Jpn. J. Cancer Res. **92**, 1–8, January 2001

Second Primary Cancers Following Breast Cancer in the Japanese Female Population

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To assess the risk of developing second primary cancers following breast cancer in Japanese females, we performed a retrospective cohort study of 2786 patients who were newly diagnosed with breast cancer at our hospital between 1970–1994, until the end of 1995 (average follow-up period, 8.6 years). The expected number of each second primary cancer was calculated by multiplying the number of appropriate person-years at risk by the corresponding age- and calendar period-specific cancer incidence rates for women obtained from the Osaka Cancer Registry. One hundred and seventeen patients developed a second primary cancer other than subsequent breast cancer, yielding an observed-to-expected ratio (O/E) of 1.3 [95% confidence interval (CI)=1.1–1.6]. The risk for developing a second primary cancer was significantly elevated during the first year following the diagnosis of breast cancer, and decreased with the passage of time to unity. A significantly increased risk was noted for the development of ovarian cancer (O/E=2.4, 95% CI=1.0–4.6), thyroid cancer (O/E=3.7, 95% CI=1.5–7.6) and non-Hodgkin's lymphoma (NHL) (O/E=3.5, 95% CI=1.4–7.1) among the breast cancer patients compared with the general population. Patients who received hormonal therapy as the breast cancer treatment showed a significantly increased risk for ovarian cancer (O/E=5.5, 95% CI=1.8–12.9). Patients who received chemotherapy as the breast cancer treatment had an increased risk for NHL (O/E=5.0, 95% CI=1.6–11.6). These findings indicate that Japanese female patients with breast cancer had a 30% higher risk of developing a second primary cancer than the general population, the higher risk being manifested in the early period following the diagnosis of breast cancer. Medical surveillance of breast cancer patients for NHL, as well as for ovarian cancer and thyroid cancer, is required.

Key words: Breast cancer — Second primary cancer — Japanese — Non-Hodgkin's lymphoma — Cohort study

The incidence of primary breast cancer among Japanese females has increased by 120% between 1975 and 1994.[1, 2] At the same time, the survival rate of breast cancer patients in the Japanese population has increased: the relative 5-year survival rate of breast cancer patients increased from 68% in 1975–77 to 81% in 1990–92.[3, 4] As a result, more women are surviving breast cancer to face the possibility of second cancers in our country.

Several studies of multiple primary cancers in patients with breast cancer have been conducted in Western countries using population- and hospital-based data. These studies have shown that breast cancer patients have an increased risk for second cancers of the contralateral breast,[5–10] endometrium,[6, 7, 10, 11] ovary,[6, 7, 10, 12, 13] colon,[6, 7] lung,[10, 14] skin,[6, 8, 10, 13] thyroid gland,[6, 7, 10, 15] and leukemia.[7, 13, 16] The development of a second cancer may be affected by genetic, hormonal or environmental risk factors common to the first and the second cancer,[17] or it may be therapy-related, for example, tamoxifen usage and the occurrence of endometrial cancer.[18–20] However, these findings can not be uniformly applied to the Japanese population because there may be different environmental and endogenous background factors between Western breast cancer patients and Japanese breast cancer patients.

Murakami *et al.*[21] reported the risk of second primary cancers among female patients with breast cancer diagnosed between 1965 and 1983 who were followed until 1984, using population-based data in Japan. The female breast cancer patients showed increased cancer risk of the contralateral breast, buccal cavity, stomach, colon and thyroid gland. Improvements in breast cancer survival seen during the past decade may have influenced the potential risk of the development of a second cancer. Therefore, we conducted a retrospective cohort study to assess the risk of second primary cancer following the diagnosis of breast cancer in Japanese female patients who were diagnosed with breast cancer one decade after the study period of Murakami *et al.*[21] A case-series study was undertaken in patients whose second cancer entailed significantly increased risk in our cohort.

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PATIENTS AND METHODS

Between January 1970 and December 1994, 3315 female patients were newly diagnosed with invasive primary breast carcinoma (ICD-9 position 174) at Osaka Medical Center for Cancer and Cardiovascular Diseases, as identified through the hospital cancer registry. This registry has continuously collected basic demographic data and medical information on all patients diagnosed as having cancer at this hospital by trained medical staff since 1964. The vital status of the registered cases is routinely confirmed by checking against the hospital records and by routinely referring to the resident registries of local municipal offices and obtaining follow-up data from the Osaka Cancer Registry (OCR; the population-based cancer registry in Osaka Prefecture, which had a population of 8.8 million in 1995). Detailed procedures and the validity of the OCR have been described elsewhere.[22, 23] Lost-to-follow-up at Osaka Medical Center has been kept to less than 1% at 5 and 10 years after diagnosis. Data on the initial treatment modalities for the primary breast cancer (chemotherapy, hormonal therapy and radiation therapy) were obtained from the hospital registry. Of the patients with breast cancer who were diagnosed at Osaka Medical Center during this period, 455 resided outside of Osaka Prefecture, 72 were younger than 20 years or older than 75 years, and two had simultaneous primary cancers (stomach cancer in one and colon cancer in one) diagnosed on the same date as breast cancer. Excluding these patients, the remaining 2786 patients were included in the study.

In order to examine the incidence of second primary cancers, a computer file of the study subjects was linked to the file of the OCR. In the OCR, second primary cancers are identified based on the rules suggested in the ICD-O second edition.[24] Cases with subsequent diagnoses of breast cancer were not considered as showing a second primary cancer, since these may have represented a progression of the initial malignancy. Detailed clinical information that was not abstracted in the registry, was obtained from the medical records.

The number of person-years of observation was defined as the number of years from the date of breast cancer diagnosis to the date of diagnosis of the second primary cancer, date of death, or the closing date of the study (December 31, 1995), whichever occurred first. The observed number of second primary cancer cases was compared with the expected number, which was calculated by applying sex-, 5-year age-, 5-year calendar time, and site-specific incidence rates among the general population of Osaka, which were prepared by the OCR. Statistical tests of the ratio of observed-to-expected numbers (O/E ratio) were based on the assumption that the observed number followed a Poisson distribution. If the lower limit of the 95% confidence interval (CI) was greater than 1.00, the O/E ratio was considered to be statistically significant ($P<0.05$). Cox proportional hazard analysis was used to obtain adjusted rate ratio estimates, with 95% CI, for the association between each treatment modality and the occurrence of a second primary cancer. In the analysis, chemotherapy, hormonal therapy and radiation therapy for primary breast cancer, and age at diagnosis were included as variables.

RESULTS

The 2786 female patients with primary breast cancer contributed 24 025 person-years of observation. The mean age at the time of diagnosis of breast cancer was 50.9 years and the mean length of follow-up was 8.6 years (range, 0.1 to 25.7 years). Of the 2786 patients, 117 were subsequently diagnosed with a second primary cancer, compared to an expected number of 90.1 cases (O/E=1.3, 95% CI=1.1–1.6) (Table I). Stomach cancer comprised one-fifth of all of the second primary cancers (O=24), but the risk for developing stomach cancer remained at an insignificant level. Compared with the general population, the breast cancer patients had a significantly increased risk for ovarian cancer (O/E=2.4, 95% CI=1.0–4.6), thyroid cancer (O/E=3.7, 95% CI=1.5–7.6) and non-Hodgkin's lymphoma (NHL) (O/E=3.5, 95% CI=1.4–7.1). The risk of cancer of the uterus corpus was elevated in the breast cancer patients, although it remained at an insignificant level. The subjects aged 20–49 years at the time of diagnosis of breast cancer had a significantly increased risk of thyroid cancer (O/E=4.8, 95% CI=1.3–12.3) and NHL (O/E=6.3, 95% CI=1.7–16.1). The patients aged 50–74 years at the time of diagnosis of breast cancer had a significantly increased risk for developing a second primary cancer (Table I).

In the breast cancer patients, the risk for developing a second primary cancer was significantly elevated within 1 year after the diagnosis of breast cancer (O/E=3.0, 95% CI=1.9–4.6), and it decreased with the passage of time (Table II). Among the breast cancer patients, the highest risk for developing colon cancer or thyroid cancer was observed within 1 year after the diagnosis of breast cancer (colon cancer, O/E=5.0, 95% CI=1.0–14.5; thyroid cancer, O/E=28.7, 95% CI=9.2–66.9). These risks decreased beyond 1 year following the diagnosis of breast cancer to unity. The risk for developing NHL rose at 1 to 4 years following the diagnosis of breast cancer (O/E=6.9, 95% CI=1.9–17.7), and continued to be higher than that in the general population beyond 5 years following the diagnosis of breast cancer, although it was at an insignificant level (Table II).

Among the 1384 subjects who received chemotherapy for the primary breast cancer, 58 developed a second primary cancer, yielding an O/E ratio of 1.3 (95% CI=1.0–

Table I. Observed (O) and Expected (E) Numbers of Second Primary Cancer among Female Patients with Breast Cancer

Cancer type or site	Total			Age at diagnosis of breast cancer					
	2786[a] 50.9 yrs[b] 24 025 P-Y[c]			20–49 yrs 1407[a] 42.8 yrs[b] 13 245 P-Y[c]			50–74 yrs 1379[a] 59.2 yrs[b] 10 780 P-Y[c]		
	O	O/E	(95% CI)	O	O/E	(95% CI)	O	O/E	(95% CI)
All second primary cancers except breast cancer	117	1.3*	(1.1–1.6)	37	1.4	(0.9–1.9)	80	1.3*	(1.0–1.6)
Stomach	24	1.2	(0.8–1.8)	10	1.6	(0.8–3.0)	14	1.0	(0.5–1.7)
Colon	13	1.5	(0.8–2.5)	1	0.4	(0.1–2.2)	12	1.9	(0.9–3.4)
Rectum	5	1.0	(0.3–2.4)	1	0.6	(0.1–3.5)	4	1.3	(0.3–3.2)
Primary liver cancer	6	1.0	(0.4–2.1)	0	—		6	1.2	(0.5–2.7)
Biliary tract	5	1.2	(0.4–2.9)	1	1.2	(0.1–6.7)	4	1.2	(0.3–3.2)
Pancreas	4	1.1	(0.3–2.7)	3	3.8	(0.8–11.1)	1	0.3	(0.0–1.9)
Lung	12	1.4	(0.7–2.4)	1	0.5	(0.1–2.9)	11	1.6	(0.8–2.9)
Uterus cervix	6	0.7	(0.3–1.5)	2	0.5	(0.1–1.6)	4	0.9	(0.3–2.3)
Uterus corpus	4	1.9	(0.5–4.9)	0	—		4	3.6	(0.9–9.2)
Ovary	8	2.4*	(1.0–4.6)	3	1.9	(0.4–5.6)	5	2.7	(0.9–6.3)
Bladder	4	3.0	(0.8–7.8)	1	3.9	(0.1–21.8)	3	2.8	(0.6–8.2)
Thyroid	7	3.7**	(1.5–7.6)	4	4.8*	(1.3–12.3)	3	2.8	(0.6–8.1)
Non-Hodgkin's lymphoma	7	3.5*	(1.4–7.1)	4	6.3**	(1.7–16.1)	3	2.2	(0.4–6.3)

a) Number of study subjects.
b) Mean age at the time of diagnosis of breast cancer (yrs).
c) Person-years (P-Y) of observation (yrs).
* $P<0.05$, ** $P<0.01$.
The other second primary cancers that are not shown in Table I are: cancer of the buccal cavity and pharynx (2 patients), esophageal cancer (1), cancer of small intestine (1), cholangiocellular carcinoma (1), cancer of maxillary sinus (1), cutaneous melanoma (1), cancers of kidney and pelvis (2), brain tumors (2), and leukemia (1).

Table II. Observed (O) and Expected (E) Numbers of Second Primary Cancer among Female Patients with Breast Cancer According to the Number of Years between the Diagnosis of Breast Cancer and Diagnosis of the Second Primary Cancer

Cancer type or site	0 yr–		1–4 yrs		5–9 yrs		10 yrs–	
	O	O/E	O	O/E	O	O/E	O	O/E
All second primary cancers except breast cancer	22	3.0**	35	1.3	32	1.2	28	0.9
Stomach	4	2.2	4	0.6	5	0.9	11	1.7
Colon	3	5.0*	3	1.3	4	1.6	3	0.9
Primary liver cancer	1	2.4	2	1.2	2	1.1	1	0.4
Biliary tract	1	3.9	1	1.0	1	0.9	2	1.2
Lung	1	1.7	5	2.2	3	1.2	3	0.9
Uterus cervix	3	2.8	2	0.6	1	0.4	0	—
Uterus corpus	1	5.4	2	3.0	0	—	1	1.7
Ovary	2	6.3	2	1.8	3	3.0	1	1.0
Bladder	0	—	2	5.9	2	5.3	0	—
Thyroid	5	28.7**	2	3.3	0	—	0	—
Non-Hodgkin's lymphoma	0	—	4	6.9**	1	1.7	2	2.8

* $P<0.05$, ** $P<0.01$.

1.7) (Table III). Those who had received chemotherapy had a significantly increased risk of developing NHL (O/E=5.0, 95% CI=1.6–11.6). Among the 1042 subjects who received hormonal therapy for the primary breast cancer, 33 cases developed a second primary cancer, yielding an O/E ratio of 1.6 (95% CI=1.1–2.2). These patients had a

Table III. Observed (O) and Expected (E) Numbers of Second Primary Cancer among Female Patients with Breast Cancer According to the Type of Treatment of Breast Cancer

Cancer type or site	Chemotherapy (+) 1384[a] 50.6 yrs[b] 12 431 P-Y[c]			Hormonal therapy (+) 1042[a] 51.9 yrs[b] 6321 P-Y[c]			Radiation therapy (+) 361[a] 50.1 yrs[b] 2488 P-Y[c]		
	O	O/E	(95% CI)	O	O/E	(95% CI)	O	O/E	(95% CI)
All second primary cancers except breast cancer	58	1.3*	(1.0–1.7)	33	1.6*	(1.1–2.2)	10	1.2	(0.6–2.1)
Stomach	14	1.4	(0.8–2.4)	8	1.8	(0.8–3.5)	1	0.5	(0.1–2.8)
Colon	5	1.2	(0.4–2.7)	5	2.2	(0.7–5.2)	0	—	
Primary liver cancer	1	0.3	(0.0–1.8)	1	0.6	(0.1–3.5)	0	—	
Biliary tract	4	2.1	(0.6–5.3)	2	2.2	(0.2–7.8)	0	—	
Lung	8	1.9	(0.8–3.8)	4	2.0	(0.5–5.0)	0	—	
Uterus cervix	3	0.7	(0.2–2.0)	0	—		0	—	
Uterus corpus	3	2.7	(0.6–8.0)	1	1.8	(0.1–9.7)	0	—	
Ovary	5	2.8	(0.9–6.6)	5	5.5**	(1.8–12.9)	1	3.0	(0.1–16.7)
Bladder	2	3.3	(0.4–11.8)	1	3.5	(0.1–19.4)	2	16.7*	(1.9–60.3)
Thyroid	1	1.0	(0.1–5.7)	1	2.0	(0.1–11.0)	1	5.5	(0.1–30.6)
Non-Hodgkin's lymphoma	5	5.0**	(1.6–11.6)	2	4.0	(0.4–14.2)	1	5.3	(0.1–29.7)

a) Number of study subjects who received the indicated treatment for breast cancer.
b) Mean age at the time of diagnosis of breast cancer (yrs).
c) Person-years (P-Y) of observation (yrs).
* $P<0.05$, ** $P<0.01$.

Table IV. Treatment Factors Associated with the Development of Second Primary Cancer in Female Patients with Breast Cancer According to Cox Proportional Hazards Analysis

Type or site of second primary cancer	Chemotherapy (+) RR (95% CI) *P* value	Hormonal therapy (+) RR (95% CI) *P* value	Radiation therapy (+) RR (95% CI) *P* value
All second primary cancers except breast cancer	1.04 (0.70–1.55) *P*=0.83	0.94 (0.61–1.47) *P*=0.79	0.73 (0.38–1.40) *P*=0.34
Stomach	1.41 (0.59–3.39) *P*=0.44	1.24 (0.49–3.12) *P*=0.65	0.32 (0.04–2.36) *P*=0.26
Ovary	0.88 (0.17–4.42) *P*=0.87	4.85 (0.86–27.27) *P*=0.07	1.23 (0.15–10.34) *P*=0.85
Non-Hodgkin's lymphoma	2.65 (0.47–14.95) *P*=0.27	0.68 (0.11–4.09) *P*=0.68	1.01 (0.11–9.23) *P*=0.99

RR, rate ratio; CI, confidence interval.
In this analysis, chemotherapy (+/−), hormonal therapy (+/−), radiation therapy (+/−) and age at diagnosis were included.
Age was used as a consecutive variable.

significantly increased risk of developing ovarian cancer (O/E=5.5, 95% CI=1.8–12.9). The patients with breast cancer who had received radiation therapy had a significantly increased risk for bladder cancer (O/E=16.7, 95% CI=1.9–60.3) (Table III).

Table IV presents the association between chemotherapy, tamoxifen use or radiation therapy, and the occurrence of all second primary cancers, stomach cancer, ovarian cancer and NHL in Cox proportional hazards analysis. There were no statistically significant associations

Table V. Characteristics of the Breast Cancer Patients Who Subsequently Developed NHL

No.	Breast cancer				NHL			
	Age (yrs)	Stage	Chemo/ Hormonal therapy	Radiation therapy	Interval (months)	Site	Stage[a)]	Histology
1.	66	lymph+	CPA 8.4 g MMC 30 mg TF 50.4 g TAM 1.7 g	—	26	paranasal sinus	I	DSC
2.	54	lymph+	CPA 5.6 g MMC 30 mg TF 33.6 g TAM 1.1 g	—	44	stomach	II	F
3.	46	localized	CPA 10.5 g	—	23	spleen, bone marrow	IV	RCS
4.	44	lymph+	CPA 39.2 g MMC 44 mg 5-FU 4500 mg	—	62	stomach	not available	
5.	43	lymph+	CPA 12.6 g MMC 30 mg	(β)16 500 rad	190	stomach	II	DSC
6.	45	localized	(surgical resection only)	—	123	not available		
7.	53	lymph+	not available	not available	16	not available		

lymph+, lymph node metastasis; CPA, cyclophosphamide (PO); MMC, mitomycin C (Nos. 1, 2, 4, IM; No.4, injection from internal mammary artery); TF, tegafur (PO); 5-FU, 5-fluorouracil (injection from internal mammary artery); TAM, tamoxifen (PO); DSC, diffuse small cleaved cell; F, follicular type; RCS, reticulum cell sarcoma.
a) Ann Arbor staging classification.

between these three treatment modalities and the occurrence of the second primary cancers mentioned above, although a higher rate ratio for ovarian cancer in patients treated by hormonal therapy, and higher rate ratio for NHL in patients treated by chemotherapy were noted (Table IV).

Table V shows the clinical findings of the seven female breast cancer patients who subsequently developed NHL. We found information on the treatment for primary breast cancer in six patients (Nos. 1–6). Patient 7 did not undergo treatment at our hospital. Of the six patients, five (Nos. 1–5) had received chemotherapy, and the remaining one had undergone surgical resection only (No. 6). Two patients (Nos. 1, 2) had received tamoxifen. Patient 5 had received both chemotherapy and radiation therapy. Cyclophosphamide had been used in all five patients treated by chemotherapy. The median duration between the diagnosis of breast cancer and the diagnosis of NHL was 44 months (range, 16 to 190 months). Information on the clinical and histological findings of NHL was obtained on four of the seven subjects (Nos. 1, 2, 3, 5). Three of five patients for whom we could specify the subsite of NHL, developed NHL in the stomach (Nos. 2, 4, 5). Based on the Ann Arbor staging classification, two patients (Nos. 2, 5) had stage II NHL, one patient (No. 3) had stage IV, and one patient (No. 1) showed stage I localized in the paranasal sinus.

DISCUSSION

In our retrospective-cohort study of female patients who were diagnosed with breast cancer at Osaka Medical Center, female breast cancer patients diagnosed in 1970–1994 have had a 30% higher risk of developing a second primary cancer than the general population. The overall risk of developing a second primary cancer at any site (except second breast cancer), was the highest within 1 year after the diagnosis of breast cancer, and it decreased with the passage of time. Significantly increased risks for second colon and thyroid cancer were noted only within 1 year after the diagnosis of breast cancer. This finding indicates that the probability of detecting early cancers in patients with breast cancer soon after its diagnosis, was higher than that in the general population.

Contrary to our expectations drawn from the findings of previous studies conducted in Western countries,[6, 7, 10, 11] a significantly increased risk for second cancer of the uterus corpus was not observed. A significantly increased risk for cancer of the uterus corpus was also not observed in the breast cancer patients who received hormonal therapy as the initial treatment. The absence of these significantly elevated risks may be partially attributed to the small number of such tumors, due to the lower incidence of endometrial cancer in Japan than in Western countries. Katase *et al.*[25] reported that the relative risk of endometrial cancer according to total dose of tamoxifen exposure, was 1.00 in patients with breast cancer who underwent a pelvic examination and cytologic and/or histologic screening of the cervix and endometrium every year. They questioned whether the increase in the incidence of endometrial carcinoma in tamoxifen-treated breast carcinoma patients in prior research studies represented a true increase or resulted from detection bias; this was not clear because tamoxifen use potentially induces gynecological symptoms.[25] Our data, however, show that the risk of cancer of the uterus corpus among breast cancer patients diagnosed at 50–74 years of age, was 3.4 times higher than that in

the general population (95% CI=0.9–9.2). This may indicate that Japanese patients who are diagnosed with breast cancer postmenopause should be carefully checked for endometrial cancer.

The risk of developing second primary ovarian cancer was significantly higher in the breast cancer patients than in the general population. The risk was as high as 5.5 times that in the general population, among the breast cancer patients who received hormonal therapy. Our multiple regression analysis showed a similar result, in that the relative risk for ovarian cancer among the breast cancer patients who underwent hormonal treatment was higher than that in the general population at a marginally significant level (P=0.07). The increased risk of ovarian cancer in the breast cancer patients in comparison with the general population may be due to shared reproductive risk factors[26–28]; inherited susceptibility, such as having a *BRCA1* mutation[29, 30]; or iatrogenic effects. Further studies are needed to clarify the relationship between treatment factors and the development of second primary ovarian cancer among the Japanese, although a positive relationship has not yet been identified in Western populations.

Our data clearly demonstrated that the breast cancer patients had an increased risk of developing second NHL. The likelihood of detecting NHL at the early stage in the breast cancer patients seems to be higher than that in the general population because of the intensive clinical surveillance. However, the median duration between the diagnosis of breast cancer and the diagnosis of subsequent NHL was relatively long (44 months, range 16 to 190 months), and the distribution of the clinical stage of NHL among the patients in our study did not shift to an earlier stage from that among the NHL patients in the general population of Japan.[31] Moreover, since the study subjects were patients who were newly diagnosed with breast cancer regardless of a pre-existing hematopoietic or immunogenic disorder at our hospital, it is difficult to consider that our subjects had a substantially higher risk of developing NHL than breast cancer patients in Japan as a whole. It is therefore unlikely that the increased risk of NHL revealed in this cohort, resulted solely from detection bias or selection bias.

To our knowledge, there were no apparent environmental or endogenous shared risk factors to explain such a high incidence of NHL among the breast cancer patients. A number of studies have observed an increased incidence of treatment-related leukemias following chemotherapy with intravenous alkylating agents,[32] but not an increased incidence of second NHL in patients with solid cancer who were treated with intravenous alkylating agents. In this study, among those who underwent chemotherapy, there was a 5.0-fold increased risk of developing NHL in comparison with that in the general population. Oral cyclophosphamide was used in all five patients treated by chemotherapy who subsequently developed NHL. Three of five patients for whom we could specify the subsite of NHL, developed NHL in the stomach. In contrast, there was only one patient who subsequently developed leukemia (Table I, footnote). These findings may support the hypothesis that oral cyclophosphamide use was associated with the development of NHL in the stomach, resulting in the increased risk of NHL in patients with breast cancer who underwent chemotherapy. Murakami *et al.*[21] reported the risk of second primary cancers among 9503 female breast cancer patients diagnosed between 1965–1983 using population-based data in Japan. They did not find an increased risk of NHL in this cohort. This discrepancy from our result may be due to the different treatment regimens for the breast cancer in the different source populations (population-based study vs. single hospital-based study) and the different period of the diagnosis. To clarify these speculations, we need more detailed information on treatment regimens, together with the total dose of each anti-cancer drug at the individual level.

In the present analysis, we assumed that a patient was alive at the end of 1995 if we had no information on his/her death or on the occurrence of a second primary cancer. The number of person-years at risk was overestimated and this leads to a larger number of expected second primary cancer cases. On the other hand, information on those who moved out of Osaka Prefecture and developed a second primary cancer at another location was not obtained. As a result, the O/E ratios would have been underestimated in comparison with actual figures.

In summary, our retrospective cohort study indicates that Japanese female patients with breast cancer have a 30% higher risk of developing a second primary cancer than the general population, and the higher risk was apparent in the early period following the diagnosis of breast cancer. The increased risk of developing NHL can not be explained solely by the methodological limitations. Further analytical studies of NHL following breast cancer are needed to assess the roles of antecedent chemotherapy and other etiologic influences.

ACKNOWLEDGMENTS

This study was financially supported, in part, by a grant for the New 10-Year Strategy for Cancer Control, Prevention of Cancer, from the Ministry of Health and Welfare of Japan. We wish to express our gratitude to the Osaka Medical Association for providing access to registry data. We also wish to thank Ms. Yasue Kotani and Ms. Ikuko Matsuo for their technical assistance.

(Received July 25, 2000/Revised September 27, 2000/Accepted October 2, 2000)

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