2. Andersson M, Storm HH, Mouridson HT. Incidence of new primary cancers after adjuvant tamoxifen therapy and radiotherapy for early breast cancer. *J Natl Cancer Inst* 1991, **83**, 1013–1017.
3. Van Leeuwen FE, Benraadt J, Coebergh JWW, *et al.* Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 1994, **343**, 448–452.
4. Powles TJ, Jones AL, Ashley SE, *et al.* The Royal Marsden Hospital pilot tamoxifen chemoprevention trial. *Breast Cancer Res Treat* 1994, **31**, 73–82.
5. Cohen I, Rosen DJD, Altaras MM, Beyth Y, Shapira J, Yigael D. Tamoxifen treatment in premenopausal breast cancer patients may be associated with ovarian overstimulation, cystic formations and fibroid overgrowth. *Br J Cancer* 1994, **63**, 620–621.
6. Boccardo F, Rubagotti A, Amoroso D, *et al.* Chemotherapy versus tamoxifen versus chemotherapy plus tamoxifen in node-positive oestrogen-receptor positive breast cancer patients. An update at 7 years of the 1st Grocta (Breast Cancer Adjuvant Chemo-hormone Therapy Cooperative Group) Trial. *Eur J Cancer* 1992, **28A**, 673–680.
7. Lanes SF, Birman B, Walker AM, Singer S. Oral contraceptive type and functional ovarian cysts. *Am J Obstet Gynecol* 1992, **166**, 956–961.
8. De Vries EGE, Mourits MJE, ten Hoor KA *et al.* Ovarian cysts in women receiving tamoxifen in a randomized adjuvant breast cancer study +/− high-dose chemotherapy. *Proc Am Soc Clin Oncol* 1997, **16**, 580.

European Journal of Cancer, Vol. 34, Suppl. 4, pp. S22–S23, 1998

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

PII: S0959-8049(98)00094-X

II.5 Tamoxifen and other Genital Tissues: Vagina, Cervix and Ovaries

I. Cohen

Department of Obstetrics and Gynecology, Sapir Medical Center, Kfar Saba, Affiliated with Sackler Faculty of Medicine, Tel-Aviv University, Israel

It has been demonstrated that postmenopausal tamoxifen (TAM) treatment induces an oestrogen-like effect on the vaginal epithelium, including gradual increase in cellular maturity with a consequent increase of intermediate and superficial cells. No association between postmenopausal TAM treatment and vaginal malignancy was reported. Several investigators could not find significant differences in the incidence of new primary cervical cancers in postmenopausal breast cancer patients with TAM treatment as compared to controls and the relative risk for the development of new cervical cancer was low. The incidence of benign ovarian pathologies among postmenopausal breast cancer patients with TAM treatment was found to be higher than that reported for similar pathologies in controls, or among non-selected, asymptomatic and untreated postmenopausal women. © **1998 Elsevier Science Ltd. All rights reserved.**

IT HAS been demonstrated that postmenopausal tamoxifen (TAM) treatment induces oestrogen-like effects on the vaginal epithelium. Maturation index (MI) and Karyopicnotic index (KPI) assessment revealed a significant gradual increase in cellular maturity with a consequent increase of intermediate and superficial cells in the vaginal epithelium of such patients, following TAM treatment for up to 8 weeks [1–4].

No association between postmenopausal TAM treatment and vaginal malignancy was reported. Several investigators could not find significant differences in the incidence of new primary cervical cancers in postmenopausal breast cancer patients with TAM treatment as compared to controls [5–7] and the relative risk for the development of new cervical cancer was low [5–7]. The effect of TAM therapy on the postmenopausal ovary, if any, is not clear. However, since TAM has been found to be a causative agent for various endometrial pathologies and bearing in mind the common ancestry of ovarian and endometrial epithelium and their stroma, it may be speculated that TAM's oestrogen-like action on the ovary may potentially stimulate either ovarian enlargement or the development of ovarian pathological conditions [8].

Several studies showed no significant differences in the incidence of new primary ovarian cancers in postmenopausal breast cancer patients with TAM treatment as compared to controls [5–7]. The relative risk for the development of new ovarian malignancy was also low [5–7]. The incidence of benign ovarian pathologies among postmenopausal breast cancer patients with TAM treatment was found to be higher than that reported for similar pathologies in controls [9] or among non-selected, asymptomatic and untreated postmenopausal women [8].

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.

European Journal of Cancer, Vol. 34, Suppl. 4, pp. S23–S24, 1998

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

PII: S0959-8049(98)00095-1

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

L. Schwartz

Reproductive Endocrinology, Department of Obstetrics and Gynaecology, NYU Medical Center, New York 10016, U.S.A.

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.