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Uterine Neoplasms in Patients Treated With Tamoxifen

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Abstract Since 1985, when Killackey originally described three cases of endometrial carcinoma in patients receiving tamoxifen, there have been several reports confirming or denying the relationship between tamoxifen and endometrial carcinoma. Our study of 15 patients treated for breast carcinoma with tamoxifen found that papillary serous carcinoma was the most common tumor in this group of patients. Several other retrospective studies reported a high incidence of high-grade endometrioid adenocarcinoma or high-risk variants of endometrial carcinoma in patients receiving tamoxifen.

Key words: Tamoxifen, uterine neoplasms

Tamoxifen was developed in 1967 by Harper while studying drugs that prevent implantation [1]. A nonsteroidal antiestrogen, tamoxifen, was originally designated as ICI46474, and is a derivative of triphenylethylene. In the original report, Harper recognized that tamoxifen was weakly and atypically estrogenic in the female genital tract based on the drug effect in the vaginal epithelium in mice and on the mild increase in uterine weight in rats [1]. These studies were confirmed in 1977 by Ferrazzi [2] and in 1981 by Boccardo [3]. Several mechanisms have been suggested to explain the action of tamoxifen, including modulating the production of transforming growth factors, increasing natural killer cells, decreasing insulin-like growth factor, and blocking the protein that binds to estradiol [4]. This last mechanism would explain the elevated serum level of estradiol reported in patients receiving tamoxifen, as well as some of the estrogenic effects of this drug.

In 1985, Killackey described three cases of endometrial carcinoma in patients receiving tamoxifen [5]. Three years later, Gottardis [6] found that tamoxifen stimulated the growth of endometrial tumor cell lines. The most convincing study showing a relationship between tamoxifen and endometrial carcinoma was published by Fornander in 1991 [7]. In this study, 1,846 patients treated for breast carcinoma were randomized into two groups. One group of 931 patients received 40 mg of tamoxifen daily. Thirteen patients in this group developed endometrial carcinoma. In the control group of 915 patients, only two developed endometrial carcinoma.

In 1994, we reviewed the pathology of 72 patients treated at the University of Texas M.D. Anderson Cancer Center who had developed a uterine malignant neoplasm after being treated for breast carcinoma [8]. Fifteen of the 72 patients had been treated with 20 mg of tamoxifen

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a day for 2–66 months with an average of 25 months. The purpose of our study was to investigate any differences in the histology of uterine malignant neoplasms between patients treated with tamoxifen and those not treated with tamoxifen. The interval between the discovery of the breast and the uterine neoplasms in patients who did not receive tamoxifen ranged from 1–33 years (mean, 8 years); in the group of patients treated with tamoxifen, it ranged from 1–13 years (mean, 6 years). Of the 57 patients not treated with tamoxifen, 3 were premenopausal, 47 were postmenopausal, and 7 had unknown menstrual status. All patients treated with tamoxifen were postmenopausal. Table I shows the neoplasms found in the 72 patients. The most common tumor (33 cases) was endometrioid carcinoma (Fig. 1). There was also a very high incidence of clear cell carcinoma (14 cases) and of leiomyosarcoma (12 cases). Nine tumors were serous carcinomas (Fig. 2), one was an adenosquamous carcinoma, and three were malignant mixed Müllerian tumors. In 10 of the 14 cases of clear cell carcinoma, the clear cell component was predominant; the other four had only focal areas of clear cell carcinoma. Of the nine serous carcinomas, six were pure or predominant focal areas of serous carcinoma in an otherwise classical endometrioid adenocarcinoma. Six of the 12 leiomyosarcomas had unusual features, including a predominant epithelioid component, clear cell areas, a myxoid component, and the presence of tubules. The most common tumor in the patients not treated with tamoxifen was endometrioid carcinoma (53% of the cases). Clear cell carcinoma and leiomyosarcoma were the next two most frequent neoplasms in this group of patients (17% each). In the 15 patients treated with tamoxifen, the most common tumor was papillary serous carcinoma (33% of the cases), followed by clear cell carcinoma (27%) and endometrioid carcinoma (25%).

We also investigated the incidence of endometrial polyps in these patients; 24 of 72 (33%) patients had endometrial polyps. However, there was a significant difference in the incidence of endometrial polyps in the two groups of patients. In patients not treated with tamoxifen, 13 of 57 (23%) had endometrial polyps; and 11 of 15 patients (73%) treated with tamoxifen had endometrial polyps. Patients treated with tamoxifen had a higher incidence of endometrial polyps than of endometrial hyperplasia.

Other studies have also shown that the endometrial carcinomas associated with tamoxifen are aggressive neoplasms. Malfetano [9] reported 6 cases of endometrial carcinoma, all involving the myometrium and Atlante [10] also reported the same finding in 4 cases [9,10]. In the

TABLE I. Malignant Neoplasms Found in Patients Treated Without and With Tamoxifen [8]

Diagnosis	Number of cases	Expected incidence*	Patients not treated with tamoxifen	Patients treated with tamoxifen
Endometrioid carcinoma	33	—	30 (53%)	3 (20%)
Clear cell carcinoma	14	3[a]	10 (17%)	4 (27%
Serous carcinoma	9	6	4 (7%)	5 (33%)[b]
Adenosquamous carcinoma	1	4	1 (2%)	—
MMMT	3	2	2 (4%)	1 (7%)
Leiomyosarcoma	12	2[a]	10 (17%)	2 (14%)
Total	**72**		**57**	**15**

* The expected incidence of the tumor was calculated based on the endometrial carcinomas found using the x2 goodness of fit test [16–22]; # Fisher's exact test; MMMT = Malignant mixed Müllerian tumor; [a] ($p < 0.01$); [b] ($p = 0.02$#)

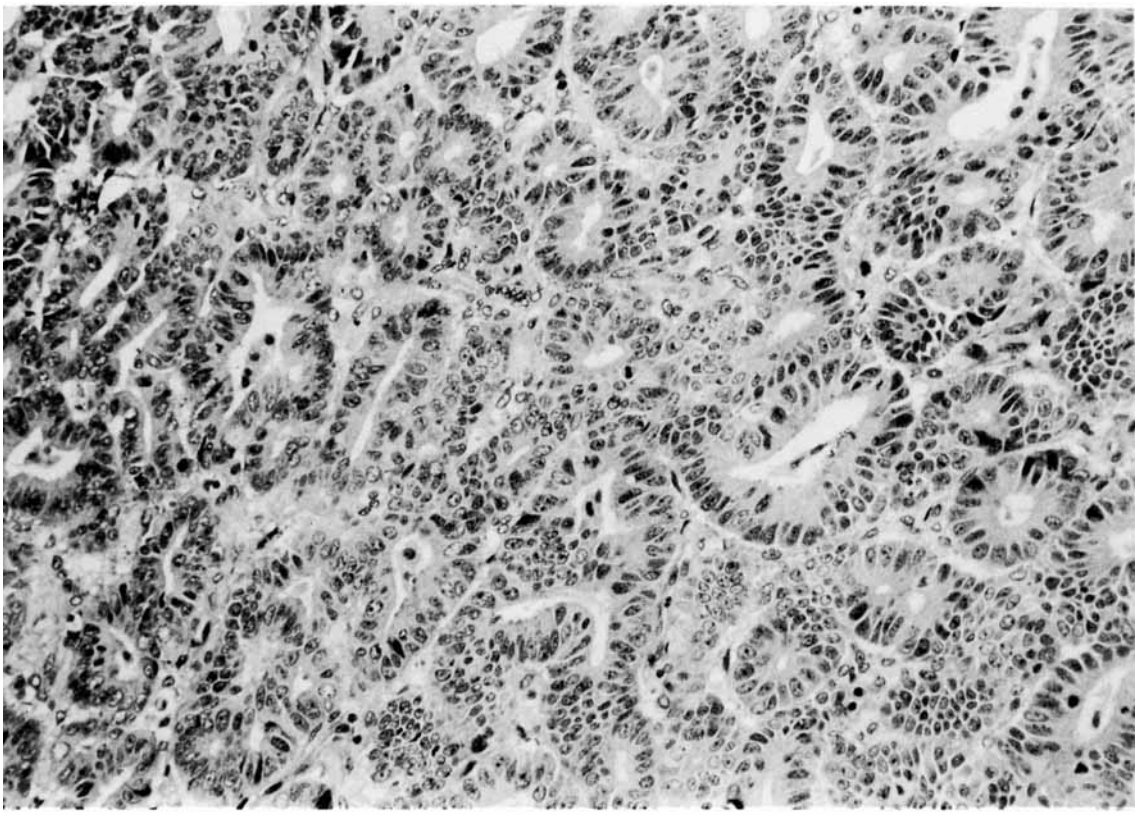

Fig. 1. Endometrial adenocarcinoma. Glands with nuclear atypia are closely arranged without stroma between them.

study by Segna [11], 6 of 11 patients had grade 2 or 3 tumors. In Magriples' [12] study, 11 of 15 patients had tumors that were high-grade or high-risk variants.

Some studies show no increased incidence, or just a moderately increased incidence, of endometrial carcinoma in patients receiving tamoxifen [13–15]. A very recent study from the National Surgical Adjuvant Breast and Bowel Project (NSABP) [13] showed an increased incidence of endometrial carcinoma, but with neoplasms no more aggressive than the usual endometrioid carcinoma [13]. In this study, 2,843 patients were randomized into two groups. One group of 1,419 patients received 20 mg of tamoxifen a day; 13 endometrial carcinomas were seen in this group. In the placebo group of 1,424 patients, no endometrial carcinomas were seen. In this study, the authors also added the 1,419 patients randomized to tamoxifen to a group of 1,220 patients treated with tamoxifen, but not in a randomized trial. Twenty endometrial carcinomas were found in these 2,639 patients, 13 from the randomized trial and 7 from the nonrandomized group. One conclusion of the study was that the neoplasms were no more aggressive than the usual endometrial carcinoma. This conclusion was based on tumor grade and survival data. The authors graded all tumors regardless of the histologic tumor type. However, if we use histologic tumor type to classify the tumors, 10 of the 20 cases (50%) were either high-grade lesions or high-risk variants. Only three of these patients died of disease; however, the follow-up in four of the other seven cases ranged from 0–12 months. It is also possible that the type of endometrial tumor found in different studies depends on the type of study. If tamoxifen induces endometrial hyperplasia and low-grade carcinoma

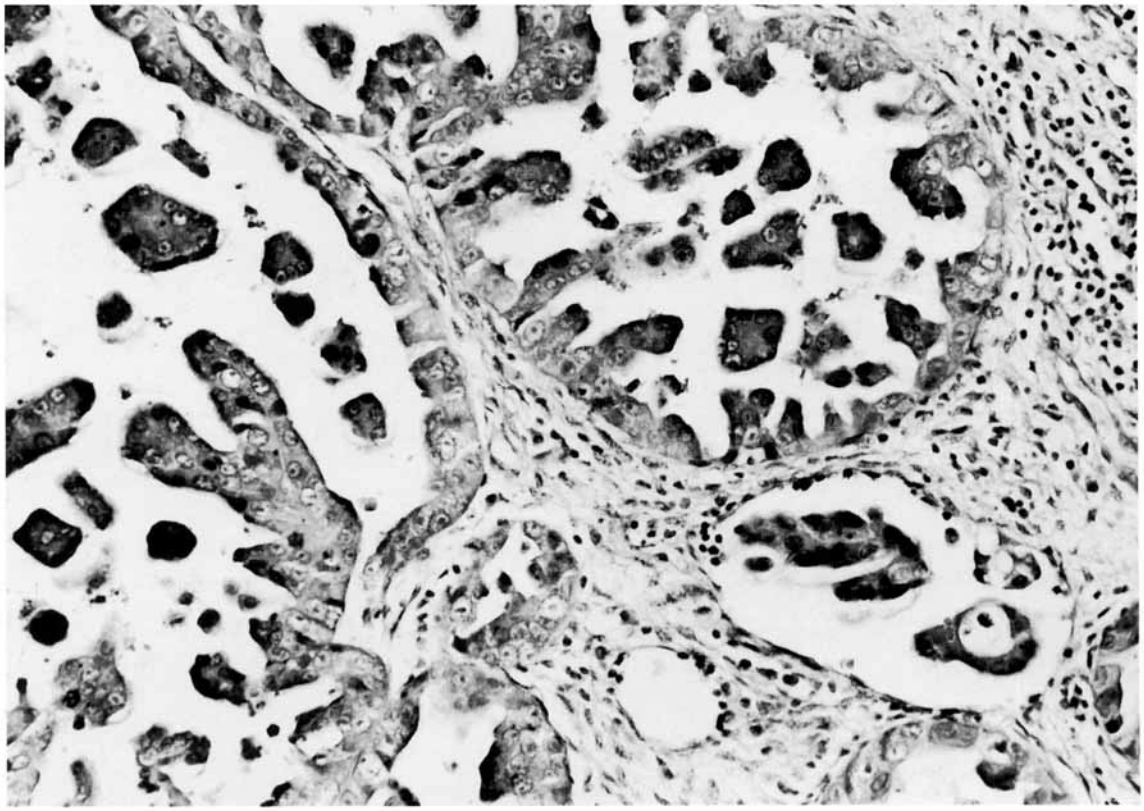

Fig. 2. Papillary serous carcinoma. Small, irregular papillary structures lined by cells with enlarged nuclei and prominent nucleoli.

TABLE II. Malignant Neoplasms of the Uterine Corpus in Patients With Breast Carcinoma

	Incidence of Endometrial Polyps versus Endometrial Hyperplasia	
	Without Tamoxifen	With Tamoxifen
Endometrial polyps	13/57 (23%)	11/15 (73%)
Endometrial hyperplasia	16/57 (28%)	6/15 (40%)

early on, and high-grade endometrial carcinoma or high-risk variants of endometrial carcinoma later on, the first group of lesions are going to be detected in randomized trials and the second group in retrospective studies. If this theory is correct, it would explain why there were more patients with high-grade endometrial carcinoma or high-risk variants in the retrospective studies (80%) than in the NSABP trial (50%).

The frequency of endometrial carcinoma in patients receiving tamoxifen is low. In the general population, the frequency of endometrial carcinoma is 0.025% [16–18]. This goes up to 0.5% in patients treated for breast carcinoma, to 10% in patients receiving tamoxifen for two years, and to 60% in patients receiving tamoxifen for more than five years [4,7].

Our study shows that papillary serous carcinoma is common in patients receiving tamoxifen, confirming the statement from Harper in the

original paper on tamoxifen that this drug has a weakly and atypically estrogenic effect [1]. However, it will be difficult to determine if tamoxifen has an atypical effect *per se* or if this is an unusual effect in the endometrium of patients with breast carcinoma.

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