The Relationship Between Thyroid Functions and Breast Cancer

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MEME KANSERİ VE TRİOİD FONKSİYONLARI ARASINDAKİ İLİŞKİ

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SUMMARY'

A possible relationship between thyroid functions and breast cancer was investigated. The plasma TSH, T_3, and T_4 levels were measured and thyroid scanning was performed on women with breast cancer. The results were compared with those of two control groups. The first control group consisted of women without any cancer, the second control group consisted of women who had cancers of various organs other than the thyroid gland and the breast. No difference ivas found betvjeen the mean TSH, T_3 and T_4 levels of the three groups. Thyroid functions were not influenced by the clinical stage of cancer. More hyperactive thyroid nodules were found in the breast cancer group in comparison with the other two groups. Although this last finding suggested that the hypothalamo-pituitary-thyroid axis might be affected in breast cancer, the results as a whole were not sufficient to prove or explain a connection between breast cancer and the thyroid gland.

Key words: Breast cancer, thyroid functions

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ÜZET

Bu çalışmada, tiroid bezi ile meme kanseri arasında bir ilişki olup olmadığı araştırıldı. Bu amaçla, meme kanserli bir grup hastanın serum T_3, T_4, TSH düzeyleri ve tiroid sintigrafileri İncelendi. Sonuçlar, ilki kanserli olmayan, ikincisi tiroid ve meme dışı kanserleri olan hastalardan oluşan iki kontrol grubu ile karştlaştırüdı. Meme kanserli hastalar ile iki kontrol grubunun hastaları arasında, tiroid hormonları ve TSH düzeyleri yönünden fark bulunmadı. Tİroid sintigrafilerinde meme kanserlilerle her iki kontrol gurubu arasında fark görüldü. Meme kanserlilerin tiroid sintigrafilerinde hiperaktif nodüllerin kontrol gruplarına göre daha fazla olması şeklinde olan bu fark. bu hastaların hipotalamo-pitüiter-dopamin sistemlerinin etkilenmiş olabileceğine işaret else de, meme kauseri-tiroid bezi ilişkisini aydınlatmaya yeterli değildir.

Anahtar kelimeler: Meme kanseri, tiroid fonksiyonları

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INTRODUCTION

Interest in a possible relationship between the thyroid gland and breast cancer started in 1896 when Beatson(l) suggested the use of thyroid extract as an adjuvant to oophorectomy in the treatment of advanced breast cancer. During the last twenty years, considerable evidence pointing to such a relationship accumulated as a reslut of experimental(2,3,4), clinical (5,6,7,8,9,10,11,12) and epidemiological 2,8) studies. Thyroid function was reported to be decreased(3,4,6, 13), unchanged (14,15,16,17,18) or increased (7,9, 11,12,) in breast cancer by different authors. Investigations pertaining to the influence of thyroid function on the development of breast cancer gave contradictory result. In the last decade, attention has been focused primarily on the steroid hormones as etiological factors in breast cancer(3,19).

The purpose of this study is to make a new explanation for the contradictory results mentioned above and to search for the presence of a relationship between breast cancer and thyroid functions

MATERIALS AND METHODS

Forty women with breast cancer were studied. The patients were classified using the Columbia criteria into four groups", each containing ten patients. Columbia A and B groups were accepted as early; C

and D groups as advanced breast cancer. The diagnosis of breast cancer was confirmed with incisional biopsy and pathological examination.

The first control group (Group I) consisted of forty women awaiting surgery for problems unrelated to any cancer. In this group, 13 patients had senile cataract, 8 patients had cholelithiasis, 6 patients had peptic ulcer and 13 patients had cosmetic defects. A second control group (Group II) was composed of forty women with cancer of the colon (7patients), the stomach (6 patients), the larynx (9patients), and the genitourinary system (18 patients). In this group, the presence of distant metastasis was searched for using liver, brain and bone scanning and was accepted as the criteria of advanced cancer.

The patients in the control groups had no prior history of thyroid or breast disease. Women who had been administered iodine containing dyes or hormonal drugs were excluded from the study. No medicine was allowed for seven days before the performance of the tests included in the study.

Methods

A. Determination of Serum T_3, T_4 and TSH:

Blood samples were taken from all of the patients at 8-10 A.M.; the serum was separated at —20°C until analysed. Serum T_3 level was determined by radioimmunological methods using the RIA-mat T_3 test (20). With this method, the normal range of serum T_3 was 0.2-0.4 ng/ml. Serum T_4 level was determined with the same test and the normal range was 4-12 ug/100 ml. Serum TSH level was assayed using indirectly coupled antibodies (20). The normal range of serum TSH was 0-5 uU/ml.

B. Thyroid Scanning Technique:

Fifteen minutes after giving 2 mCi ^{99m}Tc-Pertecnetate, thyroid scanning was performed by obtaining 100.000 Y countings with a Y camera (Phogamma 4, Chicago).

C. Statistical Analyses:

Comparison between the three groups were statistically tested by use of variation and multiple regression analyses.

RESULTS

The mean age was 50.2 years in the breast cancer group, 46.4 in control group 1 and 48.4 in control group II. There was no difference between the mean age Of the three groups (Table 1).

Table - I

The Mean Age of the patients.

Group	Mean Age	Range
Breast Cancer	50.2±1.9	24-77
Control Group I	46.4±2.1	24 - 70
Control Group II	48.4+2.3	25 - 85
F:0.825	P>0.05	

Thyroid Scanning results were classified as follows:

a) Patients with diffuse hyperplasia,
b) Patients with hypoactive nodules,
c) Patients with hyperactive nodules,
d) Patients with normal scanning results

Table - II

Thyroid Scanning Results of the Patients.

Group	Diffuse Hyperplasia		Hyperactive Nodules		Hypoactive Nodules		Normal Scanning		Total
	Number	%	Number	%	Number	%	Number	%	
Breast Cancer	16	32.6	8	72.6	2	40.0	14	25.3	40
Control Group I	11	22.5	1	9.0	2	40.0	26	47.2	40
Control Group II	22	44.9	2	18.4	1	20.0	15	27.5	40
Total	49	100.0	11	100.0	5	100.0	55	100.0	120

x^2: 13.76 P<0.05

As can be seen in Table II, 55 of the total 120 patients had normal thyroid scans and 26 of these patients belonged to control group I. Statistical analyses showed that there was significant difference between the results (x^2: 13.76, $p<0.05$) and this was found to be due to the number of normal thyroid scans in control group I. When control group I was not taken into consideration, the difference continued and this was found to be due to the excess of hyperactive thyroid nodules in the breast cancer patients (Table II).

Serum T_3, T_4 and TSH levels were within normal limits in all three groups. Furthermore, thyroid functions were not shown to be influenced by the stage of cancer (Table III).

Table III

The Mean Values of Serum T_3, T_4 and TSH in the Patients.

Group	Patient Number	Median Age	Serum T_3 (ng/ml)	Serum T_4 (ug/100 ml)	Serum TSt (uU/MI)
Early Breast Cancer (Columbia A and B)	20	47.4	1.17±0.08	8.20±0.12	1.60±0.21
Advanced Breast Cancer (Columbia C and D)	20	54.3	1.14±0.05	8.02±0.17	1.73+0.32
Early Other Cancer	30	50.1	1.01±0.03	7.82±0.27	2.83±0.61
Advanced Other Cancer	10	43.3	1.15±0.06	8.23 + 0.30	2.17±0.42
Control Group I	40	46.4	1.04±0.05	8.45+0.24	2.40+0.41

F:1.63 **P**>0.05

DISCUSSION

The role of the thyroid gland in breast cancer is still a controversial matter. In some studies, it has been demonstrated that the incidence of breast cancer is high in endemic goiter areas (2,8,21). Other studies have put forth demographic evidence in contradiction with this view (14,15,22).

In countries like Japan, Chile, Venezuela and Ceylon, the mortality of breast cancer is low in parallel with a low endemic goiter incidence. On the other hand, in countries like Belgium, Poland, Switzerland and Austria, a high endemic goiter incidence goes together with a high breast cancer mortality rate. These findings seem to support the thought of a connection between thyroid gland dysfunction and breast cancer. Mittra(23), in an effort to explain these results, has evolved a theory connecting the hypothalamo-pituitary-prolactin axis with the thyroid gland. Mittra has stated that TRH stimulates the secretion of both TSH and prolactin along this axis and that the activity of prolactin as well as TSH increases in hypothyroidism due to feedback mechanisms that cause TRH to rise. Andreassen et al (24) and Jacobs and Synder(25) have shown that an increase of thyrotropin releasing hormone results in an elevation of the plasma levels of both prolactin and thyrotropin. According to Mittra's theory, hypothyroidism may be an indirect cause of dysplasia and neoplasia in breast tissue, by way of the continuous stimulation of breast ductal epithelium effected by the increase in prolactin activity. But Mittra and others have demonstrated that the serum prolactin level does not show significant change in hypothyroidism^,26,27,28). This findings has rendered an explanation based on prolactin insufficient in elucidating the relationship between the thyroid gland and breast cancer. In addition, MacMahon has pointed out that an increase in the prolactin level does not have pathologic effect on human breast epithelium^).

According to some investigators, hypothyroidism incidence and growth rate of breast cancer(21,30). Perry(13) has found that patients with breast cancer are in a hypothyroid state and that this state shows progressive deterioration. The results of other workers(4,17,18), have not supported this thought. Eventhough considerable dispute does exist, the demonstration of thyroid hypofunction in breast cancer has given way to efforts aiming to illuminate the indirect mechanism relating the two entities. Using the TRH test, Mittra(3) and coworkers have found that the above mentioned hypofunction is not due to pituitary or hypothalamic disease. This conclusion is in accordance with the results of Sommers (31). Sommers has found that in women dead of breast cancer, there is an atrophy of the thyroid gland that seems to have evolved over a long period of time. In his postmortem studies, he has emphasized that this atrophy is frequently accompanied by changes in the endometrium and the ovaries.

Taking all of the above views into consideration and aiming to reunite and develop them, we have constructed a theoretical mechanism to explain the relationship between breast cancer and the thyroid gland. This theoretical model is schemotized in Figure I. Thyroid hypofunction constitutes the starting point in this model. Minimal decrease in the serum T_3-T_4 levels or in other words, relative thyroid hypofunction can be expected to cause an increase of TRH secretion by way of feedback effects. Increase in TRH would, in turn, cause increase in TSH secretion from the anterior pituitary. It has been postulated previously by others that to provide for this increase in TSH secretion, the pituitary must show amphophile cell hyperplasia^1). This would expectedly cause a relative increase in the levels of the gonadotropic hormones also secreted by these cells. The continous stimulation effected by the increase in gonadotropins would result in bilateral ovarian hyperplasia(31).

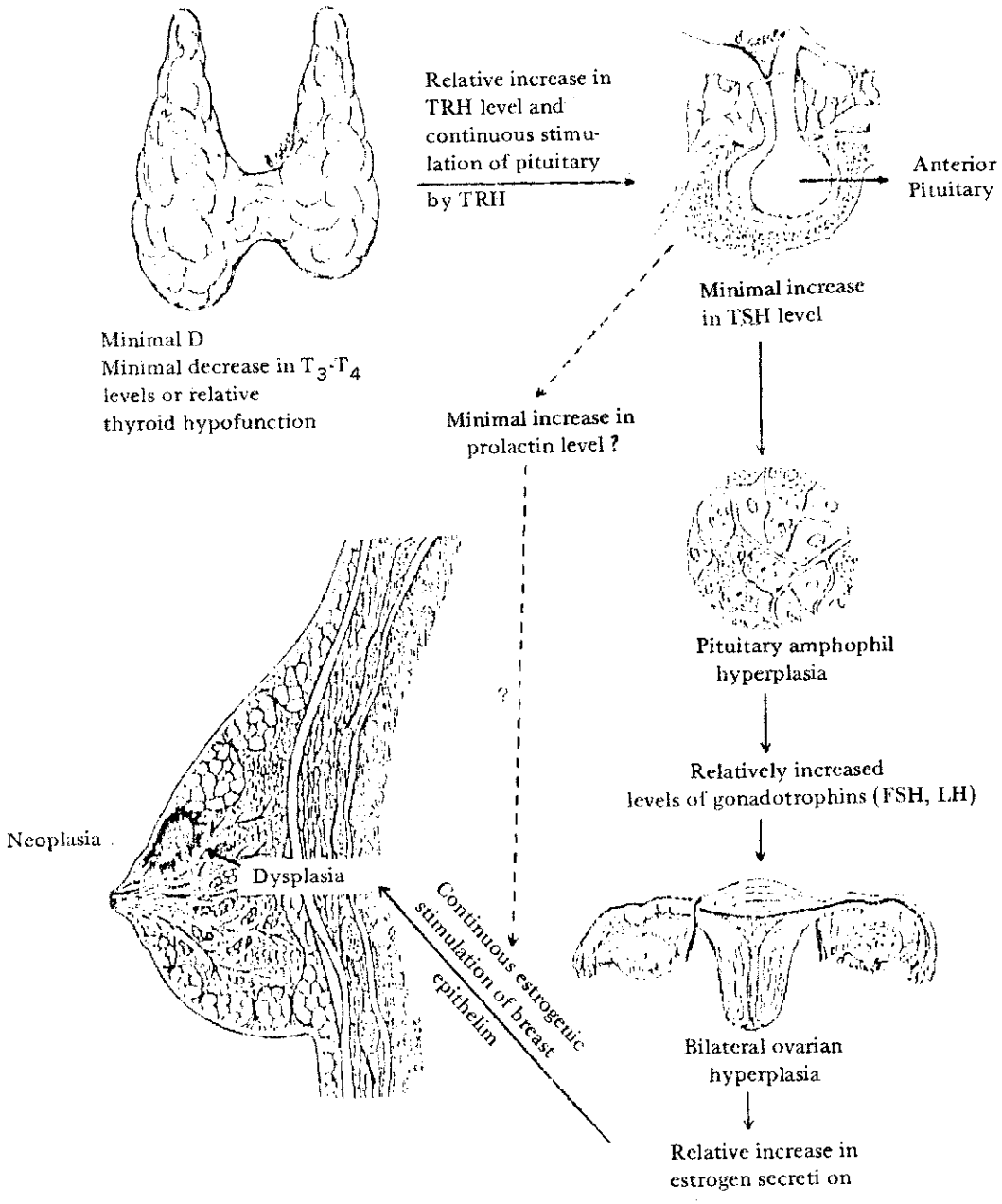

Figure 1. The probable mechanism of the relationship between thyroid hormones and breast cancer.

Increase in gonadal secretions, in trun, would cause dysplasia and neoplasia in the breast ductal epithelium by way of continous estrogenic stimulation. The increase in TRH may contribute to the changes in the ductal epithelium by increasing prolactin

The normal T_3, T_4 and TSH levels of the patients with breast cancer during this study demonstrated that they were in an euthyroid state, contrary to the expected hypothyroid state. But, hyperactive thyroid nodules were significantly increased in breast cancer patients according to scintigraphic findings ($p>0.05$). It is known that hyperplastic and nodular changes in the thyroid gland are effected by TSH and are therefore a function of the hypothalamo-pituitary-dopamine system(32). In breast cancer patients with hyperactive nodules, it can be proposed that their hypothalamo-pituitary-dopamine systems have been in operation before. Perhaps these patients were in a hypothyroid state in the beginning and became euthyroid under the influence of TSH during an undetermined time. The high rate of hyperactive nodule formation in these patients brings forward

the thought that they might have been under the influence of TSH according to the mechanism explained above. In conclusion, even though hormonal results providing direct support for this mechanism could not be obtained, the scintigraphic findings pointed out that this mechanism cold have been under operation in the past. In this case, a sequence of changes in thyroidal function following the order of a hypothyroid, euthyroid and then hyperthyroid state could be possible. This view cold explain the contradictions between the results of different investigators. Very long, randomized and prospective studies of normal women with followup of those who eventually have breast cancer are needed to definitely clarify this difficult matter.

Bubrook et al(33) have conducted a prospective study and have found that precancer cases who also had a family history of breast cancer showed a significant degree of subclinical hypothyroidism. Using serum free thyroxine as a thyroid function (TFI), Thomas et al(34) have found that the mean TFI was significantly lower in early breast cancer cases who were compared with normal controls. Kalache et al(35) have proposed that, although they did not find a relationship between clinically recognized thyroid disease and the subsequent occurrence of breast cancer, variations of thyroid function within the normal range might be of importance in the etiololgy of breast cancer, perhaps via an influence on the secretion or metabolism of sex hormones. More sensitive determination methods may show subtle changes in hormonal functions in pre-breast cancer cases. We believe that studies similar to and more extensive than Bulbrook's work, using sensitive methods and including the full biochemical spectrum of thyroid function assays as proposed by Thomas et al (34) and also hypothalamic, hypophyseal, adrenal and ovarian functions will be necessary before a final decision can be made.

REFERENCES

1. **Beatson GT. On the teratment of inoperable cases of carcinoma of the mamma. Suggestion for a new method of treatment with illustrative cases. Lancet 2:104-107, 1896.**
2. **Eskin BA. Iodine metabolism and breast cancer. A casual connection Med. Press, 235: 280, 1956.**
3. **Mittra I, JL Hayward. Hypothalamic-pituitary-thyroid axis in breast cancer. Lancet 2: 885-888, 1974.**
4. **Rose DP. Plasma thyroid-stimulating hormone and thyroxine concentrations in breast cancer. Cancer 41: 666-669,1978.**
5. **Repert RVV. Breast carcinoma study : relation to thyroid disease and diabetes mellitus. J. Michigan M. Soc. 51: 1315-1316, 1952**
6. **Edelstyn GA, AR Lyons.Thyroid function in patients with mammary cancer. Lancet 1: 670-682, 1958.**
7. **Carter G, EB Feldman : Levels of serum protein-bound iodine in patients with metastatic carcinoma of the breast. J. Clin. Endocrinol. Metab. 20: 477-483, 1960.**
8. **Bogardurs GM, JW Finley : Breast cancer and thyroid disease. Surgery 49: 461-467,1961.**
9. **Dargent M, M Berger : La function thyroidienme chez les malades attendies de cancer du sein. Acta Un Ins. Cancer 18:915-919,1962.**
10. **Humprey BJ, M Swerdlow : The relationship of breast disesase to thyroid disease. Cancer 17:1170-1175, 1964.**
11. **Bignazzi A, U Veronesi : Thyroid function in patients with cancer of breast. Tumori 51:199-203,1965.**
12. **Myhill J, TS Reeve : Thyroid function in breast cancer. Acta Endocrinol. 51: 290-294,1966.**
13. **Perry M : Thyroid function in patient with breast cancer. Ann. Roy. Coll. Surg. England 3: 290-293, 1978.**
14. **Schottenfeld K, JA Waterhouse : Thyroid activity in relation to prognosis in mammary cancer. Br. J. Cancer 21:512-519, 1968.**
15. **Hortling FI, L Hiisi:Brumer : Thyroid function in cases of mammary cancer. Ann. Med. Bui. Fin. 2: 740-752, 1959.**
16. **Stoll BA : Breast cancer and hypothyroidism. Cancer 18: 1431-1439, 1965.**
17. **Adami HO, A Rinsten, L Thoren : Thyroid disesase and function in breast cancer patients and non-hospitalized controls evaluated by determination of TSH, T3, rT3 and T4 levels in serum. Acta Chir. Scand. 144: 89-97, 1978.**
18. **McFarlane IA : Thyroid function in patients with bening and malignant breast disease. Br. J. Cancer 41: 478-480, 1980.**
19. **Bulbroke RD, DY Wang : (in) Control of Gonodal Secretion (Edited by DT Baird and JA Strong), p: 293, Edinburg, 197 L**
20. **Raith L : Einfiigrung in radioimrnunologische Byk-Mallincrodt, 1-5, 1974.**
21. **Spencer JGC : The influence of the thyroid in malignant disesase, Br. J. Cancer 8: 393-396, 1954.**
22. **Wynder ET, IJ Bross : A study of the epidemiology of cancer of the breast. Cancer 13: 559-563,1960.**
23. **Mittra I, JL Hayward : Hypothalamic-pituitary-prolactin axis in breast cancer. Lancet 2: 889-891,1974.**

24. Andreassen B, J Huth, JE Tyson : Plasma thyrotropin-releasing hormone, prolactin, thyrotropin and thyroxine concentrations following the intravenous or oral administration of thyrotropin-releasing hormone. Am. J. Obstet. Gynecol. 135: 737,1979.

25. Jacobs LS, PJ Synder : Increased serum prolactin after administration of synthetic thyrotropin-releasing horm ine (TRH) in man. JL. Clin. J. Endocrinol. Metab. 33: 996,1971.

26. Kwa HG, M De Jong-Baker, E Englsman : Plasma prolactin in human breast cancer. Lancet 1: 433-437,1974.

27. Wilson RG, R Buchan, M Roberts : Plasma prolactin in human breast cancer. Cancer 33:1325-1327,1974.

¿8. Friesen HG : The role prolactin in breast cancer. Cancer Res. 57:143-149,1976.

29. MacMahon B, P Cole, M Lin, C Lowe : Plasma Prolaction in human breast cancer. Bull. Wld. Hlth. Org. 43: 209-216,1970.

30. Moossa AR : Thyroid and breast cancer, reappraisal of an old relationship. Ann. Roy. Coll. Surg. England 4: 178-188, 1973.

31. Sommers SC : Endocrine abnormalities in women with breast cancer. Lab. Invest. 40:160-174,1955.

32. Zellmann EH : Diseases of the Thyroid, (in) Surgery of the Thyroid and Parathyroid Glands. Eds.: Sedgwick CE, Cady B. WB Saunders Company, Pniladelphia, 1980, pp: 77-78.

33. Bulbrook RD, Thomas BS, Fant VE, Hayward JL : A prospective study of the relation between thyroid function and subseguent breast cancer, (in) Banbury Report 8 : Hormones and Breast Cancer. Cold Spring Harbor Laboratory, 1981, pp: 131-141.

34. Thomas BS, Bulbrook RD, Russell MJ, Haypard JL, Millis R : Thyroid function in early breast cancer. Eur. J. Cancer Clin. Oncol. 19 (9): 1213-1219,1983.

35. Kalache A, Vessey MP, McPherson K : Thyroid disease and breast cancer findings in a large case-control study. Br. J. Surg. 69: 434-435,1982.