

The Thyroid and Breast Cancer: A Significant Association?

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The coincidence of thyroid disorders and breast cancer has long been a subject of debate. Associations with hyperthyroidism, hypothyroidism, thyroiditis and nontoxic goitre have been reported. Although no convincing evidence exists of a causal role for overt thyroid disease in breast cancer, the preponderance of published work favours an association with hypothyroidism. Geographical variations in the incidence of breast cancer have been attributed to differences in dietary iodine intake and an effect of iodide on the breast has been postulated. Recent reports have shown a direct association between thyroid enlargement, as assessed by ultrasound, and breast cancer. Although the exact mechanism for the demonstrated association between diseases of the thyroid and breast cancer remains to be elucidated, there is at least the possibility that the presence of thyroid abnormalities may influence breast cancer progression and this alone should stimulate awareness into the coincidence of the two disorders.

Key words: breast cancer; dietary iodine intake; thyroid; thyroid diseases.

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Recent reports suggest a reawakening of an interest in the long-standing observation that there may be an association between thyroid status and predisposition to or natural history of diseases of the breast, including breast cancer (1–4). Interest in such an association is not surprising as disorders of both the thyroid and the breast predominate in females from a corresponding age cohort. One of the earliest reports on the association of breast cancer with thyroid disease was that of Beatson in 1896 (5) who used oophorectomy and thyroid extract to treat breast cancer. Since that report there have been many studies showing an association of breast cancer with hyperthyroidism, hypothyroidism, thyroxine (T4) replacement therapy and thyroiditis. Equally, other reports have shown no significant association. Where an association between thyroid disease and breast cancer was shown to exist, hypothyroidism was the most frequently observed finding. In fact many reports considered hyperthyroidism to be protective against breast cancer as progression of such cancers was more frequently observed when the hyperthy-

roidism was treated. A contrary view was advanced (6) showing that patients treated for hyperthyroidism with ¹³¹I showed no increased risk of developing breast cancer. Thus, the hypothesis gained ground that higher levels of thyroid hormones restricted breast cancer growth while lower levels facilitated such growth. A role for thyroid hormones in altering oestrogen metabolism has been postulated as a possible mechanism for their involvement in breast cancer. However, it has been reported that the increase in free oestradiol observed in breast cancer did not show significant correlation with changes in free T4 (FT4) and free triiodothyronine (FT3) (7) suggesting that the observed changes in thyroid hormones may be independent of alterations in oestrogen metabolism.

A possible explanation advanced for these findings was that low levels of thyroid hormones diminished negative feedback on the hypothalamic–pituitary axis, resulting in increased secretion of prolactin as well as thyroid-stimulating hormone (TSH). Although most reports showed no increase in basal prolactin between breast cancer and controls (3), an increase in both serum prolactin responses to thyrotropin-releasing hormone (TRH) stimulation reported by Mittra et al. (8), led the authors to suggest that suboptimum levels of circulating thyroid hormones may abnormally sensitize mammary epithelial cells to prolactin stimulation, leading to dysplasia and eventual hyperplasia of mammary tissue.

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Most studies on breast cancer have shown serum levels of thyroid hormones to be within the normal range (3, 9) but both increases (10) and decreases (7) have been reported. A role for T3 as a local growth promoter was postulated (2) on the basis of increases in FT3 levels in breast cyst fluid compared to serum.

Studies on the geographical distribution of breast cancer have shown regional variations in the prevalence of the disease (12). The lower prevalence of breast cancer in Japanese subjects compared to Western subjects has been attributed, at least in part, to differences in thyroid function. Japanese women suffering from Hashimoto's disease had a 5-fold excess in breast cancer risk compared to those without evidence of autoimmune thyroid disease (13), thus bringing the incidence of breast cancer in Japanese subjects with Hashimoto's disease close to the higher rates for breast cancer observed in the USA. However, no significant association between breast cancer and Hashimoto's disease was reported in a population studied in the Mayo Clinic, USA (14). In addition to these reports, an increased prevalence of antithyroid antibodies in patients with breast cancer has been reported (4, 15).

The role of dietary iodine intake in influencing the incidence of breast cancer has also received considerable attention (12). Increased incidence of breast cancer has been reported in areas of endemic goitre but no change in incidence occurred when the goitre rate decreased after iodine prophylaxis. Nonetheless, an association of breast cancer with nontoxic goitre continues to be reported in areas of low iodine intake (9). Earlier studies on the association of breast cancer and nontoxic goitre utilized palpation to assess goitre prevalence. A more recent study from our laboratory (3) showed that, using the highly sensitive technique of diagnostic ultrasound, thyroid enlargement (thyroid volume >18.0 mL in adult females) was observed in 41% of patients with breast cancer. Such a degree of enlargement was equally prevalent when the subjects were studied prospectively (i.e. at the time of excision biopsy) or retrospectively (following various therapies for breast cancer), demonstrating that thyroid enlargement was a true phenomenon independent of therapeutic intervention.

Reports on the association of breast cancer with decreased dietary iodine intake have suggested that such deficiencies may result in subclinical hypothyroidism predisposing to breast disease. The presence of an iodine pump in both thyroid and breast (16) have led to studies on a possible direct effect of iodine on the breast (17). Studies in humans (18) have shown that treatment with elemental iodine results in the resolution of fibrocystic breast disease and breast pain.

The obvious possibility of a link between radioactive iodine ¹³¹I (RAI) therapy for hyperthyroidism and increased risk for breast cancer was studied by Hoffman et al. (19), who found no difference in breast cancer incidence when treatment with ¹³¹I was compared to surgery. Similarly, no increase in neoplasms was reported following the administration of either therapeutic or diagnostic doses of ¹³¹I for hyperthyroidism (6, 20). However, these authors reported that lower thera-

peutic doses were associated with increased numbers of cases of breast cancer. Goldman (21) reported a nonsignificant excess of breast cancer in patients assessed 10 years after RAI therapy for hyperthyroidism. Interestingly, those who subsequently became hypothyroid were not at increased risk of developing breast cancer.

Reports of an association between breast cancer and thyroid cancer are equally inconclusive. A high incidence of breast cancer in patients with thyroid cancer has been reported (22), suggesting an increased risk of breast cancer after thyroid cancer and vice versa. However, a later population-based survey (23) showed no significant association.

Not only is a possible pathogenic role for the thyroid in the genesis of breast disease unclear but conflicting views have also been recorded on the influence of the thyroid in predicting outcome in breast cancer. A follow-up study of cancer mortality in women with thyroid disease (24) found an increase in breast cancer mortality only in patients with nontoxic nodular goitre who had been on T4 therapy. A possible beneficial effect of thyroid abnormalities on outcome in breast cancer was suggested by the finding that diminished or enlarged thyroid or the presence of thyroid peroxidase antibodies (25) conferred a significant increase in disease-free or overall survival in patients with breast cancer which was independent of conventional prognostic factors and was of a similar order of magnitude as the presence or absence of axillary nodal involvement.

Despite the many different studies and approaches to the problem outlined above, there is still no definitive answer as to the significance of the association between thyroid status and breast cancer. Nonetheless, a role for some common pathogenic factors remains a possibility. Although available evidence strongly indicates that thyroid hypofunction contributes to breast cancer progression, the possibility that thyroid autoimmunity might be associated with improved prognosis deserves further investigation. The possibility of genetic predisposition to both conditions also needs to be explored. How such mechanisms might influence breast cancer progression is unknown. Whatever the actual link, there is little doubt that the perceived association between these two common disorders to affect women in the developed world will continue to stimulate interest. Increasing understanding of thyroidal involvement in breast cancer outcome offers, perhaps, the best prospects of success.

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