Commentary

The thyroid, iodine and breast cancer

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Abstract

A renewal of the search for a link between breast cancer and thyroid disease has once again demonstrated an increased prevalence of autoimmune thyroid disease in patients with breast cancer. This is the most recent of many studies showing an association between a variety of thyroid disorders and breast cancer. Such an association is not surprising as both diseases are female predominant with a similar postmenopausal peak incidence. The significance of the presence of thyroid autoantibodies, particularly thyroid peroxidase antibodies, in serum from patients with breast cancer is unknown, but it has been suggested that antibody positivity is associated with better prognosis. One area in which thyroid and breast functions overlap is in the uptake and utilization of dietary iodide. Experimental findings showing the ability of iodine or iodine-rich seaweed to inhibit breast tumour development is supported by the relatively low rate of breast cancer in Japanese women who consume a diet containing iodine-rich seaweed. However, there is as yet no direct evidence that iodine, iodinated compounds, or a combination of iodine and selenium is the antimammary carcinogenic element in the Japanese diet. It remains to be resolved whether the perceived breast cancer–thyroid disease relationship is thyroid or iodine related or, in the case of thyroid autoantibodies, is the consequence of an immune response to the carcinoma. Is this response breast specific and does it relate to iodine status? These and many other questions await resolution before a definitive role in the natural history of breast carcinoma can be assigned to the thyroid.

Keywords: antibodies, breast, cancer, iodine, thyroid

Introduction

In this issue of *Breast Cancer Research* Turken and coworkers [1] describe an association between breast cancer and autoimmune thyroid disease (AITD), showing not only an increased prevalence of thyroid peroxidase (TPO) antibodies in patients with breast cancer but also a significantly increased rate of goiter (diffuse 8%, nodular 50%) as compared with control individuals (4% and 26%, respectively). This finding is in agreement with previous studies [2,3] that showed both increased goiter rates and increased prevalence of thyroid enlargement by ultrasound in patients with breast cancer [4]. This association represents yet another page in the continuing saga of the perceived coincidence between breast cancer and diseases of the thyroid gland. The fact that both breast cancer and thyroid disease predominantly affect females and that both have a postmenopausal peak incidence has inevitably resulted in a search for an association between the two diseases [5,6]. Although many studies have shown such an association, evidence of specific causal linkage between thyroid breast cancer and thyroid disease continues to be elusive.

One of the earliest reports on the association of breast cancer with thyroid disease was that from Beatson [7] in 1896, who used oopherectomy 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 replacement therapy and thyroiditis [5,6]. Equally, other reports showed

AITD = autoimmune thyroid disease; TPO = thyroid peroxidase.

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 because progression of such cancers was more frequently observed when the hyperthyroidism was treated [5].

The increased frequency of thyroid autoantibodies, TPO antibodies and thyroglobulin antibodies described by Turken and coworkers [1] in breast cancer patients as compared with control individuals supports earlier findings [8–11]. Such differences were not observed for other autoimmune antibodies [9]. The use of specific immunoassays for TPO antibodies and thyroglobulin antibodies [12] revealed an increased prevalence of TPO antibodies in breast cancer. Although the presence of circulating TPO antibodies in asymptomatic individuals has been implicated as conferring an increased risk for future hypothyroidism [13], there is no agreement on the significance of its association with breast cancer [14]. A fivefold excess in breast cancer has been reported in Japanese patients with AITD [8]. However, no significant association between breast cancer and Hashimoto's thyroiditis was reported in a study from the Mayo Clinic in the USA [15]. Thus, like other reported associations, the relationship between AITD, iodine intake and breast cancer is far from clear. Equally, there is little agreement on the significance of any published association between a range of thyroid disorders and breast cancer [5,6].

The possibility that hypothyroidism might in itself have been beneficial in terms of outcome of breast cancer has been suggested [16]. Recent reports from our laboratory [11] have shown that the presence of TPO antibodies is associated with a significant improvement in both disease-free and overall outcome in breast cancer patients, and that the magnitude of this prognostic effect was of a similar order of magnitude to well established prognostic indices for breast cancer such as axillary nodal status or tumour size. Thus, we have the anomalous situation in which the presence of TPO antibodies, while being associated with breast cancer, also appears to confer prognostic benefits. A recent review that contained a meta-analysis of published work on breast–thyroid associations [14] found no significant association between the two disorders and attributed any positive findings of such an association to 'selection or institutional referral bias'. This negative finding was immediately followed by communications [1,17] reaffirming the association of breast cancer with hypothyroidism and AITD. It is therefore apparent that the argument about breast–thyroid associations is far from resolved.

The association of thyroid antibody positivity, sometimes with transient thyroid dysfunction, has been reported in the course of immunotherapy with recombinant cytokines interleukin-2 and interferon-α for various cancers [18,19]. Thyroid antibody related hypothyroidism has been suggested as being associated with a favourable tumour response to such therapies. In a recent report [19] it was shown in metastatic renal cell carcinoma that the presence of a positive thyroid antibody titre, either pre-existing or cytokine induced, was a highly significant independent prognostic factor. In the case of thyroid autoantibodies being associated with better disease outcome in breast cancer, renal carcinoma or melanoma, it is possible that the immune response to thyroid and tumour tissue might be similarly regulated in that it might be directed against both tumour and thyroid antigens. Another possibility is that both tumour and thyroid share the same antigens because expression of the sodium–iodide symporter has been demonstrated in both thyroid and breast tissues [20–22].

One area in which thyroid and breast functions overlap is in the uptake and utilization of iodide. In the thyroid, I^- is required for thyroid hormonogenesis whereas in the breast I^- is needed in breast milk as a source of neonatal nutrition. Both organs require a method of oxidizing I^- to I_2 (organification) in order to produce iodoproteins [23,24]. This involves the presence of H_2O_2 as an oxidizing agent catalyzed by TPO in the thyroid and by lactoperoxidases in the breast. Apart from the requirement for iodide as a nutrient in breast milk, there is no known role for iodine in the normal or diseased breast. However, a breast requirement for I_2 rather than I^- has been suggested [25]. It has been postulated that formation of iodolipids such as iodolactones or iodoaldehydes represents a form of thyroidal autoregulation [26], which may be the mode of action of iodide inhibition of thyroid function in the Wolff–Chaikoff effect [27–29].

In addition to their role in inhibiting thyroid function, these compounds may act as antiproliferative agents in the thyroid [26]. Iodinated compounds (so-called XI) may exert inhibitory effects on adenylate cyclase, NADPH (nicotinamide adenine dinucleotide phosphate, reduced form)-oxidase and TPO activities [27]. This effect seems to require oxidation of I^- to I_2 because inhibitors of TPO or I^- trapping can reverse the inhibitory effect [29]. It has also been suggested that such inhibitory actions of iodo-compounds on cell proliferation might play a role in the breast [30,31]. Some support for a role for iodine in the human breast is provided by our own findings [20], which showed that tissue iodine levels were relatively low in patients with breast cancer as compared with normal tissues or benign breast tumours (fibroadenomata). We have also recently shown ^{125}I uptake blocking effects in sera from 19% of 105 patients with breast cancer [20], as compared with a published prevalence of 30.7% of such blocking activity, believed to be of immunogenic origin, in Graves' disease [32]. The ability of the breast to express

sodium–iodide symporter [20–22] and, at least in lactation, to take up significant amounts of iodide has led to studies of the potential for use of ^{131}I ablative therapy in breast cancer, analogous to that employed in the treatment of hyperthyroidism or thyroid cancer.

An anticarcinogenic role for iodine in experimental animals was suggested by the work of Funahashi and coworkers [33], who found that administration of Lugol's iodine or iodine-rich Wakame seaweed to rats treated with the carcinogen dimethyl benzanthracene suppressed the development of mammary tumours. In further studies [34], the same group demonstrated that seaweed induced apoptosis in human breast cancer cells with greater potency than that of fluorouracil, a chemotherapeutic agent used to treat breast cancer. This finding led the authors to speculate that 'seaweed may be applicable for prevention of breast cancer'.

This hypothesis is in accord with the relatively low breast cancer rate reported in Japan [35], where the normal diet is seaweed rich, and with increasing breast cancer rates in Japanese women who emigrate [36] or consume a western style diet [37]. Interestingly this finding applies to rates of breast cancer in both males and females [38]. This evidence favours the low rate of breast cancer being environmental rather than genetic in origin. One of the main dietary differences between Japanese and western women is the consumption of large amounts of iodine-rich seaweeds by the former, yielding a dietary iodine intake of several milligrams per day in Japanese women as compared with microgram quantities in western women [31]. Of course it must be stressed that all this evidence is circumstantial because the contribution, if any, of dietary iodine intake to these findings is unknown. Equally, the possibility that this protective effect may be lost in patients with AITD [8] remains to be explored.

The frequent coexistence of iodine and selenium deficiencies and the importance of replacing both to maintain thyroid function is well established [39]. It has also been suggested that a combined iodine–selenium deficiency may facilitate the development of breast cancer [31]. Selenium deficiency results in diminution of selenium-containing antioxidative enzymes such as glutathione peroxidase, deiodinases and thioredoxine reductases [39,40], leading to increased levels of reactive oxygen species. These oxidants can inactivate many enzymes, are a feature of lipid peroxidation and DNA damage, and have been shown to be associated with carcinogenesis in the breast [41]. On the other hand, increased serum levels of antioxidants have been associated with reductions in breast cancer risk [42]. There is also some evidence that iodide itself may act as an antioxidant [43]. Selenium deficiency is associated with AITD perhaps as a result of increased inflammatory activity arising from decreased activity of selenium containing antioxidative enzymes such as glutathione peroxidase [39], whereas increasing dietary selenium or administration of selenomethionine have also been reported to diminish TPO antibody levels [44,45].

Although there is as yet no definitive evidence of a role for the thyroid in the natural history of breast cancer, the continuing reports of an association such as that in this issue of *Breast Cancer Research* [1] should not be ignored. In particular, the question of whether the presence of TPO antibodies in serum of patients with breast cancer is breast specific or part of a generalized immunogenic response needs to be explored. Also requiring study are the involvement of iodide transport in the breast and additional roles for iodinated compounds within the mammary glands, with their accompanying benefit of providing a new therapeutic pathway for radioiodine ablative therapy. Finally, it remains to be established whether iodide or selenium treatment has prophylactic potential. Whatever the future study pathways, there is little doubt that the perceived association of two of the most common female disorders will continue to intrigue investigators.

Competing interests

None declared.

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