THYROID FUNCTION IN BREAST CANCER

By

J. Myhill, T. S. Reeve and I. B. Hales

ABSTRACT

1. Thyroidal radio-¹³¹I clearance rate measured at one hour after intravenous injection of a tracer dose was significantly higher in 29 breast cancer patients with local disease only than in 37 with blood borne metastases or in 117 normal subjects.
2. Chemical protein bound iodine was significantly higher in 13 patients with blood borne metastases than in 311 normal subjects.
3. Ten patients with a history of proven breast cancer, but no present clinical or radiographic evidence of disease, evidenced a clearance rate consistent with that of patients with blood borne metastases. The PBI, however, was normal.
4. Measurements were made of 24 hour uptake, extra-thyroidal retained radioiodide at 24 hours, thyroidal radioiodine accumulation curves, renal radioiodine clearance rates and serum thyroid stimulating hormone level, with no significant findings.

An association between thyroid disease and breast cancer has been reported for decades. Beatson (1896) first reported a patient with metastatic breast cancer who improved after castration and the administration of thyroid extract. Statistical studies have shown that a high incidence of goitre and carcinoma of the breast occur in similar geographic locations (Spencer 1954; World Health Organisation 1952; Bogardus & Finley 1961) and some animal research has shown that generally the induced hyperthyroid state protects the animal against tumour growth while the contrary occurs in induced hypothyroidism, though sometimes the opposite occurs. Thyroid disease has been found to be ten times more frequent in 305 patients with carcinoma of the breast compared

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with the expected rate (Repert 1952) and an association was observed in a much larger series of 13,261 cancers (Dessaive 1956). Thyroid atrophy has been observed after breast cancer (Sommers 1955). Some clinicians treat breast cancer with thyroid hormones (Loeser 1954).

Other studies have failed to support some of these findings. In one study the incidence of carcinoma was no different before or after thyroidectomy and the occurrence of thyroid disease in patients with breast cancer was no different from that to be expected (Humphrey & Swerdlow 1964), though some other interesting interrelationships were observed.

In recent years there has been an attempt to throw some light on the conflicting clinical and epidemiological reports by performing laboratory studies of thyroidal parameters in patients with breast cancer. Table 1 summarizes the literature. Some form of $^{131}$I-uptake has been measured by five groups; one group found it to be lower in breast cancer, another that patients with blood borne metastases had a lower uptake than those without, one group that the 24-hour uptake was slightly lower in several types of cancer, and two groups failed to find any significant difference between measures of $^{131}$I uptake in patients with blood borne metastases and those with early breast cancer only. Protein bound $^{131}$I has been measured by two groups; one group finding that this parameter is lower in cancer (unclassified) and another group finding that there was no significant difference between breast cancer patients with blood borne metastases and those with initial disease only. Chemical protein bound iodine has also been measured by two groups; one finding no change with breast cancer and the other finding that the values were raised in breast cancer. Blood cholesterol was measured by two groups and no changes were found.

In view of the conflicting evidence, studies in patients in various stages of breast cancer were carried out to assess the relationship between thyroid function and breast cancer. Thyroidal clearance rate (96 studies, measured at one hour after injection of a tracer dose), 24-hour uptake, protein bound iodine and extra-thyroidal retained iodide at 24-hours were measured and the values compared between stages of cancer, and with values from normal controls as available in the laboratory.

**METHODS**

The thyroidal radioiodine clearance rate ($k_1$) was measured by the method of Oddie et al. (1955). This accurate measurement involves correction for the patient's extra-thyroidal iodide space in the neck tissues and makes allowances for the effect on uptake of the renal excretion rate. The logarithm of the clearance rate is known to be normally distributed for both euthyroid and hyperthyroid patients, and, using this parameter, a careful statistical analysis has shown significant changes in the mean
<table>
<thead>
<tr>
<th>Author</th>
<th>¹³¹I Uptake</th>
<th>PB¹³¹I</th>
<th>PBI</th>
<th>Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edelstyn et al. (1958)</td>
<td>Maximum uptake lower with blood-borne metastases (21 with metastases; 26 local disease only)</td>
<td>Not different with blood-borne metastases (18 with metastases; 14 local disease only)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carter et al. (1960)</td>
<td>-</td>
<td>-</td>
<td>Raised with blood-borne metastases (46 with metastases; 20 normals)</td>
<td>-</td>
</tr>
<tr>
<td>Sicher &amp; Waterhouse (1961)</td>
<td>24-hour uptake not different with blood-borne metastases (9 with metastases; 107 without)</td>
<td>-</td>
<td>-</td>
<td>Not different with blood-borne metastases (6 with metastases; 89 without)</td>
</tr>
<tr>
<td>Reeve et al. (1961)</td>
<td>Clearance rate measured at one hour not different with blood-borne metastases (19 with metastases; 43 without)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
<td>Control 1</td>
<td>Control 2</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td><em>Lencioni et al.</em> (1962)</td>
<td>24 hour uptake lower in breast cancer</td>
<td>–</td>
<td>No change with breast cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(31 breast cancer; 21 normals)</td>
<td></td>
<td>(37 breast cancer; 21 normals)</td>
<td></td>
</tr>
<tr>
<td><em>Pastorelle et al.</em> (1964)</td>
<td>24 hour uptake slightly lower in several cancers</td>
<td>Lower in cancer</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(55 cancer; 58 normals)</td>
<td>(55 cancer; 58 normals)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>Clearance rate measured at one hour lower with blood-borne metastases than localised disease, but not different from normal controls – see Table 2</td>
<td>–</td>
<td>Raised with blood-borne metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(37 with metastases, 29 local disease only, 117 normals)</td>
<td></td>
<td>(13 with metastases; 311 normals)</td>
<td></td>
</tr>
</tbody>
</table>

* Studies in a group of patients with unselected cancer of all types.
† The figures in brackets refer to the number of patients studied.
euthyroidal function with age, sex, goitre size, and pre-menopausal or post-menopausal state (Oddie et al. 1960).

Chemical protein bound iodine was measured by the method of Barker et al. (1951) as modified by Acland (1958) and normal values for the Sydney population are available (Radcliff et al. 1964).

The classification of cases of primary cancer of the breast followed the principles set out by Portman (1943):

Stage 1: tumour movable and localised to breast tissue; no evidence of skin or other tissue involvement.

Stage 2: as (1) but with axillary lymph-nodes involved.

Stage 3: diffuse infiltration of breast with fixation to chest wall; skin ulceration with tumour; involvement of axillary lymph-nodes; but no distant metastasis.

Stage 4: as stages 1, 2 or 3, but with clinical or radiographic evidence of widespread metastasis.

RESULTS

The mean values of the four parameters studied are listed in Table 2, which has been subdivided according to stage of breast cancer. Values for patients who had a history of breast cancer, that is, were at one time classified as either stage 1, 2 or 3, but who had no clinical or radiograph evidence of disease when thyroid function was assessed, have also been included. Values for normal controls have been included for protein-bound iodine (Radcliff et al. 1964) and thyroidal clearance rate (Oddie et al. 1960) where for the latter parameter the value listed is the mean value to be expected for a post-menopausal female of age equal to the average age in the series of patients with breast cancer (56 years), and this value was derived from considerations of the values in 117 post-menopausal euthyroid non-goitrous females. The results list the number of patients, the mean value, and the standard deviation for each clinical category and each parameter. The parameters were thyroidal clearance rate measured at one hour, 24-hour uptake, extra-thyroidal retained iodide, and protein bound iodine.

The clearance rate measured at one hour was significantly lower ($P < 0.02$) in patients with blood borne metastases (stage 4) ($k_1 = 2.21 \times 10^{-3}$) when compared with those with early breast cancer only (stage 1) ($k_1 = 2.94 \times 10^{-3}$). However, the clearance rate for stage 4 patients did not differ significantly from that for patients with no clinical evidence of disease or patients who were normal controls. For these statistical tests the logarithm of $k_1$ was used since the logarithm is a normally distributed variate and the application of the $t$-tests was then valid.

The thyroidal clearance rates of patients with no clinical evidence of cancer were significantly lower than those for stage 1 patients ($P < 0.05$).

The 24-hour uptake was lower, and the PBI and retained iodide at 24 hours both higher, in patients with blood borne metastases compared with those with
Table 2.
Measurements of thyroidal parameters.

<table>
<thead>
<tr>
<th>Classification of breast cancer</th>
<th>Thyroidal clearance rate* (measured at one hour) min.$^{-1} \times 10^3$</th>
<th>24-hour uptake**</th>
<th>Extra-thyroidal retained iodide at 24 hours***</th>
<th>Protein bound iodine $\mu g/100$ ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Mean value</td>
<td>Standard deviation</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Stage 1</td>
<td>29</td>
<td>2.94</td>
<td>1.20</td>
<td>3</td>
</tr>
<tr>
<td>Stage 2</td>
<td>14</td>
<td>2.78</td>
<td>1.79</td>
<td>2</td>
</tr>
<tr>
<td>Stage 3</td>
<td>6</td>
<td>2.79</td>
<td>2.49</td>
<td>–</td>
</tr>
<tr>
<td>Stages 1, 2, 3 combined</td>
<td>49</td>
<td>2.88</td>
<td>1.53</td>
<td>8</td>
</tr>
<tr>
<td>Stage 4</td>
<td>37</td>
<td>2.21</td>
<td>1.33</td>
<td>15</td>
</tr>
<tr>
<td>No clinical evidence</td>
<td>10</td>
<td>1.96</td>
<td>0.61</td>
<td>10</td>
</tr>
<tr>
<td>Normal controls</td>
<td>117</td>
<td>2.19</td>
<td>1.16</td>
<td>–</td>
</tr>
</tbody>
</table>

* Thyroidal clearance rate is here defined as the fraction of the circulating inorganic iodide which is cleared each minute by the thyroid (Oddie et al. 1955).

** Fraction of dose of radiiodine in thyroid at 24 hours.

*** Fraction of dose of radiiodine not excreted or in thyroid at 24 hours.
initial breast cancer, though these differences did not individually attain statistical significance.

The chemical protein bound iodine in patients with blood borne metastases was significantly higher than in normal controls ($P < 0.001$).

Since supervoltage radiotherapy used in the treatment of breast cancer may possibly have affected thyroidal function by delivering a stray radiation dose to the thyroid, the timing of any radiation therapy was evaluated in relation to the performance of the measurement of thyroidal clearance rate. Of the 29 measurements of clearance rate in stage 1 patients, 9 were performed after radiotherapy and 3 could not be traced. Of 14 measurements in stage 2 patients 4 had had previous radiotherapy and one could not be traced. Of 6 patients with stage 3 disease 2 had had previous radiotherapy. Of 36 measurements in patients with blood borne metastases only 3 were performed after radiotherapy and two could not be traced. Of ten patients with no present clinical evidence of disease none of the studies were performed after radiotherapy.

Any stray radiation fields at the thyroid would be expected to reduce the thyroidal function. Since more stage 1 patients, who had a higher mean thyroidal clearance rate, had prior radiotherapy than patients with stage 4 or no clinical evidence, any effect of possible stray radiation fields may be neglected.

In our series nine patients were measured both when they had early stages of cancer and at later times. No significant lowering in function was observed as their breast cancers progressed. In the whole series no correlation was found between thyroidal clearance rate and duration of cancer. Detailed uptake curves of five stage 4 patients and of four patients with no present clinical evidence of disease were studied over the period 0 to 24-hours and no abnormalities in curve shape were observed. The renal clearance rates of all patients were examined without any significant finding emerging. The assays of thyroid stimulating hormone in the sera of six patients were within the normal range.

**DISCUSSION**

Three criteria are necessary to validate a study such as this. Firstly, the physiological parameters being examined must be measured accurately; secondly, the groups of patients studied with respect to thyroid function must be identical in every respect except the difference in question (stage of breast cancer), and thirdly, an adequate number of patients are needed to demonstrate any latent significant differences which may be present.

There would seem to be room for improvement in the thyroidal uptake techniques used in some of the previous studies (*Edelstyn et al.* 1958; *Sicher & Waterhouse* 1961) in view of the recommendations laid down by the *International Atomic Energy Agency* (1960). The methods used in the present study
do conform to these recommendations. Tests with standard mock-iodine manikins have shown that our methods are accurate within the range of uptake from 12% to 65% (Myhill 1965). No manikins were available for tests outside this range.

The question of comparable groups is always difficult to resolve and generally the series of patients studied depends on the clinical material available to the investigator. It is important to record the mean ages of the groups, since age affects thyroidal function (Oddie et al. 1960). The possible effect of radiotherapy on the results has been examined and it does not seem to be important. Patients with other diseases or on medication were not studied. There was no obvious disparity between the groups here reported on.

Large numbers of patients allow for better statistical studies and numbers should be adequate in all sub-groups. Sicher & Waterhouse (1961) have reported studies on 119 patients, the largest series to date, but only 9 of these were patients with stage 4 cancer. Thus for the purpose of comparing the difference in thyroidal uptake between patients with blood borne metastases and those with early breast cancer only, the earlier study of Edelstyn et al. (1958) is better because they measured thyroid function in 26 cases with local disease only and 21 cases with blood borne metastases. In this regard it might be observed from the present work that when measurements on 29 stage 1 patients were compared with measurements on 19 stage 4 patients no significant difference in clearance rates could be demonstrated, but when a further 18 stage 4 patients had been studied the difference between thyroidal clearance rates attained significance at the 2% level. The number of cases studied is therefore very important.

It should be observed that neither Edelstyn et al. (1958) nor Sicher & Waterhouse (1961) carried out studies on a controlled group of normal subjects. This is a weakness of their methods since it is certain that a range of normal thyroidal uptake values obtained in one laboratory will differ from that obtained in another, both because of different patient populations and different non-standardisation in the thyroidal uptake techniques employed. The comparison in each of these reports of results in Stage 1 breast cancer patients with normal values published by other workers is therefore not necessarily correct.

The present report shows firstly that the thyroidal clearance rate in patients with blood borne metastases is statistically significantly lower than that in patients with early breast cancer only. This agrees with the findings of Edelstyn et al. (1958) and not with the finding of Sicher & Waterhouse (1961) though the latter's finding is not necessarily significant since only 9 patients with stage 4 breast cancer were studied. It has been demonstrated in the present series that the effects of any stray radiation during supervoltage radiotherapy would not be expected to produce these results.
It was found that the mean thyroidal clearance rate in patients who have had breast cancer, but who currently have no clinical evidence of the disease, is lower than in patients with early breast cancer only. The significance of this finding is not clear, but it may indicate a sub-clinical metastatic spread.

It is interesting to observe that in this series the thyroidal clearance rate of normal controls was close to that of stage 4 patients. Indeed the value for normal controls was significantly different to that for stage 1 patients only. The significance of this finding is not clear. It is not necessarily inconsistent with the reports of Edelstyn et al. (1958) or Sicher & Waterhouse (1961) since these workers did not carry out measurements on normal controls, but it does seem to be in conflict with the results obtained by Lencioni et al. (1962).

The 24-hour uptakes in stage 4 patients and in patients with no present clinical evidence of diseases were both lower than in patients with earlier stages of diseases. This agrees with the pattern observed in the clearance rate studies though these 24-hour uptake results were not themselves statistically significant. Provided renal function is not altered it would also be expected, given that thyroidal uptake is lower, that apparent extra-thyroidal retained iodide at 24 hours should be increased, and this is in fact observed when stage 4 patients are compared with earlier stages, and in this case the group of patients with no clinical evidence of disease conforms to the group of stage 4 patients.

The protein bound iodine measured in patients with blood borne metastases was higher than that measured in patients with earlier stages of cancer though the numbers were small and this difference did not attain statistical significance. However, when the mean value for stage 4 was compared with that for normal controls (where the numbers were larger) the difference was significant at the 0.1 % level. Patients with no clinical evidence of diseases, however, had a value consistent with normal and did not conform to the pattern seen in stage 4. This finding agrees with that of Carter et al. (1960).

In animal experiments the influence of thyroxine on the growth of some tumours has been clearly demonstrated (Weisburger & Weisburger 1958), and indeed it has been observed that in tumour bearing animals the iodide space measured by retained iodide is increased (Scott & Daniels 1956). It is also clear that certain human cancers, in particular breast cancer, are hormone dependent. But whether the findings of association between thyroid and breast disease, and the laboratory findings reported here and elsewhere, imply a closer relationship between the two diseases is another question. Thyroid function is so easily affected, by physiological changes or drugs or even climate, that without the assurance of strictly compatible groups it is difficult to draw a firm conclusion. The inconsistent reports in the literature (including the present report) indicate that there may be some parameters affecting this problem which have been as yet overlooked. The first step would be to study
a large number of patients (thus removing statistical uncertainties) by known
accurate means (for iodide uptake following the IAEA recommendations).
Compatible groups must somehow be arranged for this study. Perhaps the best
way to do this would be to study the same patients throughout the course of
their disease, with matched normal controls also studied for the same period
of time, but even here meticulous clinical records would need to be kept in
order to examine the effects of any changes of medication or habits that
might influence thyroidal functions.

The balance of evidence indicates that there is some effect on thyroid func-
tion in patients with breast cancer. Precisely what this effect is, let alone its
significance, is yet to be evaluated satisfactorily.

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