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Breast Cancer Followed by Second Malignancy*)

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ABSTRACT

Among 232 cases of operable breast cancer treated by the 2nd Department of Surgery, Hiroshima University School of Medicine, between 1963 and 1982, 7 cases (3.0%) were followed by a second primary malignancy. Eighty six percent of the second primary malignancies were found in digestive systems. The incidence of a second primary malignancy was 6.1%* (5/82) in the irradiated group and 1.3%* (2/150) in the non-irradiated group (*$P<0.05$). These results, however, cannot instantly be accepted because the second primary malignancy in 4 cases out of 5 in the irradiated group was found in the non-irradiated sites. Moreover, this was not a complete case control study. The effect of postoperative irradiation therapy on the incidence of second primary malignancy is expected to be elucidated by a prospective randomized study. Only 2 cases out of the 7 cases followed by a second primary malignancy could undergo curative operation and only one case survived for 5 years after the operation, which fact suggests the importance of early diagnosis and treatment.

INTRODUCTION

Multiple primary malignant tumors were firstly reported by Billroth[1] in 1879; and Warren & Gates[16] clearly defined them in 1932 as follows:

1) Each of tumors presents a definite picture of malignancy.
2) Each of tumors must be distinct.
3) The probability of one being a metastasis of other tumors must be excluded.

It has since been debated whether a primary malignant tumor may accelerate or suppress the occurrence of a second malignant tumor. Meanwhile, it was difficult to have a complete control of the cases in retrospective studies, and also the method of statistical analysis was unsatisfactory.

In 1969 Shoenberg[13] introduced Person-year analysis for data processing, and it is reported that the incidence of multiple malignant tumor was higher only in the combination of breast cancer and either colon cancer, ovarian cancer or endometrial cancer in comparison with control. As to the multiplicity of breast cancer and these cancers, hormonal factors[17,18] via dietary intake of lipid and genetic factors[7] have seriously been discussed. The recent progress of diagnostic techniques and treatment methods tends to improve patients' prognosis, but the westernizing of diet in Japanese patients may increase the incidence of second malignancy after mastectomy.

The progress of radiation therapy has greatly contributed to the recovery from malignant tumor. Nevertheless, radiation has some carcinogenic potentiality. Recently, the occurrence of second cancer after radiation therapy has increasingly been reported[11,12].

MATERIALS AND METHODS

For 20 years between 1963 and 1982, 232 breast cancer patients were admitted to the 2nd Department of Surgery, Hiroshima University School of Medicine, Japan. Among 232 patients, 10 patients (4.2%) had multiple primary

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Table 1. Breact Cancers Following First Primary Malignancy

Case	Age	Sex	F.H.	Sites & Pathology of 1st malignancy	Interval from breast cancer (years, months)	Prognosis from breast cancer
1	40	F	+	Thyroid PAC	12 y 0 m	7 y 8 m healthy
2	42	F	+	Thyroid FAC	20 y 8 m	2 y 5 m died
3	42	F	+	Skin Fibrosarcoma	9 m	4 y 1 m healthy

F.H. : Family history of cancer
PAC : Papillary Adenocarcinoma
FAC : Follicular Adenocarcinoma

Table 2. Breast Cancers Followed by Second Malignancy

Case	Age	Sex	F.H.	Adjuvant therapy for breast cancer	Sites & pathology of 2nd malignancy	Therapy for 2nd malignancy	Interval from breast cancer (years, months)	Prognosis from second cancer
1	41	F	−	RT, Chem	Stomach Adenocarcinoma	Cur.	4 y	8 m died
2	60	F	−	No	Lung Squamous cell Ca.	Cur.	4 y 2 m	5 y 10 m healthy
3	51	F	−	RT, Chem, Endo	Transverse colon No	Non-Cur.	5 y 10 m	2 m died
4	43	F	−	RT, Chem, Endo	Rectum Adenocarcinoma	Non-Cur.	6 y	4 m died
5	48	F	−	RT	Esophagus Squamous cell Ca.	Non-Cur.	6 y 8 m	8 m died
6	63	F	+	No	Stomach Adenocarcinoma	Non-Cur.	12 y 4 m	5 m died
7	45	F	+	RT	Gallbladder Adenoacanthoma	Non-Cur.	18 y 6 m	1 y 5 m died

F.H. : Family history of cancer
RT : Radiation therapy
Chem : Chemotherapy
Endo : Endocrine therapy
Cur. : Curative operation
Non-Cur. : Non-Curative operation

malignancy. Out of 10 cases, breast cancer preceded the second primary malignancy in 7 cases (3.0%). On the other hand, breast cancer followed the first primary malignancy in 3 cases (1.3%). Out of the 3 cases followed by breast cancer, 2 cases were thyroid cancers and the remaining one was fibrosarcoma of skin (Table 1). In this review, the prognosis and correlation with adjuvant therapy in the 7 cases of breast cancer followed by second primary malignancy were mainly discussed. The family history of cancer was followed up within relatives in the second degree. The patients were irradiated on their axillar region, parasternal region, supra-infraclavicular region and chest wall (over 5000 rads for each site). For chemotherapy, Tegafur was administered orally for over 2 months or over 10 mg of Mitomycin C was given by intravenous injection. The endocrine therapy adopted was androgen derivatives by intramuscular injection for over 2 months. In this study, Chi-square test was employed for statistical analysis.

RESULTS

Table 2 shows the 7 cases of breast cancer followed by second primary malignacy, all of them being female patients. Their average age at the time of diagnosis was 40.1 ± 8.5 years (range 41–63 years old). None of the patients

had histories of atomic bomb exposure. Two of 7 patients (28.6%) had family histories of cancer within their relatives in the second degree.

The average interval between the diagnosis of breast cancer and second malignancy was 8 years 3 months±5 years 4 months (range 4.0–18.5 years). The secondary sites were the stomach (2 cases), colo-rectum (2 cases) and esophagus, gallbladder, and lung (one case each). Eighty six % of secondary sites were found in the digestive system.

Curative operation was carried out for second malignancy only in two cases, one each for stomach cancer and lung cancer. Although the patient with lung cancer survived for 5 years after mastectomy, all other 6 patiens died of second malignancy within 8 months.

The histological stage of breast cancer was all relatively early according to the General Rules for Clinical and Record of Mammary Cancer edited by the Japan Mammary Cancer Society (Tis 1 case, Stage I 5 cases and Stage II 1 case as shown in Table 3).

Table 3. Pathological Diagnosis of Breast Cancer followed by Second Malignancy

Case	t	n	m*	stage*	Pathological* Classification
1	2	0	0	I	II-a-3
2	1	0	0	I	II-a-2
3	2	1β	0	II	II-a-3
4	2	0	0	I	II-a-2
5	1	0	0	Tis	I-a
6	1	0	0	I	II-a-2
7	2	0	0	I	II-a-3

* Histological diagnosis was based on General Rule for Clinical and Pathological Record of Mammary Cancer, 1982. The 6th edition, edited by Japan Mammary Cancer Society. Tokyo. (in Japanese)

The incidence of second malignancy was higher in the irradiated group (6.1%, 5/82) than in the non-irradiated group (1.3%, 2/150). The difference was statistically significant (Table 4). On the other hand, no statistically significant difference was found between the chemotherapy group (3.1%, 3/98) and the non-chemotherapy group (3.2%, 4/123) as shown in Table 5. Table 6 also shows no statistically significant difference in the incidence of second malignancy among three therapy groups (Radiation therapy group 6.1%, Chemotherapy group 3.1% and Radiation plus Chemotherapy group 7.3%).

Table 4. Incidence of Second Malignancy; Comparison between Radiation therapy group and Non-Radiation therapy group

Group	Total breast cancer patients	Breast cancer followed by second malignancy	
		Cases	Percent
Radiation therapy	82	5	6.1*
Non-Radiation therapy	150	2	1.3*

* Significant difference ($P<0.05$)

Table 5. Incidence of Second Malignancy; Comparison between Chemotherapy group and Non-Chemotherapy group

Group	Total breast cancer patients	Breast cancer followed by second malignancy	
		Cases	Percent
Chemotherapy	98	3	3.1*
Non-chemotherapy	124	4	3.2*

* No significant difference

Table 6. Incidence of Second Malignancy; Comparison between Radiation Therapy Group and Chemotherapy Group

Group	Total breast cancer patients	Breast cancer followed by second malignancy	
		Cases	Percent
Radiation therapy	82	5	6.1[a]
Chemotherapy	98	3	3.1[b]
Radiation plus Chemotherapy	41	3	7.3[c]

a-b, a-c, b-c: No significant difference

DISCUSSION

1) Frequency of occurrence:

Rosner[10] and Sommers[14] have reported fairly high incidence of multiple primary malignancy in breast cancer patients, while many others[2,3,17] have reported it to be around 3%, which is similar to the incidence found in our Department.

Herman[4] reported that the incidence of second primary malignancy was higher in bilateral breast cancer than in uni-lateral breast cancer (24.2% and 5.2% respectively). The data based on questionnaires[15] by the 38th meeting of the Japanese Research Society for Mammary Cancer showed that the incidence of second primary malignancy was 1.6% (764/47,005) among patients who had undergone mastectomy in Japan.

2) Second sites:

In Europe and America, breast cancer is often followed by colo-rectal, rectal, ovarian or endometrial cancer[2-5,13,17]. As to the close correlation of breast cancer with these cancers, Wynder et al.[17,18] have supported hormonal factors through dietary intake of lipids, while Lynch et al.[7] preferred genetic fastors.

In Japan, on the other hand, the data from the questionnaires[15] of the 38th meeting of the Japanese Research Society for Mammary Cancer, 1983, showed that the second primary malignancy was frequently found in the following sites: stomach 26.2%, colo-rectum 7.7%, uterine cervix 7.1% and thyroid 4.8%.

3) Correlation with radiation:

Penn[9] indicated from his data the cancers induced by radiation were often found in hematopoietic systems and thyroid, the latent intervals being 10 to 15 years on average. He also reported 19 cases, in which sarcomas in bone or soft tissue induced by radiation were detected in the irradiated sites after mastectomy.

In Japan, Mitsuhashi[8] and Kikuchi[6] et al. reported skin cancers and esophagus cancers induced by radiation after breast cancer surgery.

In our Department, the incidence of second malignancy was significantly higher in the irradiated group than in the non-irradiated group ($P<0.05$). However, this result cannot be instantly accepted because 86% of second cancers in the irradiated group were found in the sites unexposed to radiation. In addition, this study was not a complete case control study. Further investigation of the correlation between the incidence of second malignancy and the post-operative adjuvant therapy is expected to be made in a future prospective randomized study.

4) Post-operative follow-up:

The recent progress of diagnostic techniques and treatment methods for breast cancer has improved the prognosis for breast cancer patients, but that might mean the increasing opportunity of discovering second malignancy after mastectomy[4]. In the follow-up of post-operative breast cancer patients, it is not only necessary to be careful of relapse or metastasis, but also earlier diagnosis and treatment of second malignancy will be essential.

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