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IV.5 High Grade Endometrial Cancers Associated with Tamoxifen Use

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From April 1993 to August 1996, 7 postmenopausal women with a personal history of operable breast cancer, were treated for endometrial cancer while taking tamoxifen. Four lesions were low grade and early stage while three others were high grade endometrial cancers. 2 of the patients were known to have a normal atrophic uterine cavity, 1 prior to and 1 while she was on tamoxifen. One low grade and early stage endometrial cancer had an unusual aggressive behaviour while tamoxifen was continued.

IN OUR institute, over the past 3 years, 7 tamoxifen-treated breast cancer patients developed endometrial cancer (see Table 1) [1]. All but 1 presented with abnormal vaginal bleeding. 3 patients had a high grade endometrial cancer; 1 was a poorly differentiated endometrial adenocarcinoma with superficial invasion of the myometrium, (FIGO IB) and 2 had a seropapillary adenocarcinoma, 1 of which had a clear cell component. In the latter 2 cases, there was deep myometrial invasion with extensive peritoneal metastasis. In these 3 patients, the length of treatment with tamoxifen varied from 4–16 years at a daily dose of 20 mg. The patient given tamoxifen for 16 years underwent, following 6 years of treatment a hysteroscopy which showed an atrophic endometrium. Because of a contra-lateral breast cancer, tamoxifen treatment was prolonged for another 10 years till she presented with abnormal vaginal bleeding.

Another patient had a normal atrophic uterine cavity prior to tamoxifen treatment. She developed, after 8 years of tamoxifen treatment, a polyp cancer which was an *in situ* endometrioid adenocarcinoma. Following her initial hysteroscopy, she developed endometrial polyps on several occasions. Each time polyps were removed and the tamoxifen treatment was continued because they were benign glandulocystic polyps. Once a polyp cancer was removed a hysterectomy was performed; there was no myometrial invasion and tamoxifen was continued.

The 3 patients with a well or moderately differentiated endometrial carcinoma developed their uterine cancer within 5–24 months of having been on tamoxifen. None of these patients had hysteroscopy or endometrial biopsy before starting the treatment and therefore the presence of any tumour before starting tamoxifen cannot be excluded.

1 of these patients, aged 85 years, presented with abnormal vaginal bleeding only 5 months after initiation of tamoxifen treatment. Her grade I, endometrial cancer which superficially invaded the myometrium (FIGO IB) was treated by simple hysterectomy and tamoxifen was continued. Six months later she presented with vaginal discharge and a severe vulvar burning sensation. There were extensive vulvar and vaginal metastases from her endometrial cancer, an unusually aggressive behaviour for a well differentiated endometrial cancer.

In conclusion, in our series of 7 endometrial cancers a pretreatment uterine assessment was performed in 2 women only; 1 who developed an endometrial polyp cancer and the patient who developed a poorly differentiated endometrial cancer during tamoxifen treatment with an atrophic uterine cavity 10 years earlier. Tamoxifen, as anti-oestrogen clearly

Table 1. Characteristics of 7 cases of endometrial carcinoma diagnosed during tamoxifen treatment for breast cancer

Age	Breast cancer histology	Interval	Endometrial cancer histology	FIGO stage
79	Ductal	6 + 10 years	Endometrioid grade III	IB
83	Ductal	10 years	Seropapillary + clear cells	IIIB
71	Ductal	4 years	Seropapillary	IVB
75	Ductal	2 years	Endometrioid grade I	IB
76	Ductal	15 months	Endometrioid grade II	IC
85	Lobular	5 months	Endometrioid grade I	IB
70	Ductal	8 years	Polyp—cancer *in situ*	IA

did not prevent these women from uterine cancers but stating that all tumours were initiated by the treatment is difficult to prove. 3 of the women with low grade uterine lesions presented within 2 years of treatment with postmenopausal bleeding, a time interval too short for a drug to induce a cancer. As many authors state, treatment may have accelerated pre-existing endometrial cancers to bleed or otherwise, vaginal spotting being reported in up to 5% of long-term tamoxifen users due to endometrial atrophia, might have been the reason for further gynaecological testing with the endometrial cancer being found as a fortunate hazard. In the cases of high grade tumours [2] the interval between the start of the treatment and the first symptoms was usually much longer. Therefore, it is likely that these aggressive tumours developed while tamoxifen was taken, although only in one case was this proven by pretreatment hysteroscopy. Pretreatment assessment of the uterine cavity and avoiding tamoxifen treatment beyond 5 years might have prevented most of our endometrial cancers in long-term tamoxifen users.

1. Cohen CJ, Rahaman J. Endometrial cancer: management of high risk and recurrence including the tamoxifen controversy. *Cancer* 1995, **76**(10) Suppl., 2044–2052.
2. Magriples U, Naftolin F, Schwartz PE, Carcangiu, ML. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *J Clin Oncol* **11**, 485–490.

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IV.6 Tamoxifen and Endometrial Cancer: most Cancers are Early Stage and Highly Curable

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A large randomised trial comparing tamoxifen with placebo for breast cancer treatment has demonstrated an average annual hazard rate for endometrial cancer in the placebo group of 0.2/1000 compared to 1.6/1000 for the tamoxifen-treated group, with tamoxifen causing a 7.5-fold increase in the relative risk of endometrial cancer. If the effect of tamoxifen on the endometrium is that of a weak oestrogen agonist, one could expect associated endometrial cancers to have clinical characteristics comparable to those associated with unopposed oestrogen i.e. low stage, well differentiated tumours that are highly curable. © **1998 Elsevier Science Ltd. All rights reserved.**

A REPORT from the Yale Tumor Registry by Magriples and associates [1] suggested that uterine cancers occurring in breast cancer patients on tamoxifen may behave more aggressively and carry a worse prognosis. The authors identified 53 patients with invasive or *in situ* breast cancer who subsequently developed uterine cancer. 15 of the patients had received adjuvant tamoxifen at a dose of 40 mg/day for a mean of 4.2 years, while 38 had not received tamoxifen. Sixty-seven per cent of the uterine cancers occurring in the tamoxifen-treated patients had high grade lesions (grade 3 adenocarcinoma) or high risk histologies (papillary serous, clear cell, mixed mesodermal tumour), compared to 28% of those developing in the 38 breast cancer patients who had not received tamoxifen. In addition, patients in the tamoxifen-treated group were statistically more likely to die of endometrial cancer (33.3 versus 2.6%).

Several recent studies [2–5], however, have not been able to confirm that tamoxifen use is associated with the development of high risk endometrial cancers. Barakat and colleagues [4] reported the Memorial Sloan-Kettering Cancer Center experience in 73 patients with a history of breast cancer who subsequently developed uterine cancer. 23 (32%) had received tamoxifen for at least 1 year, with a median duration of use of 4.5 years, while 50 (68%) did not receive tamoxifen. There was no significant difference in age, mean weight, or median survival following hysterectomy between the two groups of patients. There was no significant difference in the FIGO stage of the uterine cancers occurring in those patients who had received tamoxifen compared with non-users. Seventy-four per cent of the corpus cancers occurring in the tamoxifen-treated group were endometrial adenocarcinomas, while 26% consisted of high risk histologic subtypes, including papillary serous and clear cell carcinomas, as well as uterine sarcomas. This distribution was identical to that seen in the group not receiving tamoxifen. 5 women (22%) from the tamoxifen group died of uterine