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The risk of developing uterine sarcoma after tamoxifen use

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The treatment of breast cancer with tamoxifen results in an increased risk of uterine cancer. The objective of this study was to evaluate the association between tamoxifen use and the risk of developing uterine sarcomas and endometrial carcinomas in a historical cohort of women diagnosed with breast cancer in 1987–1988. The medical records of all women diagnosed in Israel with breast cancer in the years 1987–1988 were sought. Clinical data, including use of hormone therapy, were extracted from oncology records. In 2004, patient identifiers were linked to the Israel Cancer Registry database to identify all uterine cancers that occurred within 15 years of the diagnosis of breast cancer. The records for 1507 breast cancer cases (84%) were retrieved. Among these cases, 32 uterine malignancies were identified; 11 occurred prior to the diagnosis of breast cancer and 21 occurred during the follow-up period. Eight hundred seventy-five women in the cohort had used tamoxifen (59%). There were 17 uterine cancers observed among the 875 exposed to tamoxifen (1.9%), compared to 4 uterine cancers among the 621 women (0.6%) who did not use tamoxifen (odds ratio = 3.1; 95% CI: 1.0–9.1; $P = 0.04$). There were four uterine sarcomas among the tamoxifen users, but none among nonusers ($P = 0.15$). Five of the 875 tamoxifen users (0.6%) died of uterine cancer, compared to no deaths among nonusers ($P = 0.08$). We conclude that in this national breast cancer cohort, tamoxifen use was associated with elevated risks of uterine cancer incidence and mortality. Uterine sarcomas appear to be overrepresented among women who use tamoxifen.

KEYWORDS: breast cancer, endometrial cancer, tamoxifen, uterine sarcoma.

Tamoxifen has been an important component of the treatment of estrogen receptor–positive breast cancers since the 1980s. It has proven to be an effective drug in both the adjuvant and metastatic settings[1–3]. Despite its proven effectiveness, tamoxifen is associated with a range of side effects; among the most serious is an increased risk of uterine cancer[3–6]. Among women treated with tamoxifen, the risk of endometrial carcinoma has been reported to be doubled after 2 years of treatment, and quadrupled after 5 years of use[3,7,8], this risk did not diminish for at least 5 years after the last treatment ended[7–9]. Tamoxifen use has also been associated with the occurrence of uterine sarcomas[9–13]. However, the increased long-term risk for uterine sarcomas among tamoxifen users has not been extensively studied. The objective of this study was to evaluate the association between tamoxifen use and the risk of developing endometrial carcinomas and uterine sarcomas in a historical cohort of women diagnosed with breast cancer in 1987–1988 in Israel.

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Materials and methods

All women diagnosed with breast cancer in Israel between 1987 and 1988 were identified through the

National Israeli Cancer Registry. Occurrences of other primary malignant tumors in this cohort prior to 2002 were also recorded. The information from the National Israeli Cancer Registry included the date of diagnosis and the morphology of the tumor. Medical records were sought for the study participants and information on all treatments of the primary breast cancer, including chemotherapy, radiotherapy, and hormonal therapy, were extracted from these records. The duration of tamoxifen use was estimated as the date of first use until the date of last known use. When the stopping date of tamoxifen was not recorded, we imputed the stopping date as the date of the last recorded oncology visit. Cause of death was extracted from the files of the Central Bureau of Statistics. The Central Bureau of Statistics receives all deaths certificates in Israel and codes them using the International Classification of Diseases coding system (versions 9 and 10 according to the year of death).

Statistical methods

The proportions of women who developed uterine cancer within 15 years of breast cancer diagnosis were calculated for women who did and who did not use tamoxifen. The significance of the difference of the proportions was tested using the Chi-square test. The univariate odds ratio (OR) and 95% confidence interval (CI) were estimated by standard methods. Logistic regression was used to adjust estimates by age and stage at breast carcinoma diagnosis. The median duration of tamoxifen use between women who did and who did not develop uterine cancers were compared using the Mann–Whitney test. Significance tests were two-sided with significance level set at 0.05. Statistical analysis was performed using SPSS software (version 11.5). (SPSS Inc., Chicago, IL).

Results

Women with breast carcinoma diagnosed in Israel in 1987 or 1988 were 2514. Because the present study is a component of a larger national genetic study, only patients for whom a paraffin-embedded tumor sample was available were included (1794 patients). The medical records for 1507 cases (84%) were retrieved. Eight hundred eighty-six of the cases (59%) were treated with tamoxifen after the diagnosis of breast cancer (Fig. 1). Both the dates of starting and stopping were available for 482 cases. For the remaining 404 cases, only the starting date was recorded and the duration of use was estimated as the date of the first use to the date of the last clinic visit. The median duration of

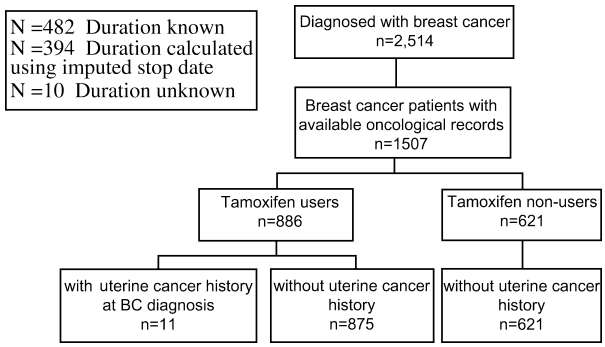

Figure 1. Risk of developing uterine cancer after use of tamoxifen: study population flowchart.

tamoxifen use was 3.1 years (interquartile range: 1–6.7 years). Two hundred sixteen (25%) patients used tamoxifen for 1 year or less, 127 (4.7%) used it for 1–2 years, 145 (16.8%) used it for 2–4 years, and 377 (43.6%) used it for 4 years or more. Women treated with tamoxifen were significantly older ($P < 0.001$) and had a higher stage at diagnosis ($P < 0.001$) than women who did not receive tamoxifen (Table 1).

Uterine cancers were identified in 32 of the 1507 breast cancer cases. However, for 11 women, the uterine malignancy was diagnosed prior to the diagnosis of the breast cancer and these are not considered further (Table 2). There were 21 women who were diagnosed with uterine cancer after the diagnosis of breast cancer, corresponding to an incidence rate of 144 cancers per 100,000 person years of follow-up.

Uterine malignancies developed in 17 of 875 tamoxifen users (1.9%), compared to 4 of 621 nonusers (0.6%)

Table 1. Distribution of demographics and stage at breast carcinoma diagnosis by tamoxifen use

	Tamoxifen use	Tamoxifen nonusers
n	857[a]	621
Age Mean (SD)[b]	61.0 (13)	54.6 (13.7)
Range	26–99	21–100
Ethnicity		
Jews (%)	844 (96.5)	609 (98.1)
Non-Jews (%)	31 (3.5)	12 (1.9)
Stage at BC diagnosis (%)		
I	164 (19.0)	280 (48.1)
II	428 (49.7)	249 (41.0)
III	24 (23.7)	57 (9.4)
IV	65 (7.5)	22 (3.6)
Person years of follow-up		
Median (interquartile range)	8 (4–15)	15 (7–15)
Sum	7616	7013

BC, breast cancer.
[a]Not including 11 tamoxifen users who started treatment after uterine cancer diagnosis.
[b]Significant difference $P < 0.001$.

Table 2. Uterine malignancies in Israeli Breast Cancer Cohort

Histologic type	Cases diagnosed before breast cancer diagnosis ($n = 11$)	Cases diagnosed after breast cancer diagnosis ($n = 21$)	
		No tamoxifen treatment	Tamoxifen treatment
Adenocarcinoma	10	3	11
Uterine serous papillary carcinoma	0	1	0
Clear cell carcinoma	0	0	1
Neuroendocrine carcinoma	0	0	1
Sarcomas	1	0	4
Leiomyosarcoma	1	0	0
Rhabdomyosarcoma	0	0	2
Mixed mesodermal tumor	0	0	1
Carcinosarcoma	0	0	1
Total	11	4	17

(OR = 3.1, 95% CI: 1.0–9.1). The result was similar after adjustment for age and breast cancer stage (OR = 3.1, 95% CI: 0.99–9.7). The cumulative probabilities of developing uterine cancer since the start of tamoxifen treatment and since breast cancer diagnosis are described in Figure 2. The median duration of use of tamoxifen among breast cancer patients who developed uterine cancer was 5.7 years, compared to 3.1 years for women who did not develop cancer (P = 0.07). Table 3 presents the risk of uterine malignancy by duration of tamoxifen use. The risk increased significantly with duration of treatment (P for trend = 0.004). For women with four or more years of treatment, compared with no use, the OR was 6.6 (95% CI: 2.0–21.1). The risk of endometrial cancer also increased with the age of the woman; a higher risk was observed among women who were diagnosed over the age of 60 than those diagnosed with breast cancer at age 60 or before (OR = 3.2; 95% CI: 1.2–8.8; $P = 0.016$).

Overall, uterine sarcomas developed in four breast cancer cases in our cohort, corresponding to an incidence rate of 27 per 100,000 per year. The four cases included three heterologous uterine sarcomas: one case of Müllerian mixed mesodermal tumor, including malignant epithelial and malignant lipoid stromal components, and two cases of pure heterologous rhabdomyosarcoma, including malignant striated muscles. The fourth case was an homologous uterine sarcoma which was classified as carcinosarcoma, including malignant epithelial and pure malignant endometrial stromal cells (Table 2). All four sarcomas occurred among tamoxifen users (0.5%) ($P = 0.15$). The average age of diagnosis for the four patients who developed sarcomas was 66.3 years (range 60–73 years).

Five of the 875 tamoxifen users (0.6%) died of uterine cancer, compared to no deaths among women who did not use tamoxifen ($P = 0.08$).

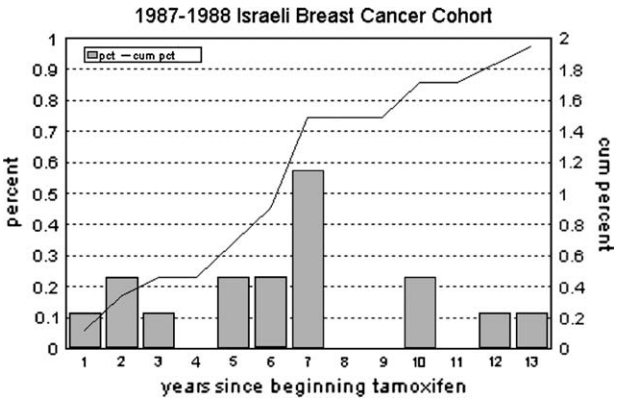

Figure 2. Incidence of uterine cancer from start of tamoxifen.

Discussion

The primary mode of action of tamoxifen is as an anti-estrogen, but the drug can also act by nonreceptor-related mechanisms. The response of estrogen-sensitive tissues to tamoxifen varies among different species and in different sites in the body[14,15]. This tissue-specific activity underlies the paradoxical observation that tamoxifen is an anticancer drug in the breast, but is an endometrial carcinogen[16].

Uterine sarcoma is a rare form of uterine malignancy and comprises from 2% to 5% of all patients with uterine malignancy[17,18]. The incidence is approximately one to two cases per 100,000 per year in the general population. However, in Israeli breast cancer patients, sarcomas comprised 4 of 17 uterine cancer cases (23%) and the incidence rate was 27 per 100,000 per year.

The National Surgical Adjuvant Breast and Bowel Project study suggested that the incidence of uterine malignancies is increased in women taking tamoxifen.

Table 3. Risk of endometrial cancer by duration of tamoxifen use

Duration of tamoxifen use	Number of women	Number of uterine cancers	OR (95% CI)	*P*	Adjusted[a] OR
Not used	621	4	1 reference	—	1 reference
<=2 years	148	2	2.1 (0.4–11.6)	0.39	2.2 (0.4–12.9)
2–4 years	81	4	8.0 (2.0–32.7)	0.004	7.6 (1.7–33.0)
Above 4 years	245	10	6.6 (2.0–21.1)	0.002	6.2 (1.9–20.4)
Unknown	401	1	0.4 (0.05–3.5)	0.39	0.7 (0.4–1.3)
Trend[b]: OR per year			1.18 (1.06–1.32)	0.004	1.16 (1.04–1.30)

[a]Adjusted to age and stage of breast cancer at breast cancer diagnosis.
[b]Trend includes zero group (ie, tamoxifen nonusers). Not including unknown duration.

Sarcomas made up approximately 10% of the uterine malignancies in these patients[2,18].

In a population-based series of 324 women diagnosed with endometrial cancer after breast cancer, identified by four Surveillance, Epidemiology, and End Results–based case-control studies, the proportion of women with uterine sarcomas was similar among those who had taken tamoxifen (7.5%) and those who had not used the drug (6.7%)[18,19]. In accordance with the National Surgical Adjuvant Breast and Bowel Project data[1,2,18] and the report by Bergman *et al.*[7], we report that tamoxifen treatment is associated with increased risks of both endometrial adenocarcinoma and uterine sarcoma. In our study, the magnitude of the relative risk was higher for uterine sarcomas than for uterine adenocarcinomas, but the number of sarcomas was too small to provide a precise risk estimate.

In addition, The British Tamoxifen Second Cancer Study Group reported that among patients treated with tamoxifen, the risk of either Müllerian mixed mesodermal tumors or sarcomas (OR = 13.5) was higher than that for adenocarcinoma (OR = 2.1)[8].

Tamoxifen exerts a variety of activities, including regulation of cytokines such as transforming growth factor beta-1[20]. As transforming growth factor beta-1 is a potent inhibitor of epithelial cells growth and a stimulator of stromal cells and angiogenesis, this cytokine might be involved in the development of uterine stromal tumors induced by tamoxifen. Whereas estrogen has been shown to play a causal role in the pathogenesis of endometrial adenocarcinoma, such a link has not been established for uterine sarcoma in general, although it may exist for the Müllerian mixed mesodermal tumors variant, which contains both epithelial and stromal neoplastic elements[21,22].

Our data are consistent with those of a recently reported study[18] in which women with long-term use of tamoxifen (four or more years) were more likely than nonusers to develop uterine sarcoma.

We therefore suggest that patients and physicians should be aware of the increased risk for uterine sarcomas among tamoxifen users, even after stopping the use of the drug.

Furthermore, surveillance for uterine cancer should be considered for women who are being treated with tamoxifen (especially long-term users). Women using tamoxifen should seek prompt medical attention if they experience any gynecological symptoms such as menstrual irregularities, vaginal bleeding, change in vaginal discharge or pelvic discomfort.

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References

1 Fisher B, Dignam J, Wolmark N *et al*. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomized controlled trial. *Lancet* 1999;**353:**1993–2000.
2 Fisher B, Constantino JP, Wickerham DL *et al*. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study l. *J Natl Cancer Inst* 1998;**90:** 1371–88.
3 Early Breast Cancer Trial Collaborative Group (EBCTCG). Tamoxifen for early breast cancer: an overview of the randomized trials. *Lancet* 1998;**351:**1451–68.
4 Bissett D, Davis JA, George WD. Gynaecological monitoring during tamoxifen therapy. *Lancet* 1994;**344:**1244–5.
5 Wysowski DK, Honing SF, Beitz J. Uterine sarcoma associated with tamoxifen use. *N Engl J Med* 2002;**346:**1832–3.
6 Meier CR, Jick H. Tamoxifen and risk of idiopathic venous thromboembolism. *Br J Clin Pharmacol* 1998;**45:**608–12.
7 Bergman L, Beelen ML, Gallee MP *et al*. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer: comprehensive Cancer Centers' ALERT group-assessment of liver and endometrial cancer risk following tamoxifen. *Lancet* 2000;**356:**881–7.
8 Swerdlow AJ, Jones ME. Tamoxifen treatment for breast cancer risk of endometrial cancer: a case control study. *J Natl Cancer Inst* 2005; **97:**375–84.
9 Silva EG, Tornos CS, Follen-Mitchell M. Malignant neoplasm of the uterine corpus in patients treated for breast carcinoma: the effect of tamoxifen. *Int J Pathology* 1994;**13:**248–58.
10 Clark MR. Uterine malignant mixed mullerian tumor in a patient on long-term tamoxifen therapy for breast cancer. *Gynecol Oncol* 1993;**51:**411–5.
11 Hubalek M, Ramoni A, Holzner E, Marth C. Malignant mixed mesodermal tumor after tamoxifen therapy for breast cancer. *Gynecol Oncol* 2004;**95:**264–6.
12 Yildrim Y, Inal MM, Sanci M *et al*. Development of uterine sarcoma after tamoxifen treatment for breast cancer: report of four cases. *Int J Gynecol Cancer* 2005;**15:**1239–42.

13 Arenas M, Roviroso A, Hernandez V *et al*. Uterine sarcoma in breast cancer patients treated with tamoxifen. *Int J Gynecol Cancer* 2006;**16:**861–5.
14 Wolf DM, Fuqua SW. Mechanisms of action of antiestrogens. *Cancer Treat Rev* 1995;**21:**247–71.
15 Pink JJ, Jordan VC. Models of estrogen receptor regulation by estrogen and antiestrogens in breast cancer cell lines. *Cancer Res* 1996; **56:**2321–30.
16 Fornander T, Rutqvist LE, Cedermark B *et al*. Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet* 1989;**1:**117–20.
17 Murphy GP, Lawrence W, Lenhard RE. Gynecologic sarcomas. In: *American Cancer Society Textbook of Clinical Oncology*, 2 edn. Atlanta: GA American Cancer Society, 1995:573–4.
18 Wickerham D, Fisher B, Wolmark N *et al*. Association of tamoxifen and uterine sarcoma. *J Clin Oncol* 2002;**20:**2758–60.
19 Bernstein LD, Deapen D, Cerhan JR *et al*.: Tamoxifen therapy for breast cancer and endometrial cancer risk. *J Natl Cancer Inst* 1999;**91:**1654–62.
20 Butta A, MacLennan K, Flanders KC *et al*. Induction of transforming growth factor beta 1 in human breast cancer in vivo following tamoxifen. *Cancer Res* 1992;**52:**4261–4.
21 Zelmanowicz A, Hildesheim A, Sherman ME *et al*. Evidence for a common ethiology for endometrial carcinomas and malignant mixed mullerian tumors. *Gynecol Oncol* 1998;**69:**253–7.
22 Altaras MM, Jaffe R, Cohen I *et al*. Role of prolonged excessive estrogen stimulation in the pathogenesis of endometrial sarcomas: two cases and a review of the literature. *Gynecol Oncol* 1990;**38:** 273–7.

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