tamoxifen could still improve compliance and should not miss any cancers.

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Absence of correlation between risk factors for endometrial cancer and the presence of tamoxifen-associated endometrial polyps in postmenopausal patients with breast cancer

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Abstract

In order to investigate the presence of established risk factors for endometrial carcinoma in postmenopausal patients with breast cancer and with tamoxifen-associated endometrial polyps we compared a group of 25 patients with tamoxifen-associated endometrial polyps with 25 tamoxifen-treated patients without endometrial polyps. No significant differences were found between both groups of patients in age, parity, time after breast cancer and after menopause, duration and daily and total cumulative dose of tamoxifen intake, body mass index and serum levels of luteinising hormone (LH), follicle-stimulating hormone (FSH), oestradiol (E2), progesterone, sex hormone-binding globulin (SHBG), tamoxifen and CA125. So far there is no evidence that these polyps are premalignant lesions.

Keywords: Tamoxifen; Endometrium; Polyps; CA125; Oestrogen; Endometrial cancer

It is well established that tamoxifen can induce endometrial hyperplasia and polyps [1–4]. The possible association between tamoxifen and the occurrence of endometrial cancer has been reviewed [5]. It has been suggested that the risk of developing endometrial cancer may be associated with the oestrogen-agonist effect of tamoxifen on the endometrium and would, therefore, increase with the duration of tamoxifen intake and with higher cumulative tamoxifen doses [6]. However, the pathogenesis of tamoxifen-associated endometrial polyps is unclear. We report here the results from a prospective study based on a randomised trial comparing transvaginal ultrasound (with sonohysterography) and office hysteroscopy [7].

1. Materials and methods

Asymptomatic postmenopausal patients with breast cancer who had taken tamoxifen for at least 6 months were eligible unless they had undergone a hysterectomy. 53 consecutive patients agreed to participate. The daily tamoxifen dosage consisted of either 20 mg ($n=24$) or 40 mg ($n=29$). The histopathological findings combined

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Table 1
Characteristics of 50 tamoxifen-treated postmenopausal patients with breast cancer

Characteristic	Without endometrial polyp ($n=25$)	With endometrial polyp ($n=25$)	P value
Age (years)[a]	59±9	62±8	0.28
Parity[b]	2 (2–3)	2 (1–3)	0.51
Years postmenopausal[b]	9 (5–12)	11 (7–17)	0.33
Years after breast cancer[b]	3 (2–4)	3 (2–7)	0.45
Months of tamoxifen intake[b]	23 (17–38)	23 (12–40)	0.87
Cumulative tamoxifen dose (g)[b]	22 (12–29)	22 (9–36)	0.93
Body mass index[a]	26±4	26±5	0.95
Luteinising hormone[b]	21.6	21.4	0.72
Follicle-stimulating hormone	35.2	33.2	0.80
Oestradiol[b]	0	0	1
Sex hormone-binding globulin[b]	2.45	2.60	0.59
Serum tamoxifen (ng/ml)[b]	192	213	0.40
Serum CA 125[b]	12.8	14.6	0.32

[a] Plus–minus values are means ±standard deviation (S.D.). Difference between 2 subgroups assessed with Student's t-test.
[b] Median (25th, 75th percentiles). Difference between two subgroups assessed with Wilcoxon rank sum test.

with operative hysteroscopic findings were used as the 'gold' standard reference point for the study. Serum tamoxifen levels were measured with reversed high performance liquid chromatography (HPLC) with ultraviolet (UV)-detection. Patients with both a negative office hysteroscopy and sonohysterography were presumed to have no significant endometrial pathology. Statistical analyses were performed using SAS® (SAS Institute Inc., Cary, NC, USA).

2. Results

One patient (with endometrial cancer) was excluded from analysis because no serum sample had been obtained and 2 patients because no resected endometrial samples were obtained.

At operative hysteroscopy, at least one endometrial polyp was confirmed in 25 patients. No significant differences were found between both groups of patients in any of the examined parameters (see Table 1).

4. Conclusion

The presence of tamoxifen-associated endometrial polyps can not be explained by the presence of established risk factors for endometrial cancer. In combination with the data on chromosomal changes detected in tamoxifen-associated polyps [8] these findings support the hypothesis that tamoxifen-associated endometrial polyps may not be induced simply by the drug's oestrogen-agonist activity but that they may be formed from (pre-existing) focal endometrial lesions. A different mechanism is responsible for endometrial polyp and endometrial cancer formation in these patients. Given the very high prevalence of endometrial polyps in tamoxifen-treated breast cancer patients and the relatively low prevalence of endometrial cancer, it does not seem likely that endometrial polyps are premalignant lesions, but obviously cancer may develop in polyps of tamoxifen-treated patients [9]. Future research is necessary to investigate whether follow-up is sufficient in cases with typical cystic tamoxifen-associated endometrial polyps. Furthermore, only a large randomised trial, where a reduction in mortality from endometrial cancer would be the endpoint, could prove that endometrial monitoring in asymptomatic tamoxifen-treated patients is useful.

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Modulation of endometrial transforming growth factor β (TGFβ) by tamoxifen

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Abstract

Transforming growth factor β (TGFβ) immunoreactivity was determined in endometria from non-drug-therapy and tamoxifen-treated patients. Sections were scored for pathology and quantity image analysis performed to determine levels of glandular- or fibrosis-associated TGFβ1. Tamoxifen-treated patients displayed greater levels of endometrial dysplasia and glandular hyperplasia, in addition to a statistically significant ($P < 0.0001$) elevation in gland-associated TGFβ1 protein.

Keywords: TGFβ; Tamoxifen; Breast; Endometria

1. Introduction

Although tamoxifen is of immense value in the treatment of breast cancer, epidemiological evidence has linked its usage with endometrial cancer [1]. We speculate that epigenetic mechanisms of carcinogenicity, involving growth factor modulation, may be responsible [2].

Tamoxifen competes with and inhibits the mitotic actions of oestradiol, yet also appears to modulate growth factors such as TGFα and TGFβ. Indeed, tamoxifen exerts some very beneficial effects on TGFs in the breast as a component of its anti-oestrogenic activity, including the downregulation of the expression of the mitogen TGFα and enhancement of the expression of TGFβ with its negative growth factor influence [3]. Hence, with regard to the pro-oestrogenic action of tamoxifen in the human uterus, a hypothesis of uterine TGFβ dysregulation appears plausible.

2. Experimental

Tissue was obtained by operative hysteroscopy or from hysterectomy and snap-frozen prior to processing. Patient ages ranged from 52 to 64 years for 10 drug-therapy-free patients and 56 to 71 years for 10 tamoxifen-treated patients. Treatment with tamoxifen (20 mg/day) was for between 25 and 91 months. Sections were prepared to provide sequential slides for both TGFβ1 immunostaining and comparative haematoxylin and eosin (H&E) staining. Sections were coded, blinded and microscopically examined/graded for areas of dysplasia, fibrosis and glandular hyperplasia.

Statistical analysis of pathology scoring using a Mann–Whitney two-tailed test, demonstrated significantly greater dysplasia and glandular hyperplasia in tamoxifen-treated patients as compared with drug therapy-free controls. A similar, but non-statistically significant, finding was found with respect to endometrial fibrosis.

Examination of slides stained for TGFβ1 immunoreactivity demonstrated that staining in tamoxifen-treated patients was mainly confined to the apical border of the epithelium together with inflammatory cell infiltrates, although some cytosolic and basolateral staining was present. Immunoreactivity associated with glandular or fibrotic elements was assessed using quantity image analysis. Fig. 1 shows the results and demonstrates the significantly greater level of gland-associated TGFβ1-staining measured in tamoxifen-treated patients, compared with drug therapy-free controls ($P < 0.0001$).

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