The Incidence of Subsequent Endometrial Carcinoma with Tamoxifen Use in Patients with Primary Breast Carcinoma

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BACKGROUND. Tamoxifen commonly is used as adjuvant therapy for all stages of breast carcinoma. However, several studies have suggested an association between the use of tamoxifen in breast carcinoma patients and the subsequent development of endometrial carcinoma. The objective of this study was to determine the relation between long term tamoxifen usage and the risk of endometrial carcinoma in patients with breast carcinoma and to determine whether the increase in the cumulative incidence of endometrial carcinoma observed in previous studies is a true increase.

METHODS. Eight hundred and twenty-five patients with primary breast carcinoma who underwent annual gynecologic examination and cancer screening were reviewed. None of the patients had undergone hysterectomy or received any prior estrogen replacement therapy. These patients underwent a pelvic examination and cytologic and/or histologic screening of the cervix and endometrium every year even if they had no gynecologic symptoms. The dose of tamoxifen, length of tamoxifen treatment, and potential confounding variables were recorded. The relative risk of subsequent endometrial carcinoma in patients with primary breast carcinoma was analyzed by the Cox proportional hazards model.

RESULTS. Thirteen of the 825 patients developed a subsequent endometrial carcinoma. The cumulative incidence of endometrial carcinoma was 1.58%. Four of 13 patients who subsequently developed endometrial carcinoma received tamoxifen and 9 had not received tamoxifen. The relative risk of endometrial carcinoma by total dose of tamoxifen exposure was 1.0001 ($P = 0.0145$). There was no statistically significant correlation between the cumulative dose of tamoxifen or the length of tamoxifen treatment and the histologic type and grade of endometrial carcinoma. In addition, there was no statistical difference in the prognosis of endometrial carcinoma between the patients who received tamoxifen and patients who did not.

CONCLUSIONS. The results of this study show that tamoxifen use does not appear to increase the incidence of subsequent endometrial carcinoma in patients with primary breast carcinoma who underwent annual screening for gynecologic carcinoma. ***Cancer* 1998;82:1698–703.** © *1998 American Cancer Society.*

KEYWORDS: tamoxifen, breast carcinoma, secondary carcinoma, endometrial carcinoma.

Tamoxifen is being used increasingly as adjuvant therapy for breast carcinoma. However, several studies have suggested an association between the use of tamoxifen in breast carcinoma patients and the subsequent development of endometrial carcinoma.[1–3] In 1996, the International Agency for Research on Cancer concluded that there is sufficient evidence in humans that the carcinogenicity of tamoxifen

is increasing the risk of endometrial carcinoma in breast carcinoma patients. We designed this study to assess the carcinogenic risks associated with the long term use of tamoxifen in breast carcinoma patients.

METHODS

During the period between January 1980 and December 1990, 4734 Japanese primary breast carcinoma patients were diagnosed and treated at the Department of Breast Surgery, Cancer Institute Hospital, Otsuka, Tokyo, Japan. In these 4734 primary breast carcinoma patients ages 20–91 years (mean ± standard deviation, 50.74 ± 11.17 years), we found 825 of these patients underwent annual gynecologic examinations and screening for gynecologic carcinoma after the diagnosis of breast carcinoma. They began to undergo screening for gynecologic carcinoma of their own initiative. All 825 patients had not undergone hysterectomy and had not received any prior estrogenic hormone replacement therapy. They underwent a pelvic examination and cytologic and/or histologic screening of the cervix and endometrium every year, even if they had no symptoms.

Screening for endometrial carcinoma was performed by endometrial aspiration cytology. If the patient reported symptoms (bleeding, discharge, etc.) or if there were cytologic abnormalities, endometrial curettage was performed.

The files of all 825 patients, including outpatient clinic records, inpatient records, and pathologic reports, were reviewed. Daily dose and duration of tamoxifen therapy were recorded as well as potential confounding variables including diabetes mellitus, hypertension, age, body mass index, age at menarche, gravity, age at menopause, menstruation status, and family history of breast or gynecologic carcinoma. The patients were followed for 5–16 years (median, 8.8 years; average, 9.2 years). All patients who had not developed endometrial carcinoma underwent cytologic and/or histologic screening of the endometrium in 1995, and it was confirmed that they did not have endometrial carcinoma.

The information included in this study was obtained from patient records that were collected at the Cancer Institute Hospital over a 10-year period and were analyzed retrospectively outside a clinical trial setting. Informed consent for publication was not obtained from the individual subjects whose data was included in the retrospective analysis. This was not considered necessary because the data presented for publication are largely epidemiologic and do not contain identifying details that would infringe on the patients' rights to privacy.

The International Federation of Gynecology and Obstetrics (FIGO) staging system[4] was used for staging of endometrial carcinoma. Two groups, a tamoxifen-treated and a nontreated group, were compared by chi-square analysis and analysis of variance (ANOVA). Relative risks of variables were observed using the Cox proportional hazards model. The difference in prevalence of the histologic type and grade of endometrial carcinoma in the two groups was examined by the test of independence. Prognosis of endometrial carcinoma in patients with breast carcinoma was analyzed by the Kaplan–Meier method. Statistical analysis was performed using the SPSS statistical package (SPSS Inc., Tokyo, Japan). Probability values of < 0.05 were regarded as statistically significant.

RESULTS

The test group was comprised of 825 patients with primary breast carcinoma and with their uterus in situ. None of these patients had received any estrogenic hormone replacement therapy. The patients were divided into two groups based on exposure to tamoxifen. Profiles of the patients and potential confounding variables are shown in Table 1. Two hundred and seventy-nine of 825 patients received tamoxifen as adjuvant therapy for breast carcinoma, whereas 546 had not received tamoxifen. All 279 of the tamoxifen-treated patients received tamoxifen for > 1 year. In the tamoxifen-treated patients, 118 were postmenopausal when they were diagnosed with breast carcinoma and 161 were premenopausal. One hundred and seventy-three patients received systemic combination chemotherapy other than tamoxifen and 30 received radiotherapy after surgical treatment. Of the 546 patients not treated by tamoxifen, 157 were postmenopausal and 389 were premenopausal at the time of diagnosis of breast carcinoma. One hundred and sixty-one patients received combination chemotherapy and 39 received radiotherapy.

The patients who received tamoxifen and those who did not receive tamoxifen had little significant differences in their menstruation status, therapy, and past history or family history of malignant tumors. However, patient age and body mass index were higher in the tamoxifen-treated group. The dose of tamoxifen used was 10 mg twice daily in 49.8% of patients, 41.9% of patients received 10 mg 3 times daily, and 7.5% of patients received 20 mg twice daily. The duration of tamoxifen use ranged from 12–157 months, with a median of 24.7 months and an average of 33.7 months. The total dose of tamoxifen used ranged from 7.84–99.93 g.

From this study population of breast carcinoma patients, 13 developed a subsequent endometrial carcinoma. The cumulative incidence of endometrial car-

TABLE 1
Comparison of Clinical Characteristics in Tamoxifen Treated and Nontreated Breast Carcinoma Patients

Demographics	Tamoxifen	No tamoxifen	*P* value
No. of patients	279	546	
Age (yrs) (mean ± SD)[a]	47.45 ± 8.47	45.54 ± 7.58	0.001
Weight (kg) (mean ± SD)	53.2 ± 7.2	51.9 ± 7.0	0.012
Height (cm) (mean ± SD)	153.5 ± 5.3	154.2 ± 5.2	NS
Body mass index (mean ± SD)	22.52 ± 3.10	21.83 ± 2.80	0.001
Age at menarche (yrs) (mean ± SD)	13.65 ± 1.54	13.52 ± 1.54	NS
Menstruation (years) (mean ± SD)[b]	34.83 ± 4.20	35.00 ± 4.32	NS
Parity (mean ± SD)	1.73 ± 1.05	1.70 ± 1.01	
Gravidity (mean ± SD)	2.87 ± 1.84	2.82 ± 1.82	NS
Irregularity of menstruation (no. of yes)	22 (7.9%)	28 (5.1%)	NS
Hypertension (no. of yes)	8 (2.9%)	9 (1.6%)	NS
Diabetes mellitus (no. of yes)	5 (1.8%)	6 (1.1%)	NS
Chemotherapy (no. of yes)	173 (62.0%)	161 (29.5%)	< 0.001
Radiotherapy (no. of yes)	30 (10.8%)	39 (7.1%)	NS
Bilateral breast carcinoma (no. of yes)	29 (10.4%)	29 (5.3%)	0.007
Family history (no. of yes)[c]	59 (21.1%)	87 (15.9%)	NS

SD: standard deviation; NS: not significant.
[a] Age at diagnosis of breast carcinoma.
[b] Years of interval between menarche and menopause or now.
[c] History of breast carcinoma or gynecologic carcinoma.

cinoma was 1.58% of all patients who underwent annual screening for gynecologic carcinoma.

In tamoxifen-treated patients, 4 of 279 patients developed endometrial carcinoma. Of the patients not treated with tamoxifen, 9 of 546 patients subsequently were diagnosed with endometrial carcinoma. Using the Cox proportional hazards model, relative risk of endometrial carcinoma by total dose of tamoxifen exposure was 1.0001 ($P = 0.0145$). In addition to the 13 patients with endometrial carcinoma, 3 cases of atypical endometrial hyperplasia occurred in this study population. Two patients were treated with tamoxifen and one was not. The relative risk of endometrial lesions, including endometrial carcinoma and atypical endometrial hyperplasia, by total dose of tamoxifen usage was 1.0000 ($P = 0.0349$).

Tamoxifen-treated patients were more likely to have symptoms of vaginal bleeding or discharge ($P < 0.0001$). Approximately 54.8% of tamoxifen-treated patients had been diagnosed with leiomyoma of the uterus or an enlarged uterus whereas 44.7% of nontreated patients had received such diagnoses ($P = 0.0058$).

Profiles of patients who developed endometrial carcinoma or atypical endometrial hyperplasia are shown in Table 2. Comparing the two groups of patients (treated and not treated with tamoxifen) there was no statistical difference in age or in the mean interval between the diagnosis of breast carcinoma and endometrial carcinoma (using ANOVA). Characteristics of subsequent endometrial carcinoma in breast carcinoma patients are shown in Table 3. No patients in this study population developed a nonepithelial malignancy. Using the test of independence, there was no statistically significant correlation between the cumulative dose of tamoxifen or the length of tamoxifen treatment and the histologic type and grade of endometrial carcinoma. In the tamoxifen-treated group, there was only one patient who died of endometrial carcinoma. The pathologic diagnosis of this patient was papillary serous adenocarcinoma of endometrium. Three patients in the group not treated with tamoxifen died of endometrial carcinoma (one of papillary serous adenocarcinoma, one of Grade 1 endometrioid adenocarcinoma, and one of Grade 3 endometrioid adenocarcinoma). There was no statistical difference in the prognosis of endometrial carcinoma between the two groups using the Kaplan–Meier survival analysis ($P = 0.6542$) (Fig. 1).

DISCUSSION

Although our study was retrospective and had a small study group, all patients had undergone annual gynecologic examinations and screening for gynecologic carcinoma. The detection rate for endometrial carcinoma and its precursors by aspiration cytology is very high.[5,6] We believe that our method of screening for endometrial carcinoma–endometrial aspiration cytology occasionally combined with endometrial curettage–is highly reliable. The incidence of subsequent

TABLE 2
Characteristics of Breast Carcinoma Patients Who Subsequently Developed an Endometrial Lesion

Patient no.	Patient age[a] (yrs)	Body mass index	Gravidity/ parity	Gynecologic symptoms	Tamoxifen treatment	Daily dose of tamoxifen (mg)	Total dose of tamoxifen (g)	Interval[b] (mos)
1	42	28.4	0/0	Yes	Yes	20	26.6	126
2	30	19.3	1/0	Yes	Yes	30	82.7	105
3	62	28.4	2/1	Yes	Yes	20	26.2	128
4	41	21.9	0/0	Yes	Yes	20	20.2	31
5	32	21.6	2/0	Yes	No			100
6	51	26.6	4/3	Yes	No			41
7	45	21.1	0/0	Yes	No			94
8	40	20.5	3/1	Yes	No			171
9	48	20.8	7/2	Yes	No			14
10	55	20.7	2/1	Yes	No			71
11	40	21.9	3/2	Yes	No			112
12	55	28.1	1/1	Yes	No			78
13	47	28.8	1/1	Yes	No			42
14	41	27.3	5/2	Yes	Yes	30	21.8	26
15	37	20.6	3/1	Yes	Yes	20	46.8	93
16	52	21.9	1/0	No	No			19

[a] Age at the time of diagnosis of breast carcinoma.

[b] Interval between diagnosis of breast carcinoma and endometrial carcinoma.

TABLE 3
Characteristics of Subsequent Endometrial Lesions in Breast Carcinoma Patients

Patient no.	Patient age[a] (yrs)	FIGO stage	Endometrial lesion histology and grade	Survival after endometrial lesion (mos)	Status	Comment
1	53	IB	EM type, GI	60.2	Dead of breast ca	
2	39	IB	EM type, G1	85.5	Alive without disease	Bilateral breast ca
3	73	IVB	Papillary serous adenoca	1.3	Dead of corpus ca	
4	43	IB	EM type, G1	70.1	Dead of breast ca	
5	40	IIIA, positive peritoneal cytology	EM type, G1 and papillary serous ca and clear cell ca	9.5	Dead of corpus ca	
6	54	IIIC, lymph nodes, MI < I/III	EM type, G3	15.1	Dead of corpus ca	
7	53	IB	EM type, G1	83.9	Alive without disease	
8	54	IB	EM type, G1	7.1	Alive without disease	
9	50	IB	EM type, G1	154.3	Alive without disease	
10	61	IB	EM type, G1	51.4	Dead of corpus ca	
11	49	IB	EM type, G2	52.7	Alive without disease	
12	61	IB	papillary serous adenoca and clear cell ca	1.0	Alive without disease	
13	51	IB	EM type, G1	24.9	Alive without disease	
14	44		Atypical hyperplasia	50.1	Dead of breast ca	
15	44		Atypical hyperplasia	1.1	Alive without disease	
16	54		Atypical hyperplasia	58.5	Alive without disease	

FIGO: International Federation of Gynecology and Obstetrics; EM: endometrioid type adenocarcinoma; ca: carcinoma; adenoca: adenocarcinoma; MI: myometrial invasion.

[a] Age at diagnosis of endometrial lesion.

endometrial carcinoma in tamoxifen-treated breast carcinoma patients in the current study was 1.4%, which is not lower than that of previous studies. However, the incidence of endometrial carcinoma in patients not treated by tamoxifen in the current study was 1.6%, which is significantly higher than in previous studies. Two large prospective trials showed that the relative risk of subsequent endometrial carcinoma was higher in breast carcinoma patients treated with tamoxifen than patients not treated with tamoxifen.[1,2]

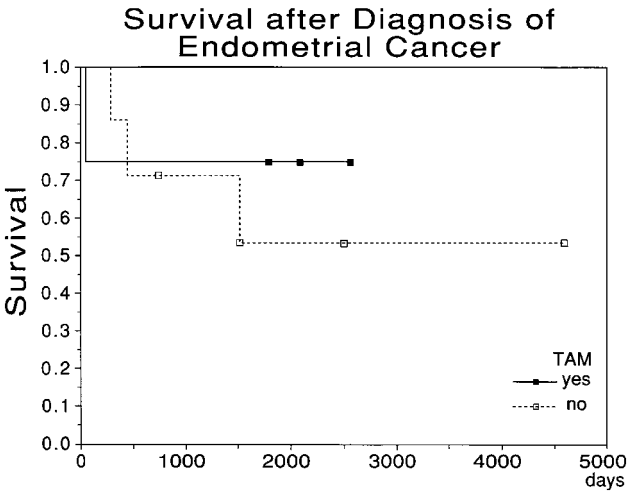

FIGURE 1. Survival after diagnosis of endometrial carcinoma in patients with primary breast carcinoma analyzed by the Kaplan–Meier method. TAM: tamoxifen.

However, previous large studies were based on computerized cancer registration, so gynecologic examinations were not recommended in the trial protocol and only might have been performed in patients with symptoms of atypical genital bleeding or discharge. Tamoxifen-treated patients may tend to be diagnosed earlier because they are more likely to have symptoms such as abnormal bleeding. Without screening for gynecologic carcinoma, endometrial carcinoma may be found in tamoxifen-treated patients more often and earlier. Whether the increase in endometrial carcinoma in tamoxifen-treated breast carcinoma patients in these prior trials represented a true increase or results from detection bias is not clear.

In the National Adjuvant Breast and Bowel Project (NSABP) trial,[2] 15 of 1419 tamoxifen-treated patients developed subsequent endometrial carcinoma, and 6 of these 15 patients had received prior hormone replacement therapy. Several studies have demonstrated that hormone replacement therapy using estrogen unopposed by progesterone increases the risk of endometrial carcinoma.[7–9] Endometrial carcinoma patients who had received hormone replacement therapy prior to tamoxifen treatment were under the compound influence of two drugs. Therefore we believe that tamoxifen was not the only factor increasing the risk of subsequent endometrial carcinoma in breast carcinoma patients in the NSABP trial. In the current study, no patient had received any prior estrogenic hormone replacement therapy. The relative risk of endometrial carcinoma by total dose of tamoxifen exposure of 1.0001 suggests that tamoxifen use does not increase the incidence of subsequent endometrial carcinoma in patients with primary breast carcinoma.

Some authors have demonstrated that endometrial carcinoma in tamoxifen-treated breast carcinoma patients is more likely to be high grade and have a histologic type with a poor prognosis.[10,11] In the current study, the histologic type of endometrial carcinoma of three tamoxifen-treated patients was Grade 1 endometrioid type adenocarcinoma, one patient had papillary serous adenocarcinoma, and two patients had endometrial atypical hyperplasia. Three of four endometrial carcinoma patients had FIGO Stage I disease but did not die of corpus carcinoma. Of the nontamoxifen-treated patients, one of nine patients had Grade 2 endometrioid type adenocarcinoma, one had Grade 3 endometrioid type adenocarcinoma two had papillary serous adenocarcinoma, and five had Grade 1 adenocarcinoma. Based on the results of our study, there was no statistical difference in the histologic type or grade of endometrial carcinoma between the tamoxifen-treated and nontamoxifen-treated patients. We could not detect any evidence to show that tamoxifen-related endometrial carcinoma in patients with primary breast carcinoma has a poor prognosis.

Tamoxifen has several effects on female reproductive organs. These effects vary depending on the dose, duration of use, age of the patient, menopausal status, organs, and species. Several authors demonstrated that tamoxifen acts on the endometrium as an estrogen receptor agonist. Tamoxifen has estrogenic effects on the vaginal epithelium and endometrium of breast carcinoma patients.[12,13] It has been reported that tamoxifen stimulates endometrial tumor growth. In fact, tamoxifen has been found to inhibit breast tumors in athymic mice.[14] Furthermore, tamoxifen has a stimulatory effect on endometrial adenocarcinoma cells in vitro.[15] Unopposed estrogenic stimulation to the endometrium is known to cause carcinogenesis.[16] Tamoxifen as a weak estrogen agonist might increase the incidence of subsequent endometrial carcinoma in patients with primary breast carcinoma. However, tamoxifen's mechanism of action is complex and its antiestrogenic and antagonistic characteristics are not yet completely recognized.

There are some authors who suggest a different mechanism of tamoxifen on endometrial cells, and that there is a direct effect of tamoxifen on the endometrium.[10,17] Rosa et al. reported that the risk of endometrial carcinoma with tamoxifen use is low.[18] To determine the various effects and true carcinogenic risk of tamoxifen on genital organs in the humans, future trials need to perform yearly gynecologic examinations and cancer screenings of breast carcinoma patients.

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