OPINION

Autoimmune thyroid disease and breast cancer: A chance association?

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Many years of speculation on possible causal factors underlying the observed association between thyroid disease and breast carcinoma have not yielded a definitive result (1, 2). 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. Therefore almost every form of thyroid disorder has at some stage been implicated as being associated with breast cancer. Analysis of these disparate findings shows hypothyroidism to be the predominant reported breast related thyroid disorder. Not surprisingly, this has led to speculation as to the relationship between autoimmune thyroid disease (AlTD) and breast cancer. Such an association is not a new observation. An earlier report (3) showed a higher prevalence of Hashimoto's thyroiditis in Japanese patients with breast cancer compared to age-matched controls. The lower rate of breast cancer in the Japanese population compared to that observed in British subjects prompted a study of thyroid antibodies in both control and breast cancer populations from Japan and the UK (4). Although the incidence of thyroid antibodies in British women was 2-3 times that of Japanese women, these workers found no differences between incidences in breast cancer and healthy women of either race.

This story was reopened by studies in Denmark (5) which showed an increased frequency of thyroid autoantibodies, microsomal, thyroglobulin, and thyrotrophin receptor antibodies (TRAb) in breast cancer patients compared to controls. Such differences were not observed for other autoimmune antibodies which confirm similar findings (4). The use of specific immunoassays for thyroid peroxidase antibodies (TPO. Ab), and thyroglobulin antibodies (Tg. Ab) (6, 7) have shown an increased prevalence of TPO.Ab in breast cancer. While the presence of circulating TPO.Ab in asymptomatic individuals has been implicated as conferring an increased risk to future hypothyroidism, there is no agreement on the significance of its association with breast cancer. Equally there is little agreement on the significance of any published association between a range of thyroid disorders and breast cancer (1, 2).

The possibility that hypothyroidism might in itself have been beneficial in terms of outcome of breast cancer has been suggested (8). Recent reports from the author's laboratory (7) have shown that the presence of TPO.Ab 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 tumor size.

The association of thyroid antibody positivity, sometimes with transient thyroid dysfunction, has been reported in the course of immunotherapy with recombinant cytokines interleukin-2 (IL-2) and interfer alpha (IFN-α) based therapies for various cancers (9, 10). Thyroid antibody related hypothyroidism has been suggested as being associated with a favorable tumor response to such therapies. In a recent report (10) it was shown that in metastatic renal cell cancer 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 tumor tissue might be similarly regulated in that it might be directed against both tumor and thyroid antigens. Another possibility is that both tumor and thyroid share the same antigens as expression of TPO and the sodium iodide symporter (NIS) has been demonstrated in both thyroid and breast tissues (11, 12). It has been reported

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that TPO.Ab plays an important role in antibody-dependent cell cytotoxicity (ADCC) in the thyroid (13). However there is no evidence of such an effect in other tumors. One area where thyroid and breast functions overlap is in the uptake and utilization of iodide. As previously stated both organs possess the iodide uptake promoter, the NIS. We have recently shown ^{125}I uptake blocking effects in sera from 19% of 105 patients with breast cancer. This compared to a published prevalence of 30.7% of such blocking activity, believed to be of immunogenic origin, in Graves' disease (14). Apart from the requirement of 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 (Eskin) (15). If such a requirement does exist, the presence of antibodies to the NIS responsible for I^- uptake may assume some importance.

In conclusion, there is in the author's opinion now a sufficient body of evidence to demonstrate an association between AITD and breast cancer. Unfortunately the precise significance of this association remains elusive. To answer the question posed in the title of this "opinion", the author believes the association to be based on more than chance. Whether that role is expressed through a generalized or specific immunogenic response, or through some as yet unknown iodine mediated mechanism, will hopefully prove a fruitful field for future investigation.

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REFERENCES

1. Goldman M.B.
Thyroid diseases and breast cancer.
Epidemiol Rev. 1990, *12:* 16-28.
2. Smyth P.P.A
The thyroid and breast cancer: a significant association?
Ann. Med. 1997, *29:* 189-191.
3. Itoh K., Maruchi N.
Breast cancer in patients with Hashimoto's thyroiditis.
Lancet *ii:* 1975, 1119-1121.
4. Mittra I., Perrin J.S.K.
Thyroid and other autoantibodies in British and Japanese women: an epidemiological study of breast cancer.
Br. Med. J. Clin. Res.1976, *i:* 257-259.
5. Rasmusson B., Feldt-Rasmussen U., Hegedus L., Perrild H., Bech K., Hoier-Madsen M.
Thyroid function in patients with breast cancer.
J. Cancer Clin. Oncol. 1987, *23:* 553-556.
6. Giani C., Fierabracci P., Bonacci R., Gigliotti A. Campani D., De Negri F., Cecchetti D., Martino E., Pinchera A.
1996 Relationship between Breast Cancer and Thyroid Disease: Relevance of Autoimmune Thyroid Disorders in Breast Malignancy.
J. Endocr. Metab. 1986, *81:* 990-994.
Metab. *81:* 990-994.
7. Smyth P.P.A., Kilbane M.T., Murray M.J., Mc Dermott E.W.M., Smith D.F., O'Higgins N.J.
Serum thyroid peroxidase autoantibodies, thyroid volume and outcome in breast cancer.
Clin. Endocr. Metab. 1988, *83:* 2711-2716.
8. Hercbergs A.
Hypothyroidism and tumor regression.[letter].
Engl. J. Med. 1988, *319:* 1351-1352.
9. Weijl N.I. VdHD, Brand A., Kooy Y., Van Luxemburg S.S.J., Lentjes E., Van Rood J.J., Cleton F.J., Osanto S.
Hypothyroidism during immunotherapy with interleukin-2 is associated with antithyroid antibodies and response to treatmen.
J. Clin. Oncol. 1993, *11:* 1376-1383.
10. Franzke A.P.D., Probst-Kepper M., Buer J., Kirchner G.I., Brabant G., Kirchner H., Ganser A., Atzpodien J.
Autoimmunity resulting from cytokine treatment predicts long term survival in patients with metastatic renal cell cancer.
J. Clin. Oncol. 1999, *17:* 529-533.
11. Spitzweg C., Joba W., Eisenmenger W., Heufelder A.
Analysis of human sodium iodide symporter gene expression in extrathyroidal tissues and cloning of its complementary deoxyribonucleic acids from salivary gland, mammary gland, and gastric mucosa.
J. Clin. Endocrinol. Metab. 1998, *83:* 1746-1751.
12. Kilbane M.T.T.A., Shering S.G., Smith D.F., McDermott E.W.M., O'Higgins N.J., Smyth P.P.A.
Thyroid peroxidase (TPO) an autoantigen common to the thyroid and breast.
J. Endocrinol. 1998, *156:* P323.
13. Rodien P.M.A.M., Ruf J., Rajas F., Bornet H., Carayon P., Orgiazzi T.
Antibody Dependent Cell-Mediated Cytotoxicity in Autoimmune Thyroid Disease: Relationship to Antithyroperoxidase Antibodies.
J. Clin. Endocrinol. Metab. 1996, *81:* 2595-2600.
14. Ajjan R.A., Findlay C., Metcalfe R.A., Watson P.F., Crisp M., Ludgate M., Weetman A.P.
The modulation of the human sodium iodide symporter activity by Graves' disease sera.
J. Clin. Endocrinol. Metab. 1998, *83:* 1217-1221.
15. Eskin B.A., Grotkowski C., Connolly C.P., Ghent W.R.
Different tissue responses for iodine and iodide in Rat thyroid and Mammary Glands.
Biological Trace Element Research 1995, *49:* 9-19.