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II.1 Tamoxifen's Oestrogen-like Effects in a Breast Cancer Chemoprevention Trial

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Tamoxifen has been shown to reduce the risk of contra-lateral breast cancers in women by about 40% [Early Breast Cancer Triallists' Collaborative Group E. *Lancet* 1992, 339, 1–15]. We have undertaken a pilot randomised controlled chemoprevention trial of tamoxifen in healthy women with a strong family history of breast cancer. Nearly 2500 healthy women have been randomised to receive either tamoxifen 20 mgs/day or placebo for up to 8 years. Compliance is maintained at over 70% for women on tamoxifen and placebo. Acute symptomatic toxicity of hot flushes, vaginal discharge and menstrual irregularities is low.

WITH SAFETY monitoring we have identified various oestrogenic and anti-oestrogenic effects of tamoxifen on cholesterol, clotting factors, bone mineral density and the uterus. Lipid studies have shown that there is a 15% reduction in total cholesterol within 6 months of starting tamoxifen compared to placebo, maintained out to at least 5 years with a similar reduction in pre- and postmenopausal women. The lipid profile in a subset of 50 pre- and postmenopausal women showed that the reduction in total cholesterol was mainly caused by a fall in the low density lipoprotein (LDL) cholesterol with no obvious reduction in the high density lipoprotein (HDL) cholesterol. These changes were similar for pre- and postmenopausal women and indicate a change in profile which may be cardioprotective [2].

With regard to clotting factors there was an initial reduction in fibrogen levels in all women on tamoxifen over the first year of follow-up and a marginal reduction in antithrombin III and protein S in postmenopausal women at 6 months. There were no changes in cross-linked fibrogen degradation products or Protein C for pre- or postmenopausal women. There was no increase in the incidence of thrombo-embolic events on tamoxifen. These changes indicated that tamoxifen has only marginal oestrogenic effects on clotting factors involved in haemostatis which are unlikely to have any significant clinical effect [3].

Evaluation of bone mineral density (BMD) using dual energy X-ray absorptiometry in 179 women in the programme showed a significant decrease in BMD in premenopausal women on tamoxifen with no change for women on placebo. The mean annual loss in lumbar BMD per year over the 3-year study period for premenopausal women was 1.44% indicating an anti-oestrogenic effect in premenopausal women. Conversely, in postmenopausal women tamoxifen caused an annual increase in BMD of 1.17% in the spine compared with a non-significant loss of BMD for women on placebo. This would indicate an oestrogenic effect of tamoxifen in postmenopausal women [4]. The changes in BMD which have been observed so far appear transient and further follow-up is required in order to evaluate the clinical significance of these changes.

We have also monitored the uterus in postmenopausal women on tamoxifen by repeated transvaginal ultrasound scanning. A persistent endometrial thickening of > 8 mm was identified in about 25% of women on tamoxifen with associated cysts in 16% and polyps in 11% of women on tamoxifen compared to < 1% of the women on placebo. Only 3 women were found to have atypical hyperplasia and 1 carcinoma of the endometrium was found. In all within the prevention programme 5 women have developed endometrial cancer (4 on tamoxifen, 1 on placebo), all in women who at the time of randomisation were premenopausal but subsequently developed amenorrhoea. Within the ultrasound screening study 33 premenopausal women have developed amenorrhoea on tamoxifen compared to only 16 on placebo. 9 of the 33 amenorrhoeic women on tamoxifen were found to have high levels of oestrogen indicating that they were still premenopausal and none of these women had evidence of endometrial thickening. Conversely, of 24 women on tamoxifen who had low levels of oestrogen 46% had evidence of endometrial thickening [5]. These results indicate that tamoxifen has an oestrogenic effect on the endometrium, causing endometrial thickening in the women who develop amenorrhoea on tamoxifen with low levels of oestrogen. In contrast, women who develop amenorrhoea with high levels of oestrogen have no evidence of endometrial thickening indicating an anti-oestrogenic effect of tamoxifen, indicating that the agonist versus antagonist effects of tamoxifen on the endometrium depends, in part, on the prevailing levels of circulating oestrogen.

In conclusion, it would seem that tamoxifen has differential effects on different tissues. Other tamoxifen-like agents might have different spectra of activity on different tissues raising the possibility that some of these agents may be useful for preventing breast cancer, heart disease and osteoporosis with no proliferative effect on the uterus.

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II.2 Tamoxifen and Benign Endometrial Lesions

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Benign endometrial lesions are common among breast cancer patients treated with tamoxifen but also among healthy women taking this drug in a breast cancer prevention trial. The most frequent lesion is glandulocystic atrophy which seems specific for this drug. Endometrial polyps are also very often seen but only a few of them could undergo malignant degeneration. Hyperplasia of the endometrium is more frequently reported among tamoxifen patients than among control patients. © **1998 Elsevier Science Ltd. All rights reserved.**

TAMOXIFEN IS a non-steroidal anti-oestrogen drug widely used as first-line endocrine therapy in breast cancer patients. However, this molecule has also some oestrogen agonist activity on the female genital tract. Our paper summarises the benign endometrial lesions related to tamoxifen use.

Endometrial atrophy remains the commonest histological finding in postmenopausal women receiving tamoxifen but endometrial proliferation, glandulocystic changes, hyperplasia, endometrial decidualisation and various sorts of polyps have all been described with the help of hysteroscopy, transvaginal ultrasound scan, saline infusion sonography, colour Doppler flow studies, Pipelle aspiration or Novak biopsy and curettage. The exact incidence of these lesions is difficult to assess precisely because most publications are describing very different and generally small groups of patients. Furthermore, various study designs are utilised and several instruments of investigation of the cavity have been used. Moreover, different parts of the same endometrium in an individual patient may display contrasting features.

Three benign endometrial lesions have been described among tamoxifen users, the first one being the most typical and specific of the effect of this drug upon the uterine cavity.

Glandulocystic atrophy [1]

Hysteroscopy shows a smooth, white but hypervascularised endometrial layer with many scattered protuberances. This pseudopolypoid glandulocystic mucosa represents an atrophic, thin epithelium overlying cystic dilatations of the endometrial glands in a dense, rich in collagen stroma containing large oedematous areas. In these cases, ultrasonography displays an irregularly thickened endometrium with Gruyère cheese pictures.

Endometrial polyps which frequently contain dilated cystic glands and sometimes also stromal decidualisation changes

Both hyperplastic and atrophic polyps have been reported but, according to Ismail [2], periglandular stromal condensation, epithelial metaplasias and proliferative activity, sometimes with various degrees of atypia, are typical for the histologic appearance of tamoxifen-induced endometrial polyps. Among these patients, ultrasonography will reveal a free-floating glandulocystic structure and hysteroscopy will confirm the diagnosis.

Endometrial hyperplasia: simple or complex, with or without atypia may be observed

Retrospective studies describing tamoxifen effects on the endometrium are numerous and of limited interest because of lack of uniform methodology. A few case–control studies did compare postmenopausal breast cancer patients treated by tamoxifen with similar breast cancer patients without this treatment. Neven [3] using hysteroscopy, Cohen [4] using endovaginal ultrasonography and Exacoustos [5] and Lahti [6] using both methods together, did report on 212 tamoxifen patients. In general they observed oestrogen-like activity (including glandulocystic atrophy) in 20–35% of tamoxifen-