THYROID STATUS AND BREAST CANCER

REAPPRAISAL OF AN OLD RELATIONSHIP

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Summary

SEVENTY-ONE PATIENTS with both breast cancer and thyroid dysfunction (hyperthyroidism, non-toxic goitre, primary myxoedema) have been treated in Liverpool hospitals since 1952. Ten-year survival data on 51 of these patients are reported. There is no statistically demonstrable association between the development of breast cancer and thyroid dysfunction. However, when the two diseases coexist the thyroid abnormality has an adverse effect on the course of the breast cancer, with shorter 5-year and 10-year survival times. Whether early detection and therapy of thyroid dysfunction will alter the deleterious effects on breast cancer remains to be determined.

Introduction

THE APPARENT ASSOCIATION between thyroid disease and cancer in general and breast cancer in particular has been known for over 25 years. Although the exact mechanism remains to be elucidated, thyroid hypofunction has been frequently implicated in the aetiology and the spread of malignant disease[1-13].

The present study is an attempt to clarify the relationship between breast cancer and thyroid function. A non-concurrent study of 71 patients with concomitant breast cancer and thyroid disease (definite history of goitre, thyroidectomy, hypothyroidism, or hyperthyroidism) was made. It was designed to answer two questions: (1) Is there a genuine relationship between breast carcinoma and thyroid disease in the Liverpool region? (2) Does the presence of thyroid dysfunction affect in any way the course and prognosis of breast cancer?

Clinical material and method

Two different series of patients from hospitals in the Liverpool region were reviewed: (1) The records of patients with breast cancer since 1952 were studied to find out how many had a history of thyroid disorder. (2) The records of patients treated for thyroid disease since 1952 were examined for evidence of breast cancer.

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A total of 713 patients were collected for this review — 462 from breast clinics and 251 from thyroid clinics. They were derived from 3 distinct and separate sources: (1) A prospective non-concurrent study of 328 consecutive breast cancer patients seen at the Liverpool Royal Infirmary between 1952 and 1960. (2) A prospective non-concurrent study of 233 consecutive patients who attended the thyroid clinic at the David Lewis Northern Hospital between 1952 and 1961. (3) A series of 152 patients with breast cancer or thyroid disease who came under the clinical care of the authors or their immediate colleagues during the period they have been interested in this study — that is, the past $2\frac{1}{2}$ years.

TEN-YEAR FOLLOW-UP OF PATIENTS WITH THYROID DYSFUNCTION AND BREAST CANCER

	Total No. of Patients Collected	*No. of Patients Followed Up for 10 Years*
1. *Hyperthyroidism associated with breast cancer.*		
Treated hyperthyroidism followed by breast cancer	31	18
Hyperthyroidism about the same time as breast cancer	3	2
Breast cancer preceding hyperthyroidism	1	1
	—	—
	35	21
2. *Non-toxic goitre associated with breast cancer.*		
Goitre treated by surgery	19	15
Untreated goitre	15	13
	—	—
	34	28
3. *Primary myxoedema associated with breast cancer.*	2	2
Grand Total	71	51

Since the tumour, nodes, metastases (TNM) international system for staging breast cancer does not appear in the early records, we decided to revert to the Manchester staging for the purpose of this study. We are aware that this classification is scientifically inaccurate, but its significance will become obvious when we describe our results. The Manchester classification still has some merit even in prospective trials, as was recently shown by Hedley Atkins *et al*[14].

Results

Among the 462 patients with breast cancer, 52 cases of thyroid disease were found, an incidence of 11.3%. Of the 251 patients with previous thyroidectomy or with a history of goitre, hypothyroidism, or hyperthyroidism, 19 developed breast cancer, an incidence of 7.6%. Thus a total of 71 patients with both breast cancer and thyroid dys-

function were collected. There were 70 females and one male. The types of thyroid disorder are summarized in the table.

Ten-year follow-up data are available on 51 of the 71 patients studied. Twenty-seven had Stage II and 24 Stage I carcinoma when first seen. The age range was from 38 to 69 years with a mean of 54.5 years. These 51 patients had the following treatment for their breast cancer:

Radical mastectomy	31
Radical mastectomy and preoperative radiotherapy	13
Radical mastectomy and postoperative radiotherapy	1
Simple mastectomy and postoperative radiotherapy	6

Forty-two of the 51 patients are dead. One patient died from myocardial infarction 11 years after mastectomy and another from cerebral haemorrhage after 8 years. There was no clinical evidence of recurrent carcinoma in either case, but postmortem examination was not performed. The remaining 40 patients died with widespread metastases, confirmed by autopsy findings in 28 cases and by clinical and radiological evidence in 12.

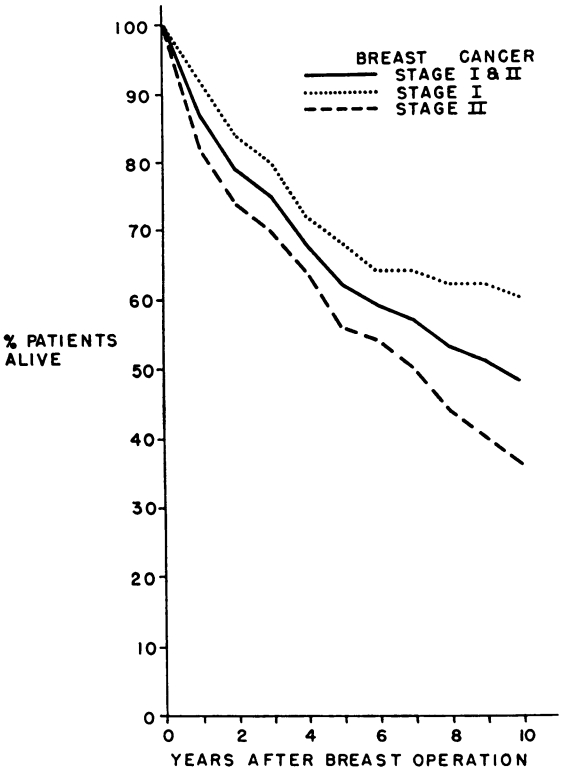

Fig. 1. Survival curves, control series.

Control series. One hundred patients with breast cancer (50 Stage I and 50 Stage II) were chosen as controls. They were consecutive patients without any evidence of thyroid disease who presented to the United Liverpool Hospitals between 1952 and 1962. Their ages ranged from 38 to 69 years, with a mean of 57.4 years. They were treated as follows:

Radical mastectomy	66
Radical mastectomy and postoperative radiotherapy	20
Radical mastectomy and preoperative radiotherapy	5
Simple mastectomy and postoperative radiotherapy	9

Five of these 100 patients died of conditions unrelated to their breast cancer 7–15 years after receiving their treatment. There was definite clinical, radiological, or postmortem evidence of disseminated carcinoma in the other patients who died. The survival curves of these 100 patients are shown in Figure 1.

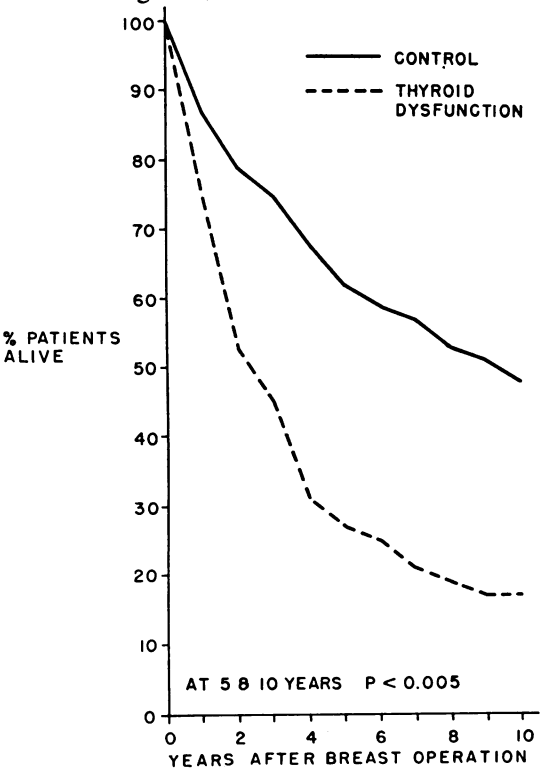

Fig. 2. Survival of all patients with thyroid dysfunction in comparison with control series.

Figure 2 shows that breast cancer patients with a history of thyroid disease have significantly lower survival rates at 5 years and at 10 years

than patients with normal thyroid function ($P < 0.005$). The mean age of the patients with thyroid disease (54.5 years) is lower than that of the control series (57.4 years). Any correction made for this would accentuate further the difference in mortality. The patients with a history of thyroid disease have a slight predominance of Stage II carcinoma (27 out of 51) compared with the controls (50 out of 100). When a 'weighted average' correction is made the results are not significantly altered.

The 51 patients with breast cancer and thyroid dysfunction have been divided into 3 groups for further analysis — 21 patients with hyperthyroidism, 28 with non-toxic goitre, and 2 with primary myxoedema.

Hyperthyroidism series (21 patients). The mean age of these patients was 50 years. They had their hyperthyroidism treated in the following ways:

Surgery (after control with antithyroid drugs)	10
Antithyroid drugs alone	6
^{131}I	4
Surgery and later ^{131}I for recurrence	1

In 19 patients the hyperthyroidism preceded the breast cancer by an interval varying from 1 to 12 years. All of them were clinically euthyroid and had normal serum cholesterol and protein-bound iodine levels when the breast carcinoma was discovered. The ^{131}I uptake, estimated in 9 of them, was normal, as was the serum thyroxine level, determined in 3 cases. Thyroid antibodies were present in 2 patients and both were given oral thyroxine.

One patient presented with a Stage II breast cancer and hyperthyroidism at about the same time. She was treated with ^{131}I and died within 4 months of disseminated carcinoma.

In the remaining patient a Stage II breast cancer preceded the hyperthyroidism by about 6 months. She was given an ablative dose of ^{131}I and died 7 months later with widespread metastases.

The survival curve of the treated hyperthyroidism/breast cancer group is compared with that of the control series in Figure 3. The higher mortality rate of the hyperthyroid group is statistically significant (at 5 years $P < 0.005$ and at 10 years $0.005 < P < 0.01$).

Non-toxic goitre series (28 patients). Fifteen of these 28 patients were treated by partial thyroidectomy, the diagnosis being non-toxic nodular goitre in 9 and solitary benign cold nodule in 6. The remaining 13 patients received no treatment for their thyroid condition, which was diagnosed as simple goitre in 5, non-toxic nodular goitre in 6, and solitary cold nodule in 2.

All the patients were clinically euthyroid, with normal serum choles-

terol and protein-bound iodine levels and ^{131}I uptake. The serum thyroxine level was determined in 2 of them and was normal.

Goitre was diagnosed in all 28 patients 2–19 years before the appearance of breast carcinoma, when their mean age was 57.3 years. The survival curve of these 28 patients is compared with that of the controls in Figure 4. The goitre group has a significantly higher mortality (at 5 years $0.025 < P < 0.05$ and at 10 years $0.005 < P < 0.01$).

Figure 5 shows the survival curves of 15 patients with treated goitre and 13 patients with untreated goitre. The treated group seems to have a higher mortality from carcinoma of the breast than the non-treated group, although the numbers are too small to be subjected to statistical analysis.

Primary myxoedema series (2 patients). Both these patients were clinically euthyroid (on oral thyroxine for 4 and 6 years respectively) when they presented with Stage II breast carcinoma. The electro-

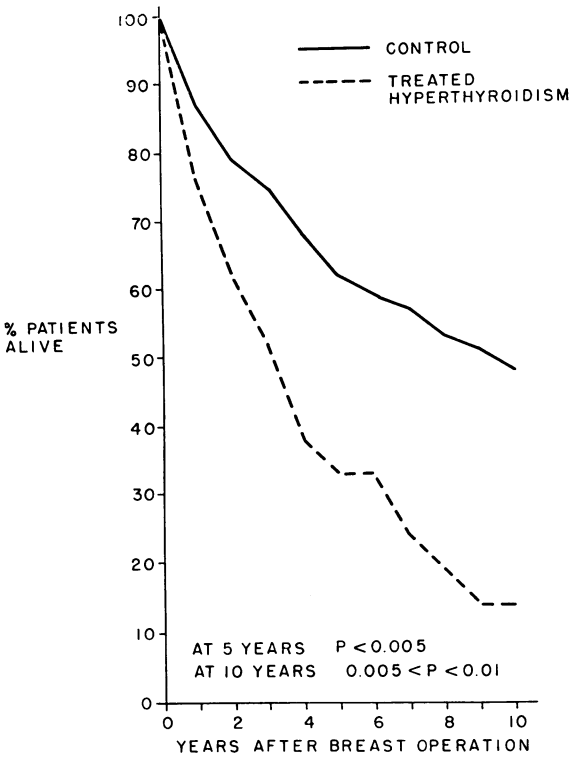

Fig. 3. Survival of patients with treated hyperthyroidism and breast cancer in comparison with control series.

cardiogram and serum cholesterol and protein-bound iodine levels were then normal. Both died with metastases 4 years and 10 years respectively after radical mastectomy.

Discussion

According to the statistics of the Metropolitan Life Insurance Company[15] the incidence of thyroid disease in women between the ages of 20 and 66 years is 10.9–14.2/1,000/year. Our figures show that the incidence in breast cancer patients between the ages of 38 and 69 years collected over a period of 12 years is 11.3%. When correction is made for the difference in age groups the incidence of thyroid disease in the two series is virtually the same.

Similarly, the incidence of breast cancer in the general population is 125–153 new cases per 100,000 women of all ages per year[16]. Our survey reveals that 7.6% of patients with thyroid disease between the ages of 38 and 69 years develop breast cancer over a period of 12 years. When correction is made for the age differences no increase in incidence of breast cancer is apparent in patients with thyroid disorders.

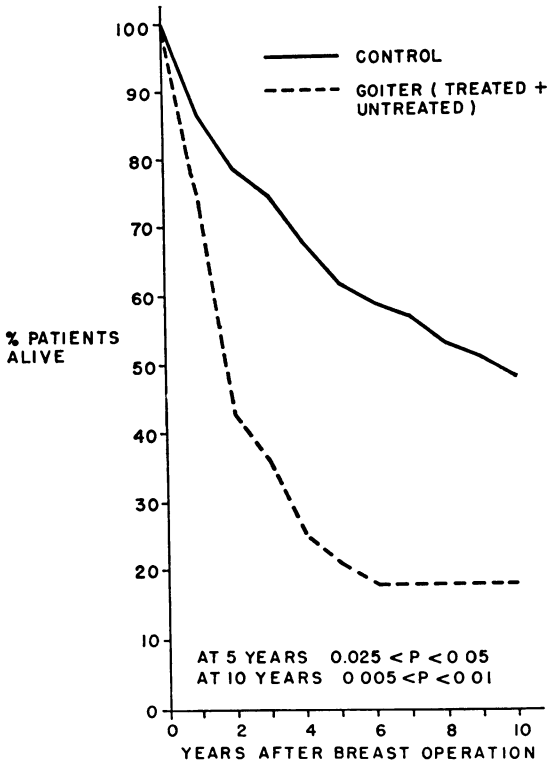

Fig. 4. Survival of 28 patients with goitre before the appearance of breast cancer.

Our study provides statistical evidence that patients with thyroid dysfunction (treated or untreated) have a higher mortality rate from breast carcinoma than control patients. As early as 1958, Edelstyn *et al.*[17] investigated patients before hypophysectomy for advanced breast cancer. Most patients with low thyroid function had blood-borne metastases, whereas most of those with normal function had local disease only. These results were questioned by Reeve *et al.*[18] but were later confirmed by Myhill *et al.*[19], who measured thyroid clearance of ^{131}I one hour after intravenous injection of a tracer dose. The clearance was significantly higher in 29 patients with local disease than in 37 patients with blood-borne metastases or 117 normal subjects.

Sicher and Waterhouse[20, 21] investigated ^{131}I uptake and serum cholesterol in 119 women with Stage I or Stage II breast carcinoma. They found no apparent association with thyroid dysfunction except a slight bias towards hypofunction in these cases.

Sommers[9] performed postmortem histological examination of endo-

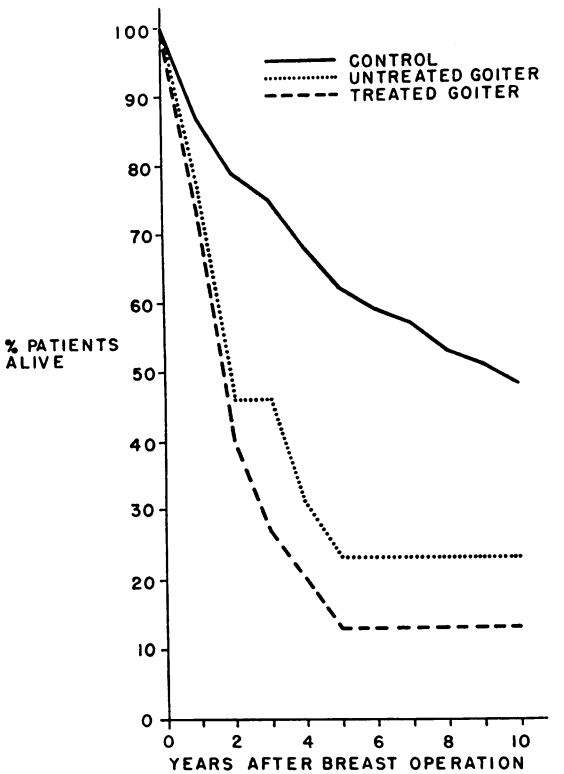

Fig. 5. Effect of treatment of goitre on survival from subsequent breast cancer.

crine glands from 207 women who died of breast cancer and 248 patients who died of non-cancer causes. Hypoplasia of the ovaries, pituitary, and adrenals was disproportionately frequent among women with breast cancer as compared with the controls. Thyroid abnormality was found in 85% of patients with breast cancer but in only 22% of non-cancer patients with similar body weights. Nodular goitre was noted in 13% of cancer patients compared with 6% of the controls.

Bogardus and Finlay[10] studied 79 patients with carcinoma of the breast and observed that 42 had some thyroid abnormality — 37 patients had a goitre and 5 had taken antithyroid drugs or had undergone thyroidectomy. They noted that both breast carcinoma and goitre have a high incidence in England, Wales, Holland, Denmark, Mexico, Thailand, and Switzerland, but are relatively uncommon in Belgium, Chile, Iceland, Venezuela, Ceylon, and Japan.

Humphrey and Swerdlow[11] followed up 196 cases of thyroidectomy for hyperthyroidism or non-toxic goitre for over 12 years at the University of Illinois and did not encounter a single case of breast cancer. They reported that patients with a past history of thyroidectomy for non-toxic goitre had a *higher* 5-year survival (71%) than those without thyroid disease (47.4%). This conflicts with previous reports in the literature and with their own findings that a past history of thyroid disease, including thyroidectomy, was present in 12% of 369 patients operated on for breast cancer at their hospital.

Backwinkel and Jackson[12] studied 280 patients with breast cancer in Wisconsin and found 52 (18.5%) of them to hypothyroid. They maintained that the higher incidence of thyroid deficiency does not prove a causal relationship with breast cancer since it reflected the overall incidence of goitre in their geographical region and particular age group. Nevertheless, the hypothyroid patients with metastases showed significantly lower survival rates. Their criteria for diagnosing hypothyroidism were vague since they included 'only those who had had previous thyroidectomy or in whom laboratory findings had confirmed the diagnosis'.

Spencer[13] studied the relationship between cancer and thyroid hormones in animal tumour models. He found that thyroxine inhibited and antithyroid drugs potentiated cancer growth.

The problem is not conclusively settled. Our survey, like the work of others, raises many more questions than it answers. If a causal relationship exists between thyroid disease and breast carcinoma, why has there not been a fall in the death rate from this cancer corresponding to the disappearance of goitre during the past 3 decades? Does thyroid hypofunction favour the spread of metastases? Does the presence of disseminated cancer depress thyroid function? What is the best parameter of thyroid activity in these patients and the optimum time at

which it ought to be determined? Should women attending thyroid clinics be periodically screened for breast cancer? Should a battery of thyroid function tests be routinely performed on breast cancer patients who are clinically euthyroid?

The therapeutic effect of thyroid hormones in cancer patients is a confusing subject. In 1896 Beatson[22] advised bilateral oophorectomy and the administration of thyroid extract for metastatic breast cancer. Since then several claims[23-25] of useful therapeutic effect have been made. In some cases it is not clear whether the benefit was due to thyroid hormones or to the concomitant administration of steroids. Others[26-28] were unable to change the survival of patients with advanced breast cancer with either thyroxine or triiodothyronine.

The problem of prophylactic administration of thyroid hormones to protect against metastatic spread of breast cancer has also been considered. Loesser[29] claimed on the basis of treating 18 patients without controls that thyroid hormones might protect women from progression of their breast cancer. A controlled trial of such treatment in 109 women with Stage I, II, or III breast cancer and 108 controls was reported by Lyons *et al.*[30] in 1965. They demonstrated no effect on the time or type of recurrence nor on the survival time.

Clearly the whole issue remains an open one and needs carefully planned investigations. Our study suffers from all the disadvantages of non-concurrent surveys, but indicates that prospective trials in breast and thyroid clinics are desirable. It has been suggested that the functional reserve of the thyroid gland should be measured using ^{131}I uptake before and after thyrotrophin stimulation[21]. Serial measurements of thyroid activity, perhaps every 3 months, are also likely to provide valuable information, but they are practicable only if, like determination of serum thyroxine and triiodothyronine, they cause minimal inconvenience for the patient. Definite associations have been demonstrated between PTC-tasting phenotype and various thyroid pathologies[31]. If a statistical association exists between thyroid disease and breast cancer, systematic investigation of PTC-tasting in a random or consecutive series of patients with breast cancer would give valuable information. The same phenotype may be liable to pathological changes at both sites.

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ST. GEORGE'S HOSPITAL AND S.W. METROPOLITAN ORTHOPAEDIC TRAINING SCHEME

TEACHING CALENDAR — AUTUMN TERM 1973

OCTOBER		
Thurs. 4	8.00	Lecture: Mr. W. T. F. Bond — Basic engineering: principles and materials.
Thurs. 11	8.00	Journal Club.
Tues. 16	2.00	Clinical Conference, St. George's Hospital, Tooting, S.W.17.
Thurs. 18	2.00	Bone tumor registry: St. Luke's Hospital, Guildford.
Thurs. 25	8.00	Registrars' meeting — Osteomalacia.
NOVEMBER		
Thurs. 1	8.00	Lecture: Mr. R. Bendall — "Is it tuberculosis?"
Thurs. 8	8.00	Journal Club.
Thurs. 15	8.00	Bone tumour registry: St. Luke's Hospital, Guildford.
Tues. 20	2.00	Clinical Conference: St. James' Hospital, Balham, S.W.12.
Thurs. 22	8.00	Registrars' meeting — Osteochondritis dissecans.
Thurs. 29	8.00	Joint meeting with S.-W. Metropolitan Orthopaedic Club: Short papers.
DECEMBER		
Thurs. 6	8.00	Lecture: Mr. A. Graham Apley — Open sesamoid.
Thurs. 13	8.00	Journal Club.
Tues. 18	2.00	Clinical Conference St. George Hospital, Tooting, S.W.17.
Thurs. 20	8.00	Lecture: Mr. T. L. Bowen — The prescription of orthopaedic appliances.

Unless stated otherwise all evening meetings at The Medical Centre, St. James' Hospital, Sarsfeld Road, Balham, S.W.12. Tel. 01-672 1222.