Letters

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Thyroid Supplements and Breast Cancer

To the Editor.—From time to time, reports are published suggesting that cancer or other forms of malignant disease may be associated with one type of medication or another. Drs Kapdi and Wolfe suggested a relationship between thyroid supplements for hypothyroidism and breast cancer (236:1124, 1976). They report that patients receiving thyroid supplements not only had a higher incidence of breast cancer than those in the general population, but also that there was a clear-cut increase in the incidence of breast cancer with advancing age (a not unexpected finding), and further, that there was a positive correlation between the duration of therapy with thyroid supplements and the incidence of breast cancer.

They quote an article by Levy and Levy (*Am Practitioner Digest Treat* 2:522-526, 1951) suggesting that hypothyroidism might have a protective effect against the development of breast cancer. They further speculate that patients who receive thyroid supplements were deprived of the supposedly beneficial effects of hypothyroidism.

May I call attention to an article in which we observed an opposite relationship between cancer and thyroid function (183:30, 1963). A total of 3,290 patients was studied, and the total number of cancers was 110 (3.34%). Twelve hundred forty patients had thyrotoxicosis, and the incidence of malignant disease among them was 2.33%. Two hundred thirty six patients were hypothyroid, and the incidence in this group was 6.78%. The remaining 1,814 patients were euthyroid; among them, 3.58% had malignant disease.

It was our impression that the thyrotoxic state might, in some patients, create an unfavorable environment for the development and growth of malignant disease, whereas hypothyroidism might have the opposite effect. Obviously, these results are contrary to those reported by Kapdi and Wolfe.

Perhaps further investigation will elucidate the mechanisms responsible for this apparent paradox.

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To the Editor.—The article of Drs Kapdi and Wolfe and subsequent reporting in the media seems, to us, to represent an incorrect review and analysis of what is already documented with respect to thyroid disease and the incidence of breast cancer in man. Contrary to what was concluded, namely, that thyroid therapy is associated with a higher incidence of breast cancer, we believe it should be concluded that there is a higher incidence of breast cancer in women with preexisting and frequently inadequately treated hypothyroidism or thyroiditis.

Several published reports now suggest that failure to adequately treat hypothyroidism, goiters, or thyroiditis with thyroxin leads to enhanced development of breast cancer in susceptible persons.[1-5] There are, for example, confirmed reports of an increased incidence of breast cancer in hypothyroid patients[1] and in patients with Hashimoto thyroiditis,[2] and a greater incidence of elevated thyroid-stimulating hormone (TSH) levels, an indication of hypothyroidism (real or incipient), has been reported in breast cancer victims.[1] Studies have also shown an enhanced mammotropic effect of prolactin in hypothyroid animals,[3] a greatly increased incidence of carcinogen-induced mammary carcinoma in hypothyroid rats when compared to euthyroid animals,[4] and that administration of thyroxin to hypothyroid animals causes ectopic mammary transplants to disappear.[3] Resting prolactin levels are elevated in hypothyroid patients,[5] and such patients manifest a supernormal TSH response to the administration of synthetic thyrotropin-releasing hormone (TRH).[1] These and other observations lead us to encourage early detection of hypothyroidism, goiter, and thyroiditis and to treat these conditions appropriately with synthetic thyroxin. Until it can be shown that thyroxin therapy can emulate what has been shown for hypothyroidism, it would be woefully wrong to incriminate thyroxin therapy in the cause of breast cancer. The weight of reports to date suggests, contrary to the implication of the article by Drs Kapdi and Wolfe, that failure to treat patients with thyroxin, when indicated, may causally contribute to the development of malignant breast disease.

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To the Editor.—Drs Kapdi and Wolfe are competent radiologists, but they missed one of the fundamentals of scientific research. *They failed to use suitable controls.* In their opening paragraph, they state that "a definite relationship between breast cancer and hypothyroidism has been established." This is certainly true, and the most convincing evidence for it are some personal, unpublished observations on the routine autopsies performed in Graz, Austria. Graz is a goiter area; the entire population suffers from a relative thyroid deficiency. Thyroid replacement is rarely employed there. Yet the incidence of breast cancer is as high as ten times that seen in the United States. If thyroid deficiency can predispose to breast cancer, the influence of thyroid therapy in the etiology of the cancer could only be measured by comparing the incidence in a group of untreated hypothyroid patients with that in a group receiving thyroid replacement. Comparing the thyroid-treated patients with the euthyroid patients having one tenth the incidence of breast cancer is inappropriate.

Since the authors found only twice the number of cancers in the thyroid-treated group as in normal women, and since the incidence in untreated hypothyroid patients is up to ten times as great, the authors should have concluded that thyroid therapy substantially reduces the incidence of breast cancer in hypothyroid women. This would be in agreement with results on experimental animals. In *Cancer Research* (16:135, 1956), Benson reported that maintaining female rats on a diet containing 20% unsatu-

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rated fat led to an incidence of breast cancer three times greater than that in the control group. The addition of thyroid therapy to the high-fat diet completely eliminated the excess of breast cancer.

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To the Editor.—Kapdi and Wolfe reported that 5,505 patients were referred for mammography; 380 (6.9%) were found to have carcinoma of the breast, and 22.6% of these breast carcinoma patients were receiving thyroid supplements for hypothyroidism or for simple goiter. They also reported that the incidence of breast cancer in patients receiving thyroid supplements for hypothyroidism is almost twice that of patients in the control group, who did not receive thyroid medication.

We reviewed the records of breast carcinoma patients at Jackson Memorial Hospital in Miami for a two-year period (April 1974 to April 1976) and found 222 patients with documented breast carcinoma. Only two of these patients (0.9%) were hypothyroid and receiving thyroid hormone supplements.

This low incidence (0.9%) in Miami is substantially different from the 22.6% incidence reported by Kapdi and Wolfe in Detroit, which leads us to believe that the problem is more complicated than stated in their article. Verification of their data is needed in other parts of the country to determine the possible regional nature of their findings, since 11.6% of their patients referred for mammographic examinations were also found to be receiving thyroid medications.

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To the Editor.—The data reported by Drs Kapdi and Wolfe does not distinguish between the use of thyroid supplements and the conditions for which the supplements were given as possible risk factors for breast cancer. A further analysis of these data is shown in the Table.[1,2] There is only a modest increase in the risk of breast cancer in women taking thyroid supplements (relative risk, 1.59 overall), and the trend toward increasing risk with increasing duration of therapy is not consistent over the three duration levels.

In a study of drug use at the time of diagnosis of cancer,[3] 7 of 708 patients with breast cancer and 16 of 1,429 patients with other cancers were taking thyroid supplements. With the other cancer patients considered as controls, the relative risk of breast cancer in users of thyroid supplements was estimated to be 0.96, with 95% confidence limits of 0.39 to 2.33. In an additional study of drug use at the time of diagnosis,[4] 5 of 156 patients with breast cancer and 19 of 624 patients without breast cancer admitted to surgical services and matched 4:1 to cases for age and hospital were taking thyroid supplements. The relative risk in users of thyroid medication was estimated to be 1.05, with 95% confidence limits of 0.46 to 2.10. Although these results are consistent with the relative risk found by Kapdi and Wolfe (1.59), they are more consistent with the absence of a positive association.

It is possible that the low prevalence of thyroid supplementation in our studies (about 1% to 3%, compared with 20% in the breast cancer patients and 11% in the other patients reported by Kapdi and Wolfe) reflects a relative absence of "simple goiter" which Kapdi and Wolfe state to have been endemic in their area. If this condition or some correlate of it, rather than the use of thyroid supplements, were causally associated with breast cancer, this could explain the positive association which they found. It might also account for the inconsistent relationship between duration of thyroid supplementation and breast cancer risk.

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Estimated Relative Risk of Breast Cancer in Patients Taking Thyroid Supplements

Duration of Thyroid Supplementation, yr	Relative Risk*	
	Point Estimate	95% Confidence Limits
1-5	1.62	1.06-2.47
6-15	1.30	0.78-2.16
>15	2.26	1.50-3.39
All	1.59	1.21-2.08

*Standardized for age by decade from <35 to >65 years.

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2. Miettinen OS: Simple interval-estimation of risk ratio. *Am J Epidemiol* 100:515-516, 1974.
3. Armstrong B, Stevens N, Doll R: Retrospective study of the association between use of *Rauwolfia* derivatives and breast cancer in English women. *Lancet* 2:672-675, 1974.
4. Reserpine and breast cancer. Boston Collaborative Drug Surveillance Program. *Lancet* 2:669-671, 1974.

To the Editor.—The article by Kapdi and Wolfe provides some very interesting data, but in order to assess its clinical and epidemiologic significance, we would like to make the following observations.

First, it is very important to note that women receiving thyroid medication are older than the control group of women not receiving thyroid medication (median age of 46 to 55 years vs 35 to 45 years). Also, women taking thyroid medication for more than 15 years are older than women taking the medication for less than 15 years (in the group receiving thyroid medication for 1 to 5 years, 47% are >45 years old; receiving thyroid medication for 6 to 15 years, 60% are >45 years old; and receiving thyroid medication for >15 years, 75% are >45 years old).

Since the risk of developing breast cancer increases with age and length of exposure to thyroid medication is directly proportional to age, we would expect that there would be an increased incidence of breast cancer in women who have been receiving thyroid medication for an extended time period. Therefore, Tables 1 through 3 and Fig 1 of their article can be largely explained by the age differences in the two populations.

In Tables 4 and 5, the authors suggest that nulliparous women who have taken thyroid medication are at a greater risk of developing breast cancer. A more likely explanation is that the thyroid users are older and are therefore at higher risk, regardless of their thyroid supplement intake.

Without age adjustment, the data in Tables 1 through 5 and Fig 1 are impossible to interpret with any validity.

The dose-response relationship that the authors are trying to establish between the use of thyroid supplements and the increased number of breast cancers is inconsistent, even when the groups are broken down into age-specific categories (Table 6). Note the error in the percentage of breast cancers in patients >65 years of age receiving thyroid medication for one to five years: 6 cancers in 9 patients is 67% and not 7%.