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Thyroid Disease and Breast Cancer*)

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ABSTRACT

Of the 210 initial operations of breast cancer performed in our department during a period of January 1971 through March 1984, 13 cases (6.2%) associated with some thyroid disease including, functionally, 5 of hypothyroidism, 4 of hyperthyroidism and 4 of euthyroidism. Of the 13, 7 (53.8%) had the history of atomic-bomb exposure and 2 (15.7%) were of double cancer with thyroid cancer. In a histological classification of breast cancer, non-invasive carcinoma reached a high rate of 3/13 (23.1%) showing no significant difference with that of overall carcinoma. It will be important to give consideration to any development of breast cancer as following up the thyroid disease patients because of a high rate of its occurrence.

INTRODUCTION

Thyroid hormone is considered to influence, due to its depletion or excess, the metabolism of sex hormones such as androgen, estrogen, etc., prolactin and chemical mitogen, which may also have an effect on the risk of breast cancer. In fact, however, no definite views have been reported on the relation between the thyroid disease and the occurrence of breast cancer. Recently, we have studied breast cancer involving throid disease, the result of which will be reported herein including some consideration for useful reference.

MATERIALS AND METHODS

Of the 210 intial operation of breast cancer performed, in our depatment from January 1971 to March 1984, 13 cases (6.2%) were under treatment for thyroid disease or diagnosed as such. They were all female at an average age of 47.8±7.5 (37-65) years old at the time of operation, including 1 nullipara and 12 multipara cases. Their average menarche age was 13.0± 1.25 years old. Six cases of them in premenopause and 7 cases were postmenopause. The history of natural or artificial abortion was observed in 7 cases. Two cases (15.7%) were found having a family history of cancer within the second-degree relative. Anamneses other than thyroid disease were found in 7 patients, of which 4 had had genital bleeding such as due to myoma uteri, etc. Seven cases (53.8%) were atomic-bomb survivors with the atomic-bomb handbook granted. Only one case showed the obesity index exceeding 20%.

The above 13 cases being the subjected of this study were discussed for the histological classification of breast cancer, combined lesion, the status of thyroid disease, the course of treatment, etc.

RESULTS

Most of the 13 cases showed breast tumors located in the outer-upper portion (C portion) on the right in 5 cases, on the left in 7 cases and on both sides in 1 case, as shown in detail in Table 1.

In the tnm classification, 9 cases belonged to Stage I, 3 to Stage II, and 1 to Stage III, while in the histological classification[8], 3 cases of non-invasive carcinema were observed (23.1 %), the rate of which was higher than 7.1% of the overall breast cancer observed here (no

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Table 1. 13 Breast Cancer Cases Accompanied by Thyroid Disease

Case	Age	tnm (stage)*	Histological chassification*	Operation	Combined disease	Thyroid function
1	46	$t_1n_0m_0$ (Ⅰ)	Ⅰ-a (Tis)	ER	mastopathy	Hyperthyroid
2	40	$t_1n_0m_0$ (Ⅰ)	Ⅱ-a-1	R	mastopathy	Hypothyroid
3	47	$t_1n_0m_0$ (Ⅰ)	Ⅱ-a-2	ER	intraductal papilloma	Euthyroid
4	41	$t_2n_0m_0$ (Ⅰ)	Ⅰ-a (Tis)	R	papillomatosis	Hyperthyroid
5	65	$t_2n_{1\beta}m_0$ (Ⅱ)	Ⅱ-a-1	ER	(—)	Hyperthyroid
6	53	$t_2n_0m_0$ (Ⅰ)	Ⅱ-a-3	MR	mastopathy	Euthyroid
7	57	$t_2n_0m_0$ (Ⅰ)	Ⅱ-b-2	MR	(—)	Euthyroid
8	47	$t_2n_{1\beta}m_0$ (Ⅱ)	Ⅱ-a-1	MR	mastopathy	Hypothyroid
9	49	$t_1n_0m_0$ (Ⅰ)	Ⅰ-a (Tis)	MR	(—)	Hypothyroid
10	50	$t_1n_0m_0$ (Ⅰ)	Ⅱ-a-2	MR	mastopathy & fibroadenoma	Hypothyroid
11	42	L : $t_3n_{1\beta}m_0$ (Ⅲ) R : $t_3n_{1\alpha}m_0$ (Ⅲ)	Ⅱ-a-3	R MR	fibroadenoma	Hypothyroid
12	48	$t_1n_0m_0$ (Ⅰ)	Ⅱ-b-1	MR	intraductal papilloma	Euthyroid
13	37	$t_2n_{1\alpha}m_0$ (Ⅱ)	Ⅱ-a-3	MR	(—)	Hyperthyroid

* Based on General Rule for Clinical and Pathological Record of Mammary Cancer[8]

ER : extended radical mastectomy
R : radical mastectomy
MR : modified radical mastectomy

significant difference). Invasive carcinoma was observed in 10 cases, including 8 of the common type and 2 of the special type. Curative operation were performed in all 13 cases, including 6 by radical mastectomy and 7 by modified radical mastectomy. The combined lesion of mammary gland was oberved in 9 cases (69.2 %), including 4 of mastopathy, 2 of intraductal papilloma, 1 of papillomatosis, 1 of fibroadenoma and 1 of mastopathy+fibroadenoma. None of the 13 cases has indicated any sign of recurrence to date.

The thyroid diseases preceding breast cancer were functionally diagnosed before operation, resulting in 5 cases of hypothyroid, 4 of hyperthyroid and 4 of euthyroid.

The 5 cases of hypothyroid status included 2 of chronic thyroiditis, 2 after thyroidectomy for thyroid cancer (papillary adenocarcinoma) and 1 after ^{131}I internal dosing for hyperthyroidism (Table 2). Cases 1 and 2 are of chronic thyroiditis having been under administration of thyroid hormone for 2 and 9 years, respectively. Case 3 subjected to subtotal thyroidectomy for thyroid cancer (PAC) at the age of 28 has been administered with thyroid hormone for 10 years after it had radical neck dissection and expossed to ^{60}Co at the age of 30. Case 4 has been under administration of thyroid hormone for 20 years since its total thyroidectomy for thyroid cancer (PAC) at the age of 32. This case was of synchronized bilateral breast cancer, both of which were histologically classified as scirrhous carcinoma (Table 3). Case 5 was administered with ^{131}I based on the diagnosis of hyperthyroidism causing hypothyroid function at the age of 30 and has been under supplement of thyroid hormone for 20 years since then.

In the 4 cases of hyperthyroid status (Table 4), Cases 1 and 3 showed little effect of ^{131}I administered. Case 1 had been further administered with thiamazole (Mercazole®) for 18 months. Case 2 had been administered with thiamazole for 6 months from the age of 50, which had been suspended till the operation. Case 3 was administered with ^{131}I twice but encountered a recurrency at the age of 20. At the age of 30, subtotal thyroidectomy was performed. No sign of recurrence has been observed since then. Although diagnosed as hyperthyroidism at the age of 43, Case 4 had been

Table 2. Hypothyroid cases

Case	Age	Thyroid antibody Microzome antibody	Pathology	Therapy
1	47	(−) (+)	Chronic thyroiditis	Thyroid hormone for 2 years
2	49	(−) (−)	Chronic thyroiditis	Thyroid hormone for 9 years
3	40	(+) (+)	Cancer (PAC)	① Subtotal thyroidectowy ② ^{60}Co irradiation ③ Thyroid hormone for 10 years
4	42	(−) (−)	Cancer (PAC)	① Total thyroidectowy ② Thyroid hormone for 20 years
5	50	(+) (+)	Hyperthyroidism ^{131}I→Hypothyroidism	① ^{131}I per. os. ② Thyroid hormone for 20 years

PAC : Papillary adenocarcinoma

Table 3. Double cancer cases of Breast cancer and Thyroid cancer

Case	Age	Menopausal state	Atomic Bomb	Pathology		Radiation	Thyroid Supplement	Interval between two cancers
				Breast	Thyroid			
1	42	Post-menopausal	(−)	Ⅱ-a-3 PAC (bilateral)		(−)	20 years	21 years
2	40	Pre-menopausal	(+) 1.3 km	Ⅱ-a-1 PAC		(+) ^{60}Co 4800 rad	10 years	12 years

Table 4. Hyperthyroid cases

Case	Age	Thyroid antibody Microzome antibody	Pathology	Therapy
1	37	(−) (+)	hyperplasia	^{131}I Thiamazole for 18 months
2	65	unknown	hyperplasia	Thiamazole for 6 months
3	41	unknown	hyperplasia	^{131}I Subtotal thyroidectomy
4	46	unknown	hyperplasia	No therapy

left as it was due to its rejection of any treatment till its operation performed after it was placed under control.

All 4 cases of euthyroid status being of nodular goiter (benign) had been given no special treatment.

Table 5 shows the details of treatment for thyroid diseases given before operation, including

Table 5. Thyroid therapy before operation for breast cancer

Therapy	No of cases
Thyroid hormone Supplement	5
Anti-thyroid hormone drug	2
Thyroidectomy	3
Radiation ^{131}I	3
^{60}Co	1

5 cases of thyroid hormone supplement, 2 of anti-thyroid drug, 3 of thyroidectomy, 3 of ^{131}I administration, and 1 of ^{60}Co irradiation. As to the period of time from the diagnosis of thyroid disease till the operation of breast cancer, relatively many cases had spent a long period of time-7 cases over 10 years including 5 over 15 years.

DISCUSSION

Recently, an increasing number of reports has been made on thyroid diseases and development of breast cancer, especially, including those on a high risk of occurrence of breast cancer to patients of hypothyroid function. Ellerker (1956)[6] has defined a clear correlation existing between hypothyroidism and the breast cancer formation. Backwinkel et al. (1964)[2] have expressed the involvement of hypothyroidism in 18.5% of breast cancer patients. Hoffman et al. (1984)[10] have reported the occurrence of breast cancer to 1.8% of hypothyroidism patients within 1 to several years. Itoh et al. (1975)[11] have also reported about 5.4 times higher incidence of breast cancer in patients of Hashimoto's disease than that in ordinary Japanese. There has also been a report stating that breast cancer patients show a higher level of plasma TSH. Thus, it is considered that the so-called hypothalamic-pituitary-thyroid axis may have some correlation with the breast cancer risk. In another report, rat hypothyroidism models have been used in an experiment to prove their higher incidence of breast cancer by DMBA than that of normal rats[7,9]. However, a contrary report states a lower occurrence rate of breast cancer in the hypothyroid status[8,13]. Although we have obtained a rate of 5/13 (38.5%) of hypothyroid, it is difficult for us from the standpoint of department of surgery to investigate the overall hypothyroidism including primary hypothyroidism. Also, from the data showing a high rate of hypothyroidism among the atomic-bomb survivors, it is impossible to judge whether a correlation exists between hypothyroidism and breast cancer.

On the other hand, there is a report showing such a correlation with hyperthyroidism, especially with thyrotoxicosis[27]. However, more reports such as by Loeser (1954)[15] and Baker (1975)[3] fall in with the low incidence of breast cancer in hyperthyroidism. During the same period, the total 223 patients were definitely diagnosed as hyperthyroidism and treated therefor, of which 4 cases (1.8%) were observed as breast cancer.

There are reports on the relation between the supplement of thyroid hormone and the occurrence of breast cancer[12,26], in which the administered group showed significantly higher occurrence rate of breast cancer than the non-administered group. Especially, Kapdi (1976)[11] has reported that a significantly high occurrence rate of breast cancer was observed in a group of nullipara under supplement of thyroid hormone for more than 15 years. However, it is not considered definite because of many other reports stating that, statistically, there is no clear correlation existing between the supplement of thyroid hormone and the occurrence of breast cancer[10,14,20,21]. Also, in our department 5 of 13 cases are under administration of thyroid hormone, but its statistical analysis have not yet been obtained.

The so-called double cancer of thyroid and breast cancers draws our great interest also in considering the trigger of its occurrence. Chalstrey (1966)[5] and Ron et al. (1984)[21] have reported that a high rate of occurrence of breast cancer reaching 2.1-8.7% of thyroid cancer patients was observed. According to Ron et al., especially, a high breast cancer incidence is observed in follicular or papillo-follicular thyroid cancer. In our departmen't 336 thyroid cancer cases were observed during the same period, of which 2 cases (0.6%) resulted in breast cancer occurrence. Both were of papillary adenocarcinoma. In any case, it is also considered necessary to perform a precise examination of breast during the follow-up period after operation of thyroid cancer.

In the histological classification of breast cancer, 3 (23.1%) of the 13 cases were of non-invasive carcinoma. This rate was higher than 14 (6.7%) of 210 cases of total initial operations of breast cancer but no significant difference was shown. From the viewpoint of the specific nature of Hiroshima exposed to an atomic-bomb explosion, we particularly examined the atomic-bomb survivors with an atomic-bomb handbook granted. Of the total 210 cases of breast cancer, 60 (38.6%) had the atomic-bomb history, while of the 13 cases of breast cancer accompanied by thyroid diseases, 7 (53.8 %) had such history showing a higher rate but no significant difference. There are no definite data about this phenomenon pending further reports.

As described above, there have been no reports giving any decisive evidence as to the correlation between the occurrence of breast cancer and thyroid diseases. However, the breast cancer risk is not considered to be independent of the thyroid function from the facts that thyroid hormone changes the peripheral metabolism of sex hormone such as androgen, estrogen, etc.[14] and that the breast cancer incidence is low in Japan where high up-take of iodine as a precursor of thyroid hormone is observed[1,20,25]. Cerbon et al. (1981)[4] have reported that the triiodothyronine receptor was all positive as primary and metastatic breast cancer. Mittra et al. (1976)[18] have discussed thyroid autoantibody on some correlation between the English and Japanese breast cancer cases, although they showed no difference. There have also been many reports stating that the thyroid function test including T4, TSH, etc., is useful as a parameter for determining the prognosis of metastasis of breast cancer, etc.[2,16,19,22].

The relation of the thyroid function and hormone with the breast cancer risk is still under discussion. This problem may be solved through prospective studies in the future including functions of thyroid, pituitary, adrenal gland, etc., as well as the clinical findings of thyroid, breast and genital organ.

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