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# Thyroid Function in Early Breast Cancer

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**Abstract**—*Serum 'free thyroxine' was measured as a thyroid function index (TFI) in 238 women with early breast cancer and 107 normal controls. The mean TFI was significantly lower in the cases compared with controls. The TFI was not related to pathological stage but correlated with histological grade, with the highest values found in well-differentiated (grade I) and the lowest in anaplastic tumours (grade III). A similar result was obtained with the urinary androsterone:aetiocholanolone (5α:5β) ratio in that the ratio was significantly lower in patients with grade III than in those with grade I tumours. These results indicate that thyroid hormones may be involved in tumour cell differentiation. Patients with low 5α/5β ratios had significantly faster recurrence rates than those with high ratios. A similar trend was found for the TFI. The TFI decreases after mastectomy and at* 12 months *after operation is still below the pre-operative basal level.*

## INTRODUCTION

IT HAS been claimed that the incidence of breast cancer in women is higher in populations with goitre or Hashimoto's thyroiditis and in patients with clinical hypothyroidism than in those who are euthyroid or hyperthyroid [1–6]. It has also been reported that there is an increased incidence of hypothyroidism in patients with breast cancer [7–12]. Other workers have not found such an association [13–17].

Once breast cancer is clinically manifest it has been claimed that patients with thyroid disease have a poor prognosis [18] and that administration of thyroid hormones is beneficial in the treatment of breast cancer [19, 20], but these results are not universally accepted [21].

The introduction of an analytical technique for the measurement of 'free thyroxine' (free T4) as a thyroid function index (TFI) [22] prompted us to re-investigate the problem in women with operable breast cancer with the particular purpose of examining the relation of thyroid function to the spread of the disease (nodal status) and the differentiation of the tumour (histological grade). The relation between thyroid function and recurrence rates after mastectomy was also examined. In addition to free T4, one of the end-points of free T4 action (i.e. the effect on the periperhal metabolism of androgens shown by the urinary ratio of androsterone to aetiocholanolone) was also assessed [23].

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## MATERIALS AND METHODS

The TFI assays were performed on blood samples obtained from 238 serial patients with operable breast cancer (age 30–79 yr; median = 53 yr) treated at the Breast Unit at Guy's Hospital, London. None of the patients had any clinical evidence of thyroid abnormality. Blood was collected between 0900 and 1130 hr, 48 hr prior to mastectomy. Collection of blood for TFI measurement was also made from 73 patients at 10 days and 3, 6 and 12 months following mastectomy. The serum was separated by centrifugation and stored at −20°C until analysis. Urine samples (24 hr) from 220 patients were collected 10 days post-mastectomy and also stored at −20°C until assay. All patients were treated by a modified radical mastectomy and were classified pathologically as stage 1 (i.e. no nodal involvement), stage 2 (1–3 nodes involved) and stage 2 (4 or more nodes involved). Histological grading of all the infiltrating duct carcinomas was assessed in 186 cases by the criteria of Bloom and Richardson [24].

Blood was also obtained from 107 normal women resident on the island of Guernsey (age 35–71 yr; median = 44 yr) for comparison of their serum TFI with that of women with breast cancer. There was no significant difference in age between patients and controls. The TFI was

assayed in duplicate by radioimmunoassay (RIA) using Quanta-Count T4/TFI $^{125}$I-labelled kits (Bio-Rad Laboratories Ltd., Watford, U.K.). A quality control (QC) serum was run in triplicate with each batch of assays. Serum free triiodothyronine (FT3) and free thyroxine (FT4) were also measured by RIA as absolute values (i.e. pmol/l) using $^{125}$I-labelled kits (Gruppo Leppetit S.P.A., Milan).

At the time when this study was carried out, the measurement of serum TFI using Quanta-Count $^{125}$I RIA kits appeared to be the most sensitive index of thyroid function then available. It must be emphasised that in prospective studies, biochemical techniques have to precede subsequent long-term follow-up of the patients and assay methods may well be superceded by the time a study is concluded.

Urinary androsterone (5α-androstan-3α-ol-17-one) and aetiocholanolone (5β-androstan-3α-ol-17-one) were measured by capillary column gas–liquid chromatography [25]. Recurrence rates were calculated and compared using the log-rank methods of life-table analysis [26].

## RESULTS

### *TFI in normal women and in patients with early breast cancer*

The mean TFI in 107 normal controls was significantly higher than in 238 women with early breast cancer (2.34 ± 0.48 S.D vs 2.19 ± 0.46; $t = 2.65$, $P < 0.01$). It was possible exactly to age-match 52 of the cases with an equal number of controls. In this sub-set the mean TFI in the controls was again significantly higher than that of the cancer cases (paired $t$ test; 2.32 ± 0.41 vs 2.11 ± 0.33; $t = 2.97$, $P < 0.01$), as shown in Fig. 1.

### *Serum TFI, urinary 5α:5β ratios and pathological stage*

The serum TFI levels were virtually identical in patients with no nodal involvement with those with 1–3 or 4 or more nodes. Similar results were found for the urinary androsterone and aetiocholanolone ratio (Table 1), where there was no relationship between the ratio and increasing nodal involvement. Thus neither measure of thyroid function related to the degree of anatomical spread of the disease.

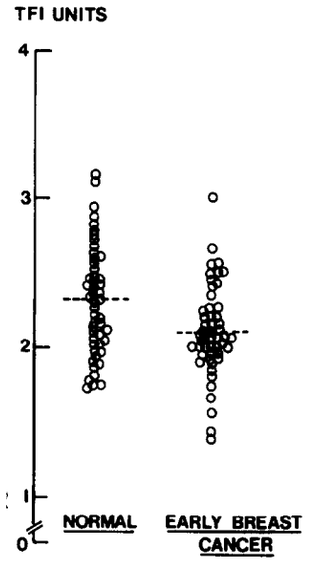


*Fig. 1. Age-matched comparison of TFI in patients with early breast cancer and controls. Normal women, arithmetical mean ± S.D. = 2.32 ± 0.41; early breast cancer, arithmetical mean ± S.D. = 2.11 ± 0.33. Paired t test = 2.97; P < 0.01. Dotted horizontal line denotes median.*

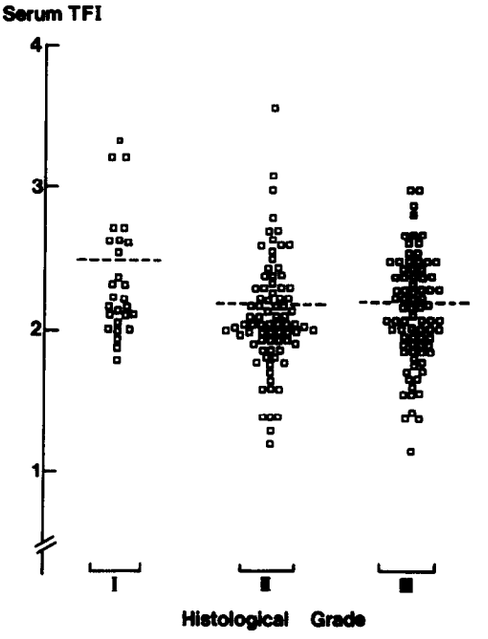


*Fig. 2. Serum TFI and histological grade. Arithmetical means ± S.D. Grade I, 2.48 ± 0.50; grade II, 2.20 ± 0.46; grade III, 2.24 ± 0.48: n = 27, 79, 80 respectively. Grade I vs II, t = 2.67; P < 0.01; I vs III, t = 2.23; P < 0.05.*

*Table 1. Arithmetical means ± S.D.*

| | Stage 1 | Stage 2 (1–3 nodes) | Stage 2 (>3 nodes) |
|---|---|---|---|
| TFI | 2.20 ± 0.46 | 2.17 ± 0.45 | 2.35 ± 0.53 |
| | (*n* = 90) | (*n* = 71) | (*n* = 49) |
| 5α/5β | 0.80 ± 0.34 | 0.74 ± 0.30 | 0.78 ± 0.25 |
| | (*n* = 96) | (*n* = 66) | (*n* = 58) |

*Serum TFI, urinary 5α:5β ratios and histological grade*

Patients with highly differentiated tumours (grade 1) have higher levels of serum TFI than those with grade II or III tumours. While the difference is small, it is significant ($P < 0.02$). The mean TFI in the patients with grade II or III tumours combined is 2.20 ± 0.46, compared with 2.50 ± 0.50 in patients with grade I tumours (see Fig. 2).

The majority of the TFI levels fall within the accepted normal range for the method (1.5–3.5) for this measurment of thyroid function, but it is noticeable that 9 cases of women with grade II or III tumours are either near or in the hypothyroid range. No such low values were found in either the grade I cases or the normal controls.

A similar pattern of results was obtained with the urinary 5α:5β ratios, significantly lower values ($P < 0.01$) being found in the grade III cases than in the grade I cases (mean 0.71 ± 0.48 vs 0.90 ± 0.34), as shown in Fig. 3.

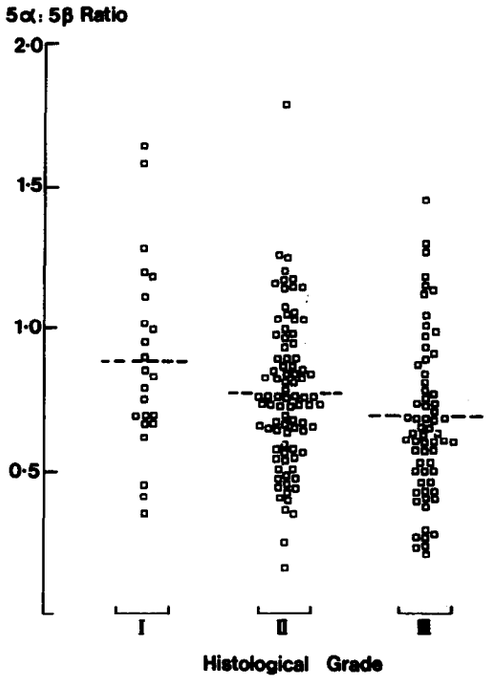


*Fig. 3. Urinary 5α:5β ratio and histological grade. Arithmetical mean ± S.D. Grade I, 0.90 ± 0.34; grade II, 0.79 ± 0.30; grade III, 0.71 ± 0.97: n = 23, 87, 64 respectively. Grade I vs III, t = 2.20; P < 0.01.*

*Thyroid function and recurrence rates*

A log-rank analysis of recurrence rates showed no significant association between recurrence time and the serum TFI in 238 patients ($\chi^2 = 1.85$), although there was an increased trend to earlier recurrence in patients with TFI values below the median for the group. Of the 81 recurrences, 48 (59.3%) of these were below the median value of 2.20.

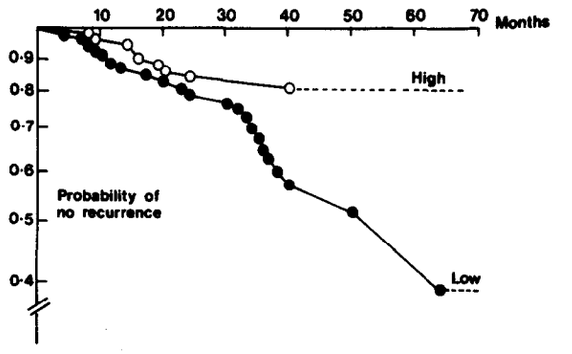


*Fig. 4. Recurrence rates after mastectomy and 5α:5β ratio. High refers to ratios above the median value (0.77) and low to ratios below the median value. Log-rank test. $\chi^2 = 4.93$; P < 0.025. n = 220. No. of recurrences = 78.*

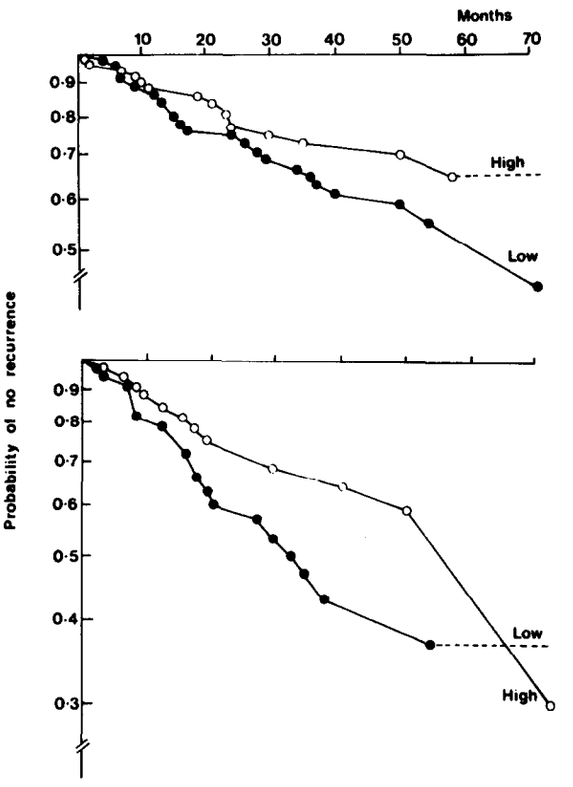


*Fig. 5. Recurrence rates by histological grade and 5α:5β ratio. Upper panel, patients with grade II tumours. n = 106. No. of recurrences = 39. High vs low 5α:5β ratio, $\chi^2 = 1.44$, N.S. Lower panel, patients with grade III tumours. n = 66. No. of recurrences = 32. High vs low 5α:5β ratio, $\chi^2$ 2.13, N.S.*

A significant relationship was found between recurrence and urinary 5α:5β values, with patients below the median recurring more rapidly than those above ($\chi^2 = 4.93$, $P < 0.025$; see Fig. 4).

The question now arises of whether the relationship between the 5α:5β ratio and recurrence is due to the correlation between this

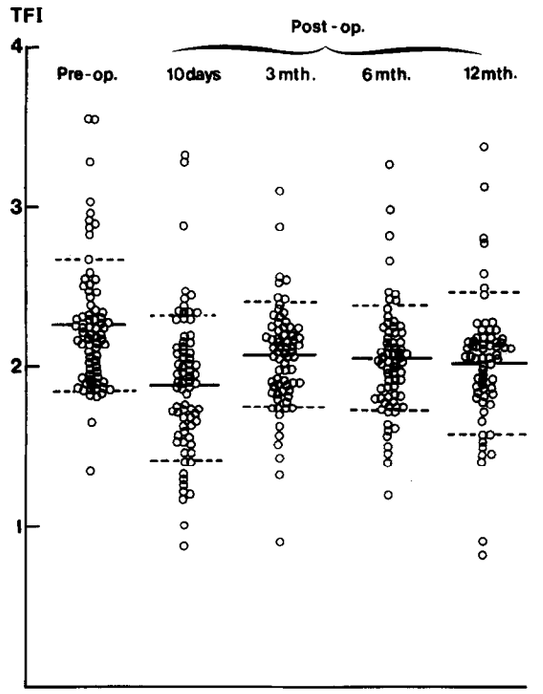


*Fig. 6. Serum TFI before and after mastectomy.*

| | | *Differences from pre-op paired* t *test* |
|---|---|---|
| *Pre-op* | n = 74, 2.25 ±0.40 | |
| *Post-op* (10 day) | n = 73, 1.89 ± 0.45 | t = 7.53 $P < 0.001$ |
| *Post-op* (3 month) | n = 69, 2.05 ± 0.34 | t = 4.06 $P < 0.001$ |
| *Post-op* (6 month) | n = 70, 2.04 ± 0.35 | t = 4.83 $P < 0.001$ |
| *Post-op* (12 month) | n = 65, 2.02 ± 0.44 | t = 2.73 $P < 0.01$ |

*Arithmetical means ± S.D.*

ratio and histological grade. It was impossible to investigate this point in patients with grade I tumours since there was only one recurrence in this group. In patients with grade II or III tumours there was a trend for more rapid recurrence in patients with low $5\alpha:5\beta$ ratios (Fig. 5). A similar trend was also found for TFI, but in neither case were the differences in recurrence rates significant.

*Mastectomy and serum TFI*

The data given above suggest that thyroid function at the lower end of normal range may be associated with an early recurrence rate. Since major sugery affects some aspects of thyroid function [27], the effects of mastectomy on the serum TFI were examined (Fig. 6). In 73 patients there was a marked fall in the mean TFI value 10 days after mastectomy compared with the pre-operative value (paired $t$ test, $t = 7.55$, $P < 0.001$). Although there was an increase toward the pre-operative basal level at 3, 6 and 12 months following mastectomy, in no instance did the mean TFI rise to the pre-operative level. There was no relationship between the post-operative values and recurrence rate.

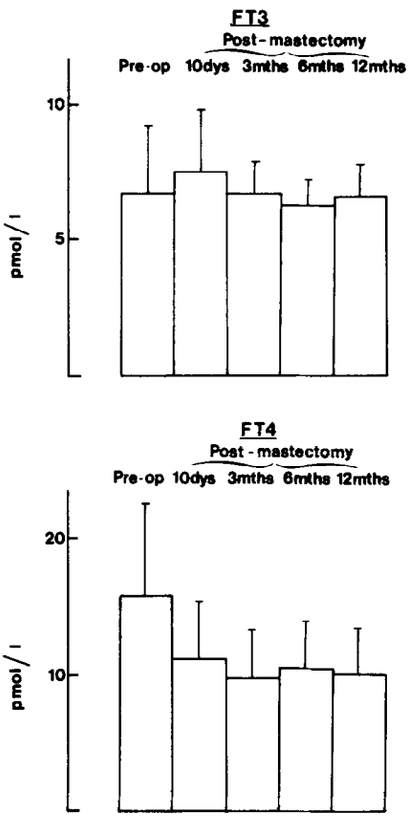


*Fig. 7 Serum free $T_3$ and $T_4$* (pmol/l) *before and after mastectomy.*

| | n | $FT_3$* | $FT_4$* |
|---|---|---|---|
| *Pre-op* | 12 | 6.70 ± 2.44 | 15.84 ± 7.13 |
| *Post-op* (10 days) | 12 | 7.89 ± 2.45 | 11.23 ± 4.20 |
| *Post-op* (3 months) | 12 | 6.50 ± 1.40 | 9.83 ± 3.68 |
| *Post-op* (6 months) | 12 | 6.30 ± 1.05 | 10.40 ± 3.75 |
| *Post-op* (12 months) | 12 | 6.60 ± 1.10 | 10.30 ± 3.74 |

**Arithmetic mean ± S.D. None of the post-op $FT_3$ values were significantly different (paired 't' test) from the pre-op. $FT_4$ differences from pre-op values (paired 't' test): vs* 10 days *post-op*, t = 2.58, P < 0.05; *vs* 3 months *post-op*, t = 2.11, *N.S.; vs* 6 months *post-op*, t = 2.96, P < 0.02; *vs* 12 months *post-op*, t = 3.05, P < 0.02.

*Mastectomy and absolute free* T3 *and* T4

In view of the changes observed in serum TFI levels following mastectomy, a pilot study on the measurement of the absolute values of serum FT3 and FT4 before and after operation was performed on 12 patients, the results of which are shown in Fig. 7. As can be seen, the pattern of the TFI results before and up to 12 months post-operation (shown in Fig. 6) are mirrored by those found with the FT4. The fall in FT4 is significantly different from the pre-mastectomy levels 10 days after mastectomy (paired $t = 3.05$, $P < 0.02$).

Mastectomy brought about no significant changes in the FT3 values, although an overall 10% rise at 10 days post-mastectomy was found.

## DISCUSSION

Our results show that the degree of differentiation of the tumour at diagnosis is related to thyroid function. Patients with anaplastic tumours tend to have a serum TFI at the lower end of the normal range, while patients with well-differentiated tumours have TFI levels at the upper end of the range.

It is now generally recognised that thyroid function is a continuous variable and that some patients with minor and non-specific symptoms may be diagnosed as hypothyroid on the basis of biochemical tests [28]. Women with undifferentiated tumours may well be exhibiting such changes, which in some cases may increase as breast cancer progresses [10].

The discovery of Gudernatsch [29, 30] that thyroid extract could induce precocious metamorphosis in the tadpole was an important demonstration that thyroid hormones were involved in cell differentiation. Thus our finding that there is a correlation between thyroid status and histological grading may indicate that thyroid hormones are possibly intrinsic factors in determining the degree of malignancy of the tumour. It has been demonstrated that mammary epithelial tissue from hypothyroid mice is fully capable of differentiation when exposed to an optimal thyroid hormonal environment [31]. Therefore it is not inconceivable that a critical level of circulating thyroid hormones may be one of the factors required to ensure that breast cancer cells remain in a differentiated state.

The subnormal TFI values found in women with early breast cancer support the reports of other workers that lower thyroid function is related to the incidence of breast cancer [1, 8–11]. Our results do not show subnormal TFI values in the accepted clinical sense, but thyroid function could well be described as suboptimal. In fact, patients with well-differentiated tumours (grade I) have serum TFI levels which are not different from those in the normal controls. This point is particularly important when classical case-control studies are concerned. For example, Kalache *et al.* [32] have recently found no relation between any form of thyroid disease and breast cancer, but their results are based on gross thyroid disease. In our experience the finding of abnormal levels of TFI in both normal women and patients with breast cancer has led to a re-examination of the subjects and to a diagnosis of clinically apparent thyroid disease which had been previously overlooked.

In a previous study [17], no significant differences in total T3, T4 and TSH were found between controls and pre-cancer cases (that is, women taking part in a prospective study who subsequently developed breast cancer), although the trends were in the same direction as those reported in this paper. There was, however, a significant degree of sub-clinical hypothyroidism in pre-cancer cases who also had a family history of breast cancer. The confounding effects of family history have not been investigated in the current study but such a survey might be of value.

Both the serum TFI and the urinary $5\alpha$:$5\beta$ results indicate some degree of thyroid involvement in early recurrence of breast cancer, but this does not appear to be a major influence on the course of the disease. Nevertheless, the log-rank analyses on the grade II and III cases show a tendency for earlier recurrence among those with lower TFI and $5\alpha$:$5\beta$ results. Therefore this is not due to the influence of the grade I cases causing statistical bias due to the higher values in this grade.

The marked drop in the TFI levels following mastectomy is not consistent with the findings of Perry *et al.* [10] but no explanation can be offered for this discrepancy. Neither do the low TFI results following mastectomy reflect those reported immediately following any major surgery where low T3 and high T4 levels are found [33]. In fact, pilot studies on measurement of absolute values of FT4 on 12 patients confirm lower results following mastectomy over a 12-month period, whereas FT3 appears unchanged, except for a small rise at 10 days post-operation. These findings do not necessarily mean a lowering of thyroid stimuli following mastectomy. Because of its biological potency, an almost indiscernible rise in serum FT3 would be needed to compensate for any loss in physiological activity due to the decreased TF4 levels. Our results do not agree with the findings of Adami *et al.* [27].

Conversely, the argument that the pre-mastectomy TFI levels are unduly high because of pre-operative stress must also be discounted as these are significantly lower than their normal controls.

The urinary $5\alpha$:$5\beta$ ratio reflects the effect of thyroid hormones on the hepatic $5\alpha$:$5\beta$ reductase enzymes which convert dehydroepiandrosterone to androsterone and aetiocholanolone [23, 34]. It must, however, be emphasised that these two assays are not necessarily measurements of the same aspect of thyroid function and it is probably only in grossly abnormal thyroid states that they would be in agreement.

Whether the low serum TFI and urinary $5\alpha$:$5\beta$ values we have found during the course of this

study reflect a degree of primary hypothyroid involvement in early breast cancer or a secondary condition due to pituitary/hypothalmic deficiency is not clear. Without a comprehensive investigation of the full biochemical spectrum of thyroid function assays in relation to this problem there is insufficient evidence available for a full understanding of the mechanisms involved.

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