We have reported on a 5.7% incidence rate of benign ovarian pathologies among 175 postmenopausal breast cancer patients with TAM treatment who were all diagnosed by histopathological examination [8]. A high rate (50%) of bilaterality was also noted [8]. Finally, the results of ovarian volume, as detected by transvaginal ultrasonography, in 65 postmenopausal breast cancer patients who were treated for at least 6 months with TAM, were compared to that observed in 311 healthy postmenopausal women with no exposure to hormone therapy. After matching for menopausal age, the mean ovarian volume of the postmenopausal TAM-treated women was persistently low during the menopause, while it was gradually decreasing up to the tenth menopausal year ($8.6 \pm 2.3\ cm^3$ and $2.8 \pm 2.1\ cm^3$, respectively). Mean ovarian volume of the TAM-treated patients was significantly lower than that of the controls during the initial menopausal years [10]. It was therefore concluded that an ovarian volume that is considered to be within normal range for a specific menopausal age in a healthy postmenopausal woman, is abnormal for a postmenopausal TAM-treated patient [10].

1. Ferrazzie E, Cartei G, Mattarazzo R, Fiorentino M. Oestrogen-like effect of tamoxifen on vaginal epithelium. *Br Med J* 1977, **i**, 1351–1352.
2. Boccardo F, Berazzi P, Rubagotti A, *et al.* Estrogen-like action of tamoxifen on vaginal epithelium in breast cancer patients. *Oncology* 1981, **38**, 281–285.
3. Yokosuka K, Teshima H, Kstase K, *et al.* Effects of long-term administration of tamoxifen on vaginal epithelium and complications of endometrial lesions in breast cancer patients. *Nippon-Sanka Fujinka Gakkai Zasshi* 1985, **47**, 125–132.
4. Lahti E, Vuopala S, Kauppila A, *et al.* Moderation of vaginal and endometrial epithelium in postmenopausal breast cancer patients receiving long term tamoxifen. *Gynecol Oncol* 1994, **55**, 410–414.
5. Fornander T, Cedermork B, Mattsson A, *et al.* Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancer. *Lancet* 1984, **21**, 117–120.
6. Andersson M, Storm HH, Mouridsen HT. Incidence of new primary cancer after adjuvant tamoxifen therapy and radiotherapy for early breast cancer. *J Natl Cancer Inst* 1991, **83**, 1013–1017.
7. Rutqvist LE, Johansson H, Signomaklo T, *et al.* Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. *J Natl Cancer Inst* 1995, **87**, 645–651.
8. Cohen I, Beyth Y, Tepper R, *et al.* Ovarian tumours in post menopausal breast cancer patients treated with tamoxifen. *Gynecol Oncol* 1996, **60**, 54–58.
9. Kedar RP, Bourne TH, Powles TH, *et al.* Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomized breast cancer prevention trial. *Lancet* 1994, **343**, 1318–1321.
10. Cohen I, Altaras MM, Beyth Y, *et al.* Ovarian volume in postmenopausal breast cancer patients treated with tamoxifen. *Gynecol Oncol* 1996, **64**, 105–108.

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II.6 Alterations in Steroid Hormone Receptors in the Tamoxifen-treated Endometrium

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Although the mechanism of tamoxifen-induced endometrial neoplasia is thought to be via an oestrogenic effect of tamoxifen, there are few data confirming this. Since sex steroid hormones regulate endometrial growth via interaction with their receptors, oestrogen receptor (ER) and progesterone receptor (PR), a clinicopathological evaluation was performed to determine if these seemingly oestrogenic-like actions of tamoxifen on the uterus are associated with alterations in the expression of endometrial steroid receptors. To evaluate whether tamoxifen has oestrogenic endometrial effects as defined by histology or alterations in steroid receptor expression, 19 postmenopausal (PMP) tamoxifen-treated breast cancer patients who also had endometrial sampling were identified. To examine the subgroup of 15 polyps, age-matched, non-hormonally treated patients with polyps ($n = 8$) or atrophic endometria ($n = 5$) served as comparison groups. Proliferative ($n = 3$) and secretory ($n = 5$) endometria were procedural controls. Immunohistochemistry (IH) for steroid receptor ER and PR was performed.

GLANDULAR CELL progesterone receptors (PR) were significantly increased and stromal cell oestrogen receptors (ER) were significantly decreased in tamoxifen-treated versus atrophic endometria. PR staining was not significantly different in tamoxifen-treated versus control polyps, although staining was high in both groups.

Stromal cell ER staining was significantly reduced in tamoxifen-treated versus control polyps. The immunohistochemistry (IH) scores of the two adenocarcinomas in tamoxifen-treated patients were high for PR and low for ER in glands. The pattern of reduced stromal cell ER IH scores and increased glandular cell PR IH scores was consistently found in all tamoxifen-treated patients regardless of endometrial diagnosis.

There were no significant differences between the subgroups of tamoxifen-treated patients with benign versus malignant or premalignant endometrial pathologies in either the mean number of years of tamoxifen use (4.3 ± 0.8 versus 3.8 ± 1.4, respectively, $P = 0.71$) or endometrial steroid receptor status. There was no significant difference in the mean number of years of tamoxifen use in the women with postmenopausal (PMP) bleeding (3.5 ± 1.1) versus those without bleeding (4.6 ± 0.9) ($P = 0.42$).

There were no significant differences in the histological features of polyps from tamoxifen-treated versus non-hormonally treated patients, including the mean number ($P = 0.87$) and thickness ($P = 0.87$) of blood vessels and the mean stromal cellularity ($P = 0.39$). Every polyp in both the tamoxifen-treated and untreated groups contained dilated, cystic glands, and secretions within the glands. The polyps in each group exhibited other similar typical histological features including variations of glands and spindled-shaped stroma. The tamoxifen-associated polyps did not display any unusual histological features, except for one polyp that contained adenocarcinoma in which there was focal adipose cells within the stroma.

The tamoxifen-associated changes in endometrial steroid receptors and their persistent distinct pattern when compared to all the other study groups supports an oestrogenic uterine effect. This effect is independent of the type of endometrial pathological diagnosis, and the duration of tamoxifen use. This oestrogen-like action of tamoxifen at the endometrial steroid receptor level may contribute to the pathogenesis or growth of endometrial polyps and carcinomas in these patients.

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II.7 The Progestin-like Activity of Tamoxifen on the Endometrium

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We examined 17 carcinomas, one adenosarcoma, one malignant mesenchymal mixed tumour and 100 endometrial biopsies with non-neoplastic lesions from patients under tamoxifen therapy. Of the 17 carcinomas 12 were mucinous, four were of clear-cell type and one was a serous-papillary carcinoma. All carcinomas arose within atrophic endometrium from endocervical type mucinous, clear cell or serous-papillary metaplasias. Fifty-seven of the non-neoplastic specimens showed simple or cystic atrophy, 44 contained atrophic polyps with stromal fibrosis, 28 had moderately proliferating endometria, 32 had endocervical type metaplasias. Our histological studies support the assumption that tamoxifen has an anti-oestrogenic progestin-like action on the endometrium. Adjuvant gestagen therapy given to patients with endometrial carcinoma therefore appears contra-indicated in patients with tamoxifen-induced carcinomas. © **1998 Elsevier Science Ltd. All rights reserved.**

IN RECENT years tamoxifen therapy for breast carcinoma has been associated with endometrial carcinoma. In the literature more than 350 endometrial carcinomas have been reported developing in breast cancer patients during or after tamoxifen therapy [1]. Most of these reports, however, do not provide histological descriptions or microphotographs of the endometrial cancer. This lack of information has led to the false assumption that the tamoxifen-related carcinomas are of the oestrogen-stimulated endometrioid type. Furthermore, sonographic thickening of the endometrium and the detection of

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