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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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,

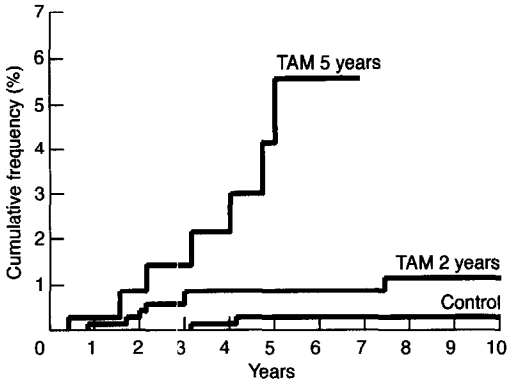

Figure 1. Cumulative frequency of uterine cancer by allocated treatment in the Stockholm Trial. Tam, tamoxifen reproduced by permission from Fornander T, Rutqvist LE, Cedemark B, *et al.* Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancer. *Lancet* 1989, i, 117–120.

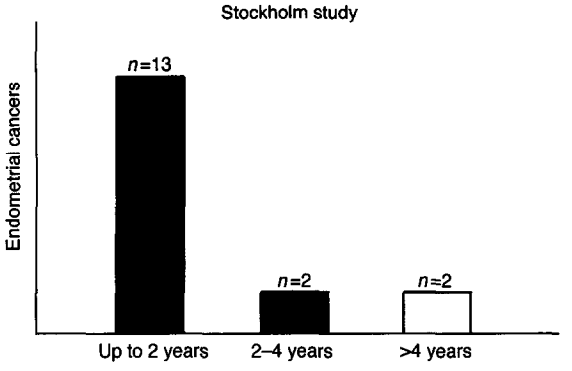

Figure 2. Incidence of endometrial cancer from Fernando T, Hellstrom AC, Moberger B. *J Natl Cancer Inst* 1993, 85, 1850–1955.

following the report by Fornander and colleagues [3] on the histopathology of the endometrial tumours in the Stockholm Trial, we noted that patients receiving tamoxifen usually developed endometrial cancer in less than 2 years (12/16) [4] (Figure 2). We therefore concluded that occult disease was being detected. Indeed the idea is based on the known fact that postmenopausal women harbour five times more endometrial cancers than are presented clinically [5]. Clearly, if this is the case all studies that include monitoring of tamoxifen-treated patients will naturally become biased because those patients will be screened who are concerned or have a vaginal discharge (a known side-effect of tamoxifen).

In summary, the initial paper [1] that called for screening of patients taking tamoxifen has resulted in a detection bias based on overscreening. The epidemiology data base is flawed because of the selective screening of women. However, the idea that tamoxifen is detecting occult disease rather than causing cancer still holds true. Most endometrial cancers are detected within 5 years rather than the 10 year minimum required for carcinogenesis through initiation and promotion.

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IV.8 Tamoxifen to Treat Endometrial Cancer

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THE EPITHELIAL and stromal transformations induced by tamoxifen in cultures of normal and neoplastic endometrium show its oestrogenic, antagonistic and agonistic action, inhibiting on one side the proliferation of the endometrial adenocarcinoma, on the other side causing polypoid endometrial hypertrophy in some breast cancer patients under long-term tamoxifen treatment.

Adjuvant therapy in early endometrial cancer and hormonal treatment of advanced or recurrent adenocarcinoma by means of tamoxifen or of a combination of tamoxifen and high-dose medroxyprogesterone acetate will be discussed.

The histological response, *in vivo*, of primary endometrial adenocarcinoma to short-term tamoxifen treatment is characterised by rapid transformation of pseudostratified carcinomatous