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Perspectives and Commentaries

Thyroid Function in Benign and Malignant Breast Disease

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(A COMMENT ON: Lemaire M, Baugnet-Mahieu L. Thyroid function in women with breast cancer. *Eur J Cancer Clin Oncol* 1986, **22**, 301–307.)

THYROID hormone(s) influences development and growth of tissues and may alter metabolism of estrogens, prolactin and chemical carcinogens, and thereby possibly protect from development and growth of neoplastic cells. It is also hypothesized that thyroid hormone antagonizes the proliferative effect of estrogens on breast tissues. Hyperthyroidism has been said to be protective against development of breast cancer via an increase of sex-steroid globulin binding, decreased estrogen activity on mammary tissues, and increased estrone-estradiol metabolism to weak estrogens. In contrast, during hypothyroidism, breast epithelium supposedly becomes sensitized to estrogens, prolactin and carcinogens; furthermore, the ovaries are rendered more sensitive to gonadotropin stimulation resulting in increased estrogen secretion. Thus hypothyroidism is thought to favor breast cancer growth and metastasis. Moreover, in hypothyroid patients an increase in serum cholesterol may promote development of breast cancer; i.e. sterols may function as cocarcinogens or carcinogens. In contrast, increased survival has been reported for hypothyroid breast cancer patients. In laboratory experiments, thyroid hormone has been found to be both a promotor of, and protector against, neoplasia [1, 2].

THYROID HORMONE AND BENIGN BREAST DISEASE

Hypothyroidism was predominant in patients with benign breast disease [3]. Thyroid hormone replacement therapy or correction of iodine deficiency are thought to improve benign breast disease. In contrast, serum levels of thyroid hormone (triiodothyronine: T_3; thyroxine: T_4) have been found to be elevated in patients with benign breast disease. However, according to Lemaire and Baugnet-Mahieu [4] and other authors [5] no hyperthyroidism exists in benign breast disease. Higher levels of T_3 and T_4 in breast cyst fluid than in plasma have been related to development and maintenance of benign breast disease. This, however, is not substantiated by evidence.

THYROID FUNCTION AND BREAST CANCER

Hypothyroidism, as well as hyperthyroidism, have been associated with an increased, decreased or unchanged risk and survival of breast cancer [2]. The report of Kapdi and Wolfe [6] about an increased risk of breast cancer with thyroid medication aroused concern; however, most studies do not confirm this. Various risk factors for breast cancer may influence the results of such investigations. Accordingly, the risk of breast cancer was increased 4.2-fold in women receiving thyroid medication for fertility problems; 2.6-fold when there was a family history of breast cancer; and 2.4-fold when first childbirth occurred at a late age [7]. Recently, it was again observed that thyroid supplementation did not increase the risk of breast cancer, except for women with previous breast biopsy; an increased risk was also observed in euthyroid patients with breast biopsy [8]. In view of the questionable breast cancer risk with thyroid hormone supplementation, it would be poor judgement not to provide thyroid medication to patients in need of it. Lemaire and Baugnet-Mahieu [4] report an increase of T_3 and T_4 serum

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concentrations in patients with breast cancer. Others found T_3 decreased in breast cancer patients while total T_4 was normal and free serum T_4 was decreased. Radiotherapy of breast cancer has been associated with thyroid dysfunction (hypothytroidism) and disturbed peripheral metabolism of T_4 to T_3 resulting in normal T_4 and decreased T_3 levels [9]. According to most reports, T_3, T_4, and TSH levels are normal in patients with breast cancer. Additionally, thyroid studies do not allow prediction of breast cancer recurrence [5, 10].

THYROID ABNORMALITIES IN BREAST CANCER PATIENTS

Thyroid disease has been reported to be more frequent in breast cancer patients but the prevailing view is that thyroid function is not impaired. Thyroid hormone levels were normal in patients with advanced breast cancer [11]. Also, prognosis of breast cancer is not influenced by hypo- or hyperthyroidism. The value of thyroid hormone application in prevention of breast cancer recurrence or for the treatment of systemic disease has been widely contested. Rather, thyroid medication of breast cancer patients was followed by a two- to three-times greater relapse rate supposedly due to activation of dormant cancer cells [12].

Development of breast cancer may be associated with thyroid cancer and *vice versa*, the risk being increased almost 2-fold [13]; however, this too has been debated. Thyroid hormone (T_3) receptors in breast cancer tissue are not correlated with estrogen and progesterone receptors [14]. In contrast to breast cancer, the risk of thyroid cancer is increased in parous women [15]. Exogenous estrogens supposedly increase the risk of thyroid cancer [16]. A relatively high incidence of breast cancer metastasis into the thyroid gland has been reported [17].

Specific comments

Lemaire and Baugnet-Mahieu [4] point out the conflicting literature reports on thyroid function and breast cancer. They also recognize that most prospective and retrospective studies show no association of thyroid function with breast cancer. Nevertheless, they find significantly higher levels of thyroid hormones in patients with breast cancer in contrast to patients with benign breast disease or with cancers of other organs. However, "significantly higher" serum levels of thyroid hormones (T_3: 1.8 ng/ml; T_4: 9.68 μg%) in breast cancer patients are still within the normal range. Also, the authors are aware that: (1) the influence of emotional and surgical stress cannot be ruled out as cause for increased thyroid function and (2) that pre-operative thyroid tests are essential. In view of the literature and their own data, Lemaire and Baugnet-Mahieu [4] justifiably conclude that "a specific role of pituitary–thyroid function in the etiology of human breast cancer remains to be unequivocally demonstrated".

The reasons for conflicting reports on thyroid function in relation to breast cancer are manifold. Besides circadian rhythm, therapy with tamoxifen, 5-fluorouracil, aminoglutethimide, medroxyprogesterone acetate, as well as surgery and radiotherapy of breast cancer can alter thyroid function and $T_{3/4}$ serum levels. As suggested before [1], more insight may be gained by prospective studies which interrelate parameters of pituitary, thyroid, adrenal, and ovarian function with other factors that influence thyroid function and breast cancer risk. The major questions to be answered are: (1) Do thyroid studies allow identification of patients at high risk of breast cancer? (2) Do they permit prognostic evaluation of the patient with breast cancer? (3) Is thyroid medication or suppression of thyroid function of value in the management of the breast cancer patient?

Conclusions

Thyroid hormones may influence metabolism of hormones (estrogens) and carcinogens and hyperthyroidism is thought to be protective against breast cancer. In thyroid hormone deficiency, sensitization of breast epithelium toward estrogens, prolactin, and carcinogens has been suggested; increase in serum cholesterol (carinogenic sterols) may support neoplasia. Hypothyroidism has been associated with development of benign breast disease, thereby increasing the risk of breast cancer; however, this relationship has been questioned. Risk and survival of breast cancer have been reported to be either increased, decreased, or unchanged in patients with hypo- or hyperthyroidism. In addition, thyroid hormone medication has been related to an increased risk of breast cancer. Most studies, however, do not support such a causative relationship. Thus, it would be poor judgement not to provide thyroid medication to patients in need of it. Conflicting reports on thyroid function and breast cancer may be the consequence of inadequate consideration of circadian thyroid rhythm, psychoemotional and surgical stress, endocrine- and chemotherapy; also, various risk factors of breast cancer including radiation exposure in childhood often have not been properly evaluated. To resolve the "thyroid–breast cancer controversy" future prospective studies are warranted which interrelate parameters of pituitary, thyroid, adrenal, and ovarian function with factors that influence thyroid activity and breast cancer risk.

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