BRIEF COMMUNICATION

Second Cancers After Adjuvant Tamoxifen Therapy for Breast Cancer

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Since the early 1980s, adjuvant tamoxifen therapy has been commonly used in the treatment of early stage breast cancer to improve survival and to reduce the incidence of contralateral breast cancer among postmenopausal women (*1*). However, the estrogenic effect of tamoxifen on the uterus (*2*) has been reported to increase the risk of uterine corpus cancer by twofold to threefold (*3-6*). Recently, an elevated risk of gastrointestinal cancer, particularly colorectal and stomach cancers, was associated with tamoxifen therapy in clinical trials (*7*). Because late effects of tamoxifen could adversely affect the risk–benefit ratio in ongoing chemoprevention trials, we evaluated the risk of second cancers among 87 323 women with breast cancer reported to the Surveillance, Epidemiology, and End Results (SEER) Program[1] (*8*).

To select women who were most likely to have received tamoxifen, we included patients with breast cancer who were 50 years of age or older, who were diagnosed with early stage disease (i.e., localized or regional) from 1980 through 1992, and who survived at least 2 months (n = 101 930). Since many women given chemotherapy also received steroids, which are classified as hormones in SEER, we excluded those individuals from the analysis (n = 14 607). Of the remaining 87 323 women, 14 358 were known to have received hormones for their first course of therapy (designated as the tamoxifen group, since approximately 90%-95% of these patients received tamoxifen [Hankey B, Harlan L: personal communication]), whereas 72 965 women were not known to have received hormones (the no/unknown tamoxifen group). Observed-to-expected ratios (O/E) of second cancers were calculated using standard methods[2] (*9,10*).

Patients with breast cancer initially treated with tamoxifen developed second cancers at a rate slightly higher than that expected in the general population (O/E = 1.12; 95% confidence interval [CI] = 1.03-1.21) and identical to that experienced by patients with no/unknown tamoxifen therapy (O/E = 1.12; 95% CI = 1.09-1.15) (Table 1). Significant excesses of uterine corpus cancer were seen in both treatment groups, with higher risks following tamoxifen therapy (O/E = 2.03; 95% CI = 1.59-2.55 versus O/E = 1.23; 95% CI = 1.11-1.36). We observed little difference in the severity of grade or stage of uterine corpus cancer on the basis of initial therapy (Table 1), in contrast with a previous report suggesting a tendency toward higher grade lesions following tamoxifen treatment (*11*). Of the 73 women who developed uterine corpus cancer after tamoxifen therapy, six died of this cancer. The actuarial risk of uterine corpus cancer among postmenopausal women after adjuvant tamoxifen therapy was 1.8% at 10 years, compared with 0.9% expected in the general population.

Cancers of the colon and rectum were not in excess following tamoxifen therapy (O/E = 1.04; 95% CI = 0.83-1.30 and O/E = 1.02; 95% CI = 0.66-1.49, respectively), and stomach cancer was not significantly increased (O/E = 1.23; 95% CI = 0.69-2.03), in contrast with the findings of a recent report (*7*). Tamoxifen therapy appeared to decrease the risk of contralateral breast cancer (O/E = 1.12; 95% CI = 0.96-1.30 versus O/E = 1.62; 95% CI = 1.55-1.69), and a more detailed report of this result is planned. Women in the no/unknown tamoxifen group had a statistically significant lower risk of leukemia and of cancers of the liver, lung, and brain (Table 1).

To sharpen the treatment comparisons, we evaluated a subgroup of women for whom adjuvant tamoxifen was infrequently used, so that misclassification of therapy would be small. Among 17 952 patients with localized breast cancer initially treated between 1980 and 1984, the risk of uterine corpus cancer was nearly identical to that experienced in the general population (O = 121 and O/E = 0.99; 95% CI = 0.82-1.19). This finding suggests that at least part of the excess risk observed in the no/unknown tamoxifen group is related to tamoxifen therapy not reported to the SEER Program.

Among tamoxifen-treated patients, the risk of all second cancers, excluding contralateral breast cancer, was significantly increased among survivors of 5 or more years (O/E = 1.32; 95% CI = 1.02-1.68), whereas no excess cancer risk was found for the no/unknown tamoxifen group in this follow-up interval (O/E = 0.96; 95% CI = 0.90-1.02) (Table 2). A notable increase in uterine corpus cancer (O/E = 3.59; 95% CI = 1.96-6.02) and a nonsignificant excess of stomach cancer (four cases; O/E = 2.61; 95% CI = 0.70-6.69) were observed 5 years or more after breast cancer diagnosis among women who received tamoxifen therapy.

Although the number of patients with breast cancer evaluated in this study is large, few tamoxifen-treated patients have been followed for more than 10 years, limiting our ability to evaluate long-term survivors. Other limitations include a lack of detailed information on initial and subsequent therapy and an absence of data on other factors affecting second cancer risk, such as menopausal estrogen use and hysterectomy.

Our results support the link between tamoxifen therapy and subsequent de-

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See "Notes" section following "References."

Table 1. Observed (O) numbers and observed-to-expected (O/E) ratios of second primary cancers among women, aged 50 years or more, who were diagnosed with localized or regional stage breast cancer from 1980 through 1992 and who did not receive chemotherapy, by site and initial therapy

	Initial breast cancer therapy					
	Tamoxifen*			No/unknown tamoxifen*		
Second cancer site	O	O/E	95% confidence interval	O	O/E	95% confidence interval
All second cancers†	644	1.12	1.03-1.21	5516	1.12	1.09-1.15
Buccal cavity, pharynx	13	1.24	0.66-2.12	88	0.97	0.78-1.19
Digestive system†	153	1.02	0.86-1.19	1186	0.93	0.87-0.98
Esophagus	6	1.49	0.54-3.24	38	1.11	0.78-1.52
Stomach	15	1.23	0.69-2.03	118	1.13	0.93-1.35
Colon	80	1.04	0.83-1.30	613	0.94	0.87-1.02
Rectum	26	1.02	0.66-1.49	197	0.90	0.78-1.03
Liver	3	1.10	0.22-3.20	8	0.35	0.15-0.68
Biliary tract	6	0.94	0.34-2.05	47	0.86	0.63-1.14
Pancreas	15	0.77	0.43-1.28	142	0.86	0.73-1.02
Trachea, bronchus, lung	70	1.02	0.80-1.29	525	0.91	0.84-0.99
Breast (contralateral)	177	1.12	0.96-1.30	2177	1.62	1.55-1.69
Cervix uteri	8	1.09	0.47-2.14	53	0.81	0.61-1.06
Uterine corpus, uterus not otherwise specified	73‡	2.03	1.59-2.55	384§	1.23	1.11-1.36
Ovary	20	0.97	0.59-1.50	203	1.14	0.99-1.31
Kidney, renal pelvis, ureter	14	1.29	0.70-2.16	103	1.12	0.91-1.36
Bladder, other urinary	19	1.11	0.66-1.73	136	0.93	0.78-1.10
Melanoma of skin	12	1.41	0.73-2.47	85	1.16	0.93-1.44
Brain, central nervous system	7	1.17	0.47-2.42	35	0.69	0.48-0.96
Thyroid gland	7	1.90	0.76-3.92	42	1.31	0.94-1.77
Bone, connective tissue	4	1.58	0.42-4.03	30	1.37	0.93-1.96
Non-Hodgkin's lymphoma	21	1.02	0.63-1.56	164	0.95	0.81-1.10
Hodgkin's disease	2	1.82	0.20-6.57	10	1.04	0.50-1.90
Multiple myeloma	5	0.62	0.20-1.44	73	1.06	0.83-1.34
Leukemia	15	1.07	0.60-1.77	89	0.75	0.60-0.92
No. of patients	14 358			72 965		
Person-years at risk	39 736			348 393		
Mean age at breast cancer diagnosis, y	70.0			68.9		

*Tamoxifen group = patients given hormones for initial therapy; no/unknown tamoxifen group = no mention of hormones for initial therapy in medical records.

†Not all second cancer sites are listed; therefore, individual sites do not sum to totals.

‡Grades 1 and 2 = 59%; grades 3 and 4 = 25%; unknown grade = 16%; stage distribution: localized (78%), regional (12%), distant (4%), and unknown (6%).

§Grades 1 and 2 = 63%; grades 3 and 4 = 21%; unknown grade = 16%; stage distribution: localized (76%), regional (11%), distant (8%), and unknown (5%). (For comparison, grade and stage distribution of first primary uterine corpus cancers in SEER, 1980-1992: grades 1 and 2 = 67%; grades 3 and 4 = 19%; unknown grade = 14%; stage distribution: localized [75%], regional [12%], distant [9%], and unknown [4%]).

velopment of uterine corpus cancer that has been described in previous investigations (*3-7*). However, we found little evidence that tamoxifen treatment increases the incidence of colorectal or stomach cancer significantly, as reported by Rutqvist et al. (*7*). Liver cancer risk was not elevated, despite evidence that tamoxifen is a liver carcinogen in rats (*12*). Further studies of breast cancer survivors are needed to monitor site-specific risks of cancer over time in relation to total dose, dose intensity, and duration of tamoxifen use.

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Table 2. Risk of selected second primary cancers among women, aged 50 years or more, who were diagnosed with localized or regional stage breast cancer from 1980 through 1992 and who did not receive chemotherapy, by site, initial therapy, and time since breast cancer diagnosis*

	Time since breast cancer diagnosis								
	2 mo-1 y		1-5 y		≥5 y		All y		
Second site/therapy	O	O/E	O	O/E	O	O/E	O	O/E	P†
All second cancers, excluding breast									
Tamoxifen	119	1.11	283	1.08	65	1.32‡	467	1.12‡	.27
No/unknown tamoxifen	465	0.85‡	1834	0.95‡	1040	0.96	3339	0.94‡	.11
All digestive cancers									
Tamoxifen	35	0.92	94	1.00	24	1.29	153	1.02	.21
No/unknown tamoxifen	165	0.85‡	668	0.97	353	0.89‡	1186	0.93‡	.75
Stomach									
Tamoxifen	4	1.31	7	0.92	4	2.61	15	1.23	.25
No/unknown tamoxifen	20	1.26	64	1.13	34	1.05	118	1.13	.56
Colon, rectum									
Tamoxifen	23	0.89	67	1.05	16	1.26	106	1.04	.29
No/unknown tamoxifen	108	0.82‡	460	0.98	242	0.90	810	0.93‡	.96
Liver, biliary tract									
Tamoxifen	2	0.87	7	1.23	0	0.00	9	0.99	.47
No/unknown tamoxifen	9	0.76	28	0.67‡	18	0.75	55	0.71‡	.87
Uterine corpus									
Tamoxifen	17	1.78‡	42	1.87‡	14	3.59‡	73	2.03‡	.046
No/unknown tamoxifen	74	1.46‡	204	1.18‡	106	1.17	384	1.23‡	.29
No. of patients									
Tamoxifen	14 358		11 606		2293§		14 358		
No/unknown tamoxifen	72 965		65 595		32 802§		72 965		
Person-years at risk									
Tamoxifen	10 701		24 811		4225		39 736		
No/unknown tamoxifen	57 419		192 679		98 295		348 393		

*O = observed number of second cancers; O/E = observed-to-expected ratio; tamoxifen group = patients given hormones for initial therapy; no/unknown tamoxifen group = no mention of hormones for initial therapy in medical records.

†Two-sided *P* value for test of linear trend over the three follow-up intervals (time since breast cancer).

‡95% confidence interval excludes 1.0.

§Includes 153 (tamoxifen therapy) and 7136 (no/unknown tamoxifen therapy) women who survived 10 or more years after their breast cancer diagnosis.

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Notes

[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. The computer tapes are then edited by the NCI and made available for analysis. The SEER Program records all treatment given for the first course of therapy in broad categories, i.e., surgery, radiotherapy, chemotherapy, and hormonal therapy; therapy given subsequent to the first course is not recorded.

[2]SEER registry incidence files were searched for second primary cancers that developed 2 months or more following the initial diagnoses of breast cancer. For each patient, person-years at risk were accrued beginning 2 months after the first primary breast cancer diagnosis until the date of death, the date of last follow-up, the date of diagnosis of a subsequent primary cancer, or the study end, whichever came first. Age- and calendar-specific incidence rates from SEER for females for all cancers combined and for cancers at specific sites were applied to the appropriate person-years to compute the expected number of cancer cases. Tests of significance (two-sided) of the observed-to-expected (O/E) ratios and 95% confidence intervals (CI) of subsequent cancers were calculated assuming that the observed number of second cancers followed a Poisson distribution. Tests for linear trend were conducted according to the methods of Breslow et al. (*10*).

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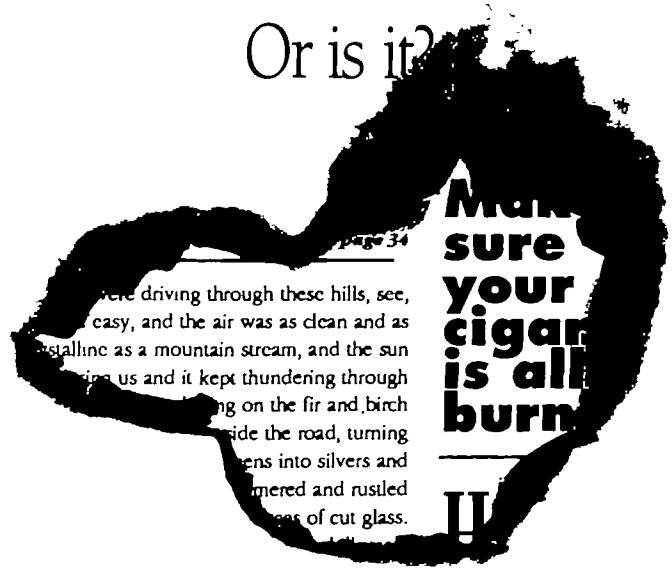

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