7

1) 2) After the exclusion of one woman who developed overt hypothyroidism the corresponding values were [1)] 2.69±1.30 and [2)] 2.58±0.35.

Our results were also analyzed after subdivision of the material according to the clinical and histopathological classification. This analyses did not reveal any significant differences between the stages, which is in accordance with our previous findings (2), and no significant changes in thyroid function in any of the stages during this observational period.

One 78 year old woman developed an overt hypothyroidism during an observation time of two years with an increase in TSH from 3.0 to 56 mU/l with a concomitantly subnormal T3, rT3 and T4 value. Except for this woman only one had a TSH-value slightly exceeding the upper limit of the reference range. The T3-values were normal in all other women before treatment as well as at the time of follow-up.

DISCUSSION

A thyroid dysfunction might be involved in breast cancer disease both by influencing the etiologic process and the progress of the disease. It might be reasonable then to assume that such a dysfunction should take the form of a hypothyroidism or a hyperthyroidism. The hypothesis of hypothyroidism as a risk factor has at the present time been supported by the uniform finding of a higher mean TSH-concentration in breast cancer women at the time of diagnosis than in comparable controls (2, 9, 11, 14). Values exceeding the upper limit of the reference ragne were in these studies found in 8.5% (2) - 36% (3) of the patients. A concomitantly exaggerated TSH-response to TRH-stimulation was also shown in some of the patients (3, 9, 14). Women with breast cancer were therefore considered to have an increased frequency of hypothyroidism - usually subclinic (9, 11). These findings were suggested to reflect subnormal thyroid hormone levels by Mittra (9). He also proposed - with support from experimental research (8) - that low thyroid hormone levels render the breast epithelium more sensitive to prolactin stimulation and hypothyroidism thereby to be involved in the etiologic process.

The later finding of normal plasma T4-levels (2, 3, 14) and also a normal free T4-index (2) appears to invalidate this hypothesis although one recent study in fact showed a slightly decreased free T4-index (11). The whole concept of hypothyroidism was questioned when thyroid function was more completely assessed by the concomitant determination of TSH, T3, rT3, T4 and T3-resin uptake (2). The pattern of differences between patients and controls was then considered inconsistent with a hypothyroidism but in agreement with that found in many non-thyroidal diseases (2, 5).

The concept that slight changes in thyroid hormone metabolism are secondary to stress and disease in women with breast cancer might also explain why a significant increase in TSH was restricted to (14) or more pronounced in (9) women with an advanced disease.

The present study was primarily aimed at evaluating the hypothesis of progressive changes in thyroid function after the primary treatment which made a control group superfluous. The study has however further confirmed our previous finding of euthyroidism in breast cancer patients.

The very close agreement between the values from the first and the second sampling period is in disagreement with the findings that the thyroid function is, for one reason or another, continuously decreasing after the initial treatment as reported by Perry et al. (11). This study showed a significant decrease in free T4-index at a follow-up after 6 months. The follow-up was, however, incomplete and included only 29 of 40 patients. The concomitant increase in TSH was also insignificant. We have therefore condluded from our study - based on a more extensive assessment of thyroid function, a longer observation time and a complete follow-up - that there is no systematic change in thyroid function after the primary treatment.

The thyroid function in patients who developed distant metastases and therefore ultimately will die due to the disease, has to be interpreted with caution due to the small number of patients. There is no indication from our results that recurrent disease is proceded or accompanied by a decreased thyroid function as previously suggested.

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Address for reprints:
Hans-Olov Adami, M.D.
Department of Surgery
University Hospital
S-750 14 Uppsala
Sweden