Adjuvant Tamoxifen in Breast Cancer Patients Affects the Endometrium by Time, an Effect Remaining Years after End of Treatment and Results in an Increased Frequency of Endometrial Carcinoma

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Abstract. *Tamoxifen is the most used adjuvant drug in breast cancer treatment. Its main action is as an anti-oestrogen, but in the endometrium of some patients it acts as an oestrogen. Some investigators have even reported an increased risk of developing endometrial carcinoma. The question of how to follow-up these patients and how to identify patients at risk of developing endometrial premalignant changes was investigated by the non-invasive ultrasound method. The follow-up of 292 patients from before the start of adjuvant treatment with tamoxifen and 94 without tamoxifen treatment was conducted at regular intervals. The changes in endometrial thickness as measured by ultrasound and histopathological changes are reported. A thicker endometrium was found in patients with receptor positive breast cancer even before the treatment with tamoxifen started. Cumulative increasing thickness was found during treatment and this thicker endometrium remained until almost 3 years after the end of treatment. If the endometrium was <3 mm after 3 months of treatment the probability that it would be thin after 5 years was high. An increased risk of developing endometrial carcinoma was found, however due to this regular follow-up the cancer was identified at an early stage.*

Tamoxifen is the most used anti-hormonal adjuvant medicine in breast cancer treatment for more than 25 years. Its main action is as an anti-oestrogen, by blocking the oestrogen-receptor on the breast cancer cells, thus reducing proliferation. Tamoxifen, however, also has an oestrogen effect and thereby different actions in different organs. It acts as a pure oestrogen in the skeleton and endometrium but as an anti-oestrogen in the vagina and bladder. Climacteric symptoms might also be aggravated by tamoxifen. Effects on the endometrium do not occur in all patients and are of differing magnitude. Few Swedish patients stop taking tamoxifen in the adjuvant setting due to side-effects, which are thus hard to anticipate for individual patients. These differences might be explained by recent results indicating that more than one kind of oestrogen receptor exists (1, 2). The oestrogen action in the endometrium has been reported to cause a two-to-seven-fold increase in endometrial carcinoma (3, 4) while others have found no increased risk (5).

This has raised the question of whether it is possible to identify individual patients at risk of developing endometrial changes and eventually cancer and whether a non-invasive method such as ultrasound could identify those at risk.

The aim of this longitudinal study on breast cancer patients was to gain information by ultrasound measurements regarding the development of endometrial thickness before the start of tamoxifen treatment and then at regular intervals including the years after the end of treatment. The risk of developing endometrial changes connected to increasing endometrial thickness was also estimated by curettage. In cases with thicker endometria by ultrasound also hysteroscopy was also performed.

Patients and Methods

Since 1987 patients with breast cancer treated at the University Hospital in Lund have been invited to follow-up at the department of Obstetrics and Gynaecology. They were all treated as ordinary patients paying for their visits. Four hundred and fourteen patients accepted the offer. There were 386 patients of more than 55 years of age at the first visit. Initially younger patients in cases of cessation of menstruation during treatment were included.

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Key Words: Adjuvant tamoxifen, endometrial carcinoma, breast cancer, ultrasound.

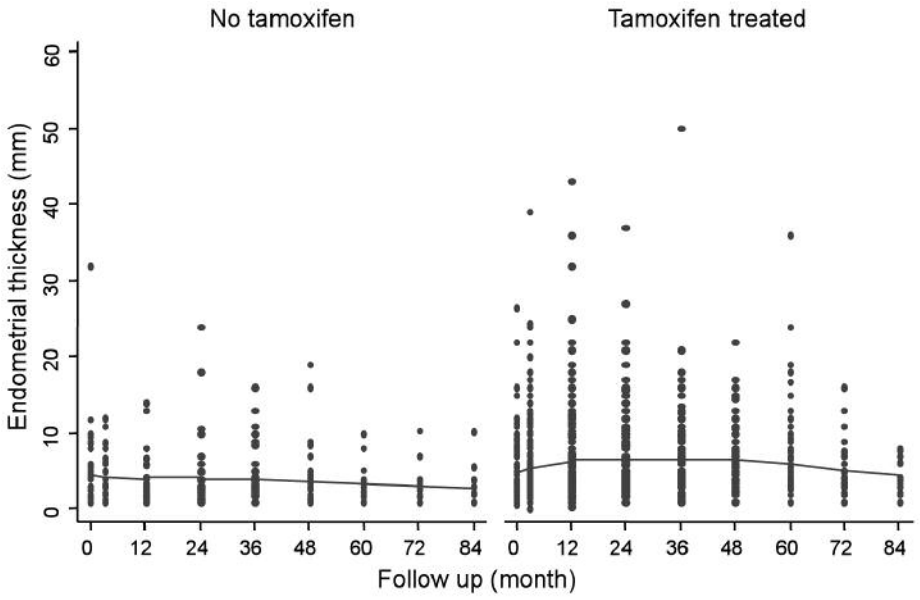

Figure 1. *Those patients on tamoxifen were generally treated for 5 years. The endometria of those treated with Tamoxifen are thicker as among those not treated with Tamoxifen. This thickness remains for several years after end of treatment.*

Out of these patients 292 were receptor-positive and thus treated with adjuvant tamoxifen and 94 patients were followed-up without tamoxifen treatment. The first assessment took place after the primary operation of the breast cancer *before* the start of the adjuvant treatment, the second after 3 months of treatment and then at yearly intervals. The assessment included a routine gynaecological examination and ultrasonographic examination of the endometrium. Endometrial sampling was suggested if the endometrium was between 4-6 mm in a postmenopausal patient and if thicker than 6-8 mm a hysteroscopy was suggested. The dose of tamoxifen used in this study was 20 mg daily until the end of treatment after 5 years or until the patient or her treating doctor decided otherwise. Some patients initially included in the study continued tamoxifen treatment for only two years and were subsequently excluded. The medial follow-up time was 24 months with minimum 3 months and maximum 108 months follow-up.

Statistics. Change in endometrial thickness during follow up was analysed using a random intercepts model including time, age, and an indicator for tamoxifen treatment. Time was included with a second degree term to capture decreasing marginal change. Data in Figure 1 are presented with locally weighted regression (loess) curves.

STATA v9 (Stata corp, 4905 Lakeway Drive, College Station, Texas 77845, USA) was used for the calculations.

Results

Endometrial thickness as by ultrasound. The endometrium was thicker in patients with receptor positive breast cancer before the start of treatment (Figure 1). This thickness was also correlated with the concentration of estrogen receptors in the mammary carcinoma. The mean value of estrogen receptor concentration was 110.3 (134 std) as measured in 159 patients. R=–0.29 and p=0.0040 using Spearman's rank correlation. The individual endometrial thickness before the start of tamoxifen treatment had no predictive value for the later endometrial thickness.

There was a strong correlation between the endometrial thickness in the individual patient over time (intraclass correlation 0.45 (0.39-0.51), Figure 1). The sensitivity was 316/377 (84%) but the specificity only 3/26(12%). Thus most of those with increasing endometrial thickness could be identified but too many patients with sudden endometrial growth were missed.

The endometrial thickness in the tamoxifen treated patients was on average 1.7 mm (95% confidence interval 0.73-2.74 mm) during follow-up. Time and time squared were statistically significant (both p<0.0001), but age was not (p=0.205). However, the time effect seemed to be restricted to tamoxifen treated patients only. When analysed separately the measurements showed an initial increase of 0.091 mm/month with a marginal reduction of 0.002 mm. Both effects were statistically significant (p<0.0001). Among the patients without tamoxifen treatment these time change measurements were both negative, and neither of them were statistically significant (p=0.8 and p=0.5, respectively).

Histopathology. For the patients with receptor positive tumours the rate of endometrial thickness of 4-6 mm and >6 mm is shown in Table I. Before the start of tamoxifen

Table I. *The results of follow-up indicated an increased risk of developing endometrial carcinoma as well as endometrial hyperplasia following Tamoxifen treatment.*

Time for investigation no invest patients	3 months 279	1 year 294	2 years 231	3 years 200	4 years 162	5 years 136	6 years 95
4-6 mm	75 (26%)	64 (22%)	72(31%)	54 (27%)	41 (25%)	35 (26%)	25 (26%)
>6 mm	93 (33%)	101 (34%)	57(25%)	58 (29%)	46 (28%)	36 (26%)	11 (12%)
Histopathology							
atrophy	40	52	31	29	20	18	8
polyp	13	18	16	13	10	11	3
hyperplasia	0	1	2	4	0	0	2
endometrial carcinoma	1	2	0	2	2	0	1

treatment 220 patients aged >55 years were investigated and 17 had an endometrial thickness >6 mm. Five patients refused sampling, 5 presented atrophic endometrium, 5 polyps and 1 atypical hyperplasia and 1 poorly differentiated endometrial carcinoma.

In the 94 patients without tamoxifen treatment 5 showed increased thickness during follow-up 4 at 4-mm, 3 with atrophy and one proliferatory and one >6 mm with atrophy. There was also one patient with bleeding and thickness <4 mm with poorly differentiated endometrial carcinoma.

Thus we followed 292 patients with adjuvant tamoxifen treatment for five years. In 9 patients endometrial hyperplasia was diagnosed and in 8 endometrial carcinomas.

Discussion

The positive clinical outcome of tamoxifen treatment for oestrogen and/or progesterone-receptor positive breast cancers has been continuously monitored by the Early Breast Cancer Trialist' Collaborative Group (6).

As we reported previously (7) a thicker endometrium was found in patients with receptor positive breast tumours as compared to receptor negative breast tumours even before the start of adjuvant therapy however in the present study increased endometrial thickness before start of treatment did not increase the risk of developing endometrial malignancy in contrast to an earlier report by Berliére *et al*. (8) . If the endometrium remained atrophic (<3mm) after 3 months of treatment there was a substantially lower risk that it would be increased after 5 years of treatment, but the specificity was only 12%. This indicate that too many patients would be missed if follow-up of those expected thin endometrium was stopped. In the remaining patients the thickening increased during treatment and remained so until 2.5 years after the end of treatment. This increase in endometrial thickness succeeded although patients with endometrial thickness >8 mm underwent hysteroscopic removal of polyps and fibroids when found. In contrast to the results of Patriarca *et al*. (9) that the thickened endometria caused by oestrogen decreased to pre-treatment thickness in 90% of the patients within 7 days after ending oestrogen, in the present study the effect of tamoxifen remained for a much longer period of time. Stromal proliferation and histopathological changes in the endometrium have been linked to a thick endometrium (10).

Increased thickness was a normal finding in the tamoxifen-treated patients in the present study and not a pathological finding. As many as 50-60% of patients on tamoxifen had an endometial thickness as measured by ultrasound of more than 4 mm. The vast majority had atrophic endometria or benign polyps when examined histopathollogically. However an increased frequency of endometrial hyperplasia (nine patients) and carcinoma (eight patients) was found versus expected one. All the endometrial carcinomas were identified before signs of bleeding and treated with a simple hysterectomy. To date no relaps has occurred.

Later in this clinical program endometrial ablatio was performed in patients with endometrial thickening to avoid the development of endometrial changes. The result of this treatment has not yet been evaluated.

As an increased frequency of endometrial hyperplasia (9/294=3%) with a concomitant risk of developing endometrial carcinoma (11) as well as endometrial carcinoma (8/294=3%), compared to 27/100000 in a published study (12) was found in the present study, regular follow-up with ultrasound during tamoxifen treatment could be useful. This follow-up should continue at least until more than one year after the end of therapy. When hysteroscopy is performed it is a simple act to perform endometrial ablation. This may prevent the development of malignancy.

Acknowledgements

We thank the Anna and Bror Bjorusson Foundation, as well as the Funds of Uppsala University Hospital, Sweden.

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Received November 7, 2007
Revised January 17, 2008
Accepted February 6, 2008