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.

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European Journal of Cancer, Vol. 34, Suppl. 4, pp. S49–S50, 1998

Printed in Great Britain
0959-8049/98$—see front matter

PII: S0959-8049(98)00112-9

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

cancer, as did 13 (26%) of those who did not receive tamoxifen. The authors concluded that there was no difference in the stage, grade or histological subtype of corpus cancers that develop in breast cancer patients based on tamoxifen use. Other authors have reported similar results. Fornander and colleagues [5] recently reported the clinicopathological findings of endometrial cancers occurring as second primaries in 931 tamoxifen-treated patients with early breast cancer from the Stockholm Adjuvant Tamoxifen Trial. The median duration of tamoxifen use was 24 months, given at a dose of 40 mg/day. On histological review of these cancers, 82% were FIGO Stage I and all were histological grades 1 or 2. Three deaths (18%) were attributable to endometrial cancer. van Leeuwen and colleagues [2] recently reported the results of a case–control study from The Netherlands Cancer Registry. There was no difference in the FIGO stage or histological distribution of endometrial cancers that occurred in 23 breast cancer patients who received tamoxifen compared to 75 who did not. None of the tamoxifen-treated patients died of endometrial cancer, while 4 who did not receive tamoxifen died. Finally, the results of the NSABP B-14 trial [3] also confirmed that uterine cancers occurring in tamoxifen-treated breast cancer patients were not associated with a higher incidence of adverse histological features. Eighty-eight per cent of the tamoxifen-associated endometrial cancers were FIGO stage I. In addition, 71% were endometroid adenocarcinomas and 78% were low grade lesions. 4 deaths (16.7%) were due to endometrial cancer.

CONCLUSION

The published data would appear to support an association between tamoxifen and the development of both benign and malignant endometrial neoplasia. The increased risk of endometrial cancer associated with tamoxifen use will lead to increased morbidity in breast cancer patients, but this does not appear to outweigh the significant advantage that tamoxifen offers by controlling breast cancer.

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European Journal of Cancer, Vol. 34, Suppl. 4, pp. S50–S51, 1998

Printed in Great Britain
0959-8049/98$—see front matter

PII: S0959-8049(98)00113-0

IV.7 Tamoxifen and Uterine Cancer: Confounding Variables

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The idea that tamoxifen could encourage the growth of pre-existing endometrial cancer caused an increase in the screening and subsequent detection of endometrial cancer in tamoxifen-treated patients. These data are biased because controls were not screened. © **1998 Elsevier Science Ltd. All rights reserved.**

IN 1988 WE demonstrated in the laboratory that tamoxifen could encourage the growth of human endometrial carcinoma but block the oestrogen-stimulated growth of breast carcinoma [1]. These data illustrated the target site specific activity of tamoxifen in different organs. We were concerned that patients who were being treated with long-term adjuvant tamoxifen therapy would have continued growth of occult endometrial disease so we suggested that patients should be screened if they had completed 5 years of therapy.

The Stockholm Trial was the first randomised clinical trial to address the issue [2]. They found that patients randomised to receive up to 5 years of tamoxifen had a 6-fold increase risk of endometrial cancer compared to patients receiving either 2 years of tamoxifen or the control group (Figure 1). However,