High Incidence of Synchronous or Metachronous Breast Cancer in Patients with Malignant and Benign Thyroid Tumor or Tumor-like Disorders

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Abstract. *Background: Although many reports indicated an association between thyroid diseases and breast cancer, such an association still remains controversial. The present study was aimed to clarify the association of thyroid diseases with the breast cancer incidence. In the patients with benign and malignant thyroid tumor or tumor-like disorders, the incidence of other malignancies was surveyed, and the frequency of thyroid cancer in patients with breast cancer was also surveyed. Patients and Methods: Between 1982 and 2005, a total of 201 female patients received surgery for tumor or tumor-like disorders, including 65 carcinoma, 68 adenoma, 61 adenomatous goiter and 7 chronic thyroiditis cases. Their outcomes were surveyed in December 2006. Furthermore, during the same periods, 340 female patients underwent breast cancer surgery and their outcomes were also surveyed in December 2006. Results: The overall incidence rate of breast cancer was 16.4% (33/201) in the patients, who received thyroid surgeries and was much higher than other malignancies: 2.0% gastric cancer, 1.0% uterine and colorectal cancer. The incidence rate of breast cancer in each disease was 13.8% for thyroid cancer, 16.2% for adenoma and 21.3% for adenomatous goiter, but no incidence for chronic thyroiditis. On the other hand, in the patients with breast cancer during the same period in our department, the frequency of thyroid cancer was only 2.1% (7/340). Conclusion: It appears that thyroid cancer, adenoma and adenomatous goiter were associated with the risk of breast cancer, but chronic thyroiditis was not related.*

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Many studies have suggested that there is an association between thyroid diseases and breast carcinoma (1-3). Many recent reports have shown that primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma, especially in post-menopausal women (4, 5); however, it was also reported that hypothyroidism and low-normal FT4 are related to an increased risk of breast cancer in post-menopausal women (6). On the other hand, the hyperthyroid state is indicated to be associated with increased risk of breast cancer (7, 8). Furthermore, a possible relationship between thyroid cancer and breast cancer has been suggested and it was reported that women with a history of thyroid cancer are at an increased risk of developing breast cancer, and this risk is noted in premenopausal women (9-11). However, it was also reported that breast cancer risk was not associated with a history of any thyroid disorders or their associated treatments (12).

Although many reports indicated an association between thyroid diseases and breast cancer, such an association still remains controversial. The present study was aimed to clarify the association of thyroid diseases with breast cancer incidence, and the outcome of the patients with benign and malignant thyroid tumor or tumor-like disorders who underwent thyroid surgeries in our department were surveyed, especially from the viewpoint of the incidence of other malignancies, and furthermore the frequency of thyroid cancer in patients with breast cancer was also surveyed.

Table I. *Incidence of non-thyroid malignancies in various thyroid disorders.*

	Overall n=201	Carcinoma n=65	Adenoma n=68	Adenomatous goiter n=61	Chronic thyroiditis n=7
No incidence	153 (76.1%)	51 (78.5%)	52 (76.5%)	43 (70.5%)	7 (100%)
Incidence					
Overall	48 (23.9%)	14 (21.5%)	16 (23.5%)	18 (29.5%)	0 (0%)
Breast ca	33 (16.4%)	9 (13.8%)	11 (16.2%)	13 (21.3%)	-
Alone	30	8	10	12	-
+ Stomach ca*	1	-	1	-	-
+ Colorectal ca**	1	-	-	1	-
+ Osteosarcoma***	1	1	-	-	-
Stomach ca	4 (2.0%)	0 (0%)	2 (2.9%)	2 (3.3%)	-
alone	3	-	1	2	-
+ Breast ca*	1	-	1	-	-
Uterine ca	2 (1.0%)	-	-	2 (3.3%)	-
Malignant thymoma	2 (1.0%)	1 (1.5%)	1 (1.5%)	-	-
Colorectal ca	2 (1.0%)	1 (1.5%)	-	-	-
alone	1	1	-	-	-
+ Breast ca**	1	-	-	1	-
Myeloma	1 (0.5%)	-	1 (1.5%)	-	-
Neck SCC	1 (0.5%)	1 (1.5%)	-	-	-
ML	1 (0.5%)	1 (1.5%)	-	-	-
Esophageal ca	1 (0.5%)	-	-	1(1.6%)	-
Pheochromocytoma	1 (0.5%)	1 (1.5%)	-	-	-
Bladder ca	1 (0.5%)	-	1 (1.5%)	-	-
Osteosarcoma	1 (0.5%)	-	1 (1.5%)	-	-
+ Breast ca***	1	1	-	-	-

*, ** and *** indicate same patients.

Patients and Methods

Between 1982 and 2005, a total of 201 female patients received surgery for tumor or tumor-like disorders in the First Department of Surgery, Shimane University School of Medicine. They included 65 carcinoma, 68 adenoma, 61 adenomatous goiter and 7 chronic thyroiditis cases. All were pathologically diagnosed. All thyroid carcinomas were histologically diagnosed as papillary carcinomas and as clinical stage 1 for all patients. The mean ages were 55.6±14.3 years for patients overall; 52.8±14.1 for thyroid cancer patients; 56.2±15.8 for adenoma patients; 58.6±12.0 for adenomatous goiter patients; and 50.1±17.6 for chronic thyroiditis patients. There was a significant difference in age between patients with thyroid cancer and those with adenomatous goiter (p=0.0134). Their outcome was surveyed in December 2006, by telephone or mail. Furthermore, during the same periods, 340 female patients underwent breast cancer surgery, and their outcome was also surveyed in December 2006.

Results

The frequency of various types of cancer in the case of thyroid tumor or tumor-like disorders is summarized in Table I. Malignancies were seen in 23.9% (48/201) of the patients with thyroid tumors or tumor-like disorders: 29.5% (18/61) in the patients with adenomatous goiter, 23.5% (16/68) in those with adenomas and 21.5% (14/65) in those with carcinoma. On the other hand, there was no incidence of malignancy in the patients with chronic thyroiditis, although the number of patients was rather small (n=7). Among the malignancies, breast cancer was seen in 33 patients (16.4%), followed by gastric cancer (4 patients, 2.0%). The incidence rate of breast cancer was 21.3% (13/61) for patients with adenomatous goiter, 16.2% (11/68) for those with adenoma, and 13.8% (9/65) for those with carcinoma. Among 33 patients with breast cancer and thyroid diseases, 3 had another malignancy, including gastric and colon cancer, and osteosarcoma.

The time of occurrence of breast cancer is summarized in Figure 1. Among 33 breast cancer patients, 17 underwent breast cancer and thyroid disease surgery at the same time; in 15, breast surgery preceded the thyroid disease surgery; and only one patients underwent breast surgery after receiving thyroid surgery. The mean period between the breast cancer surgery and the thyroid surgery was 3.2 years.

On the other hand, in the patients with breast cancer during the same period in our department, the frequency of the thyroid cancer was only 2.1% (7/340) (Table II).

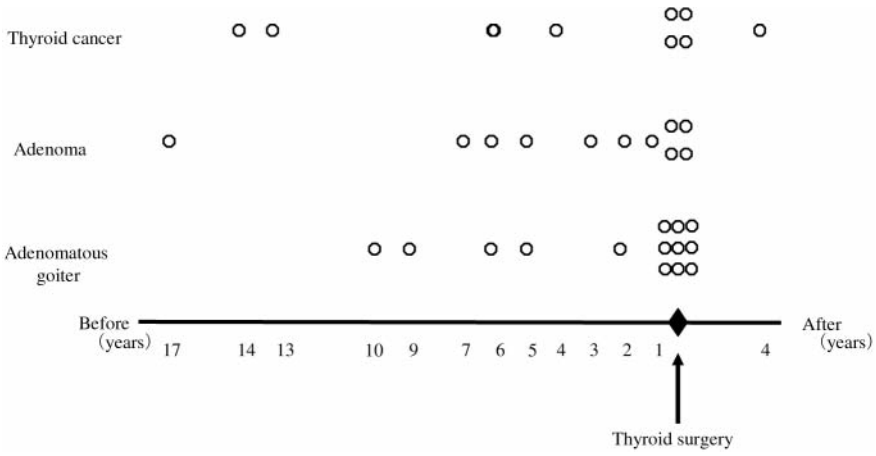

Figure 1. *Incidence time of breast cancer before and after thyroid surgery. Among 33 breast cancers, 17 were coincident with thyroid diseases, 15 proceded to thyroid surgery, and only one was after thyroid surgery. The mean period between the breast cancer surgery and the thyroid surgery was 3.2 years for overall: 3.9 years for thyroid cancer; 3.7 years for adenoma; and 2.3 years for adenomatous goiter.*

Discussion

The present study demonstrated the high incidence rate of breast cancer (16.4%) in patients who underwent thyroid surgery: 13.8% for thyroid cancer, 16.2% for adenoma and 21.3% for adenomatous goiter, but no incidence in the patients with chronic thyroiditis. The incidence of breast cancer was much higher than that of other malignancies: 2.0% of gastric cancer, and 1.0% of uterine and colorectal cancer (Table I). These results are compatible with the previous reports (4, 5, 9-11). Accordingly, it is suggested that thyroid diseases such as carcinoma, adenoma and adenomatous goiter might have an influence on the carcinogenesis of the breast.

On the other hand, the frequency of non-toxic goiter and thyroid swelling was high in breast cancer patients (13), and the incidence of autoimmune and non-autoimmune thyroid diseases were prevalent in breast cancer patients (3). However, in the present study, the frequency of thyroid cancer in the patients with breast cancer was not so high (2.1%) and was similar to that (1.8%) of gastric cancer, as shown in Table II. Previous reports also indicated that thyroid cancer is not prevalent in breast cancer patients, and that second non-breast malignancies in breast cancer might be affected by ethnic and racial influences: it was reported that stomach cancer was the most frequent second cancer in Japan (14), while in Philadelphia, USA, the most common types of non-breast second malignancies were skin cancer, followed by endometrial cancer and colorectal cancer (15). Furthermore, adjuvant therapies also have a great influence on the risk of second malignancies: post-mastectomy radiotherapy is indicated to be associated with an increased incidence of subsequent primary lung cancer (16, 17); some chemotherapeutic and endocrine-therapeutic agents are indicated to increase the risk of leukemia and endometrial malignancy (18, 19).

Table II. *Incidence of non-breast malignancies in breast cancer.*

Non-breast malignancies	
(−)	305 (89.7%)
(+)	35 (10.3%)
Their origin	
Thyroid	7 (2.1%)
Stomach	6 (1.8%)
Uterine	4 (1.2%)
Colon & rectum	4 (1.2%)
Bone	2 (0.6%)
Bile duct	2 (0.6%)
Malignant lymphoma	2 (0.6%)
Myeloma	2 (0.6%)
Kidney	1 (0.3%)
Lung	1 (0.3%)
Urinary bladder	1 (0.3%)

In the present survey, surgery for breast cancer was carried out simultaneously with thyroid surgery in half of the patients, while most of the remaining patients underwent breast surgery several years before thyroid surgery. These data suggest that breast cancer might affect thyroid tumorigenesis, but this possibility is contradicted by the present result that the incidence rate of thyroid cancer in breast cancer patients was much lower than that of breast cancer in patients with thyroid tumors. One possible mechanism responsible for the present result that breast cancer proceeded the thyroid tumors is that genesis of the thyroid tumors or tumor-like diseases and that of the breast cancer may occur at almost same time, but the growth of breast cancer might be faster than that of thyroid tumors or tumor-like diseases, because it is well known that the growth of thyroid tumors including carcinomas is very slow.

The mechanisms underlying the relationship between thyroid diseases and breast cancer is unclear; however, it was reported that triiodothyronine receptor was present in all primary and metastatic breast cancers at highly variable levels (20). Furthermore, specific alterations in the expression of thyroid hormone receptor genes was reported in a subset of human breast cancer (21). These reports suggest that thyroid hormone or its receptors may be involved in the generation or progression of breast cancer. On the other hand, it was reported that most thyroid neoplastic and normal tissues were positive for mRNA of both P450 aromatase and estrogen receptor, suggesting that the human thyroid gland has the potential for both estrogen synthesis and intracrine or paracrine estrogen responsiveness (22). This report also suggests a significant relationship between breast cancer and thyroid cancer.

As discussed above, the present results indicated an association of thyroid benign and malignant tumors and tumor-like diseases with breast cancer. However, it is also true that there are several controversial reports on the relationship between thyroid disorders and breast cancer. One of the possible reasons for this is that thyroid diseases are also affected by geographic and ethnic factors, such as idodine intake. Since the Shimane prefecture is located at the seaside, iodine intake of people living in Shimane may be higher than that of those of the urban area (no official survey). Therefore, a survey in the urban area may produce interesting results.

The present study demonstrated an association of thyroid benign and malignant tumors and tumor-like diseases with breast cancer, but the underlying reason for this is unclear.

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