

Endometrial Changes in Women on Tamoxifen for Breast Cancer

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Abstract

- Background** Tamoxifen is a selective estrogen receptor modulator (SERM) that is widely used in the treatment of patients with breast cancer and for chemoprophylaxis in high risk women. Tamoxifen results in a spectrum of endometrial changes due to its estrogenic effect on the endometrium.
- Objectives** To evaluate the extent of endometrial pathologies that might develop in postmenopausal breast cancer patients following treatment with tamoxifen.
- Methods** Sixty postmenopausal with breast carcinoma women were involved in this study, Thirty women were receiving 20-40 mg of tamoxifen daily for a period of 6 to 60 months constitutes the study group, and a control group included 30 postmenopausal breast carcinoma patients who were not receiving tamoxifen. Transvaginal sonography was performed for the measurements of the endometrial thickness and the presence of endometrial pathology. All the patients underwent endometrial sampling and the curetting were sent for histopathological examination.
- Results** There was statistically significant increase in the frequency of endometrial pathology in those on tamoxifen; there was 11 endometrial pathologies in the case group, while the control group was associated with only 3 pathologies ($p=0.015$). There was significant difference in endometrial thickness between case group (0.73 ± 0.32 mm) and the control group (0.5 ± 0.16 mm) with p value 0.002. Only patients with endometrial thickness of more than 5mm were associated with pathologies, 7 (38.8%) of the endometrial biopsies revealed normal endometrium, whereas, 11 (61.1%) had endometrial pathology like hyperplasia, endometrial polyp or carcinoma. The rate of endometrial pathologies considerably increase with increasing duration of treatment.
- Conclusion** The long term use of tamoxifen as adjuvant therapy for carcinoma breast is associated with increase frequency of endometrial pathology. Endometrial thickness is increased in such patients and is related to the duration of tamoxifen use.
- Key Words** Tamoxifen, Endometrial pathology, Breast cancer.

Introduction

Tamoxifen, A nonsteroidal antiestrogen, was first approved by the Food and Drug Administration for the treatment of patients with breast cancer in 1978. Large clinical trials involving over 75,000 patients have demonstrated an improved recurrence-free and overall survival benefit in both pre- and postmenopausal women ⁽¹⁾. Long-term adjuvant tamoxifen is the endocrine treatment of choice

for selected patients with breast cancer, and there are currently large-scale trials continuing to evaluate its role as a chemopreventative agent in healthy women at risk for breast cancer. One of the most significant complications of long-term tamoxifen use is the possible development of endometrial cancer. Although tamoxifen is believed to exert its main effect by blocking the binding of estrogen to the estrogen receptor (ER), it exhibits a wide range of biologic

effects that may account for its activity in ER-negative tumors as well as some of its unwanted side effects. These include inhibition of calmodulin, stimulation of transforming growth factor beta secretion, induction of apoptosis, interaction with P-glycoprotein, inhibition of protein kinase and phospholipase C, and stimulation of phosphoinositide kinase activity⁽²⁾.

Although primarily an antiestrogen, tamoxifen may also exhibit some mild estrogenic effects. After an initial report by Killackey et al⁽³⁾ which suggested a possible link between tamoxifen use and the development of endometrial carcinoma in three patients. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14⁽⁴⁾ performed a randomized trial of tamoxifen versus placebo in women with ER-positive breast cancer confined to the breast with negative axillary nodes. Results from this trial of 4,063 patients revealed a 7.5-fold increase in the risk of developing endometrial cancer in the tamoxifen-treated group. The average annual hazard rate for endometrial cancer was 0.2 per 1,000 women in the placebo group and 1.6 per 1,000 women in the randomized tamoxifen-treated group.

Indications for tamoxifen use have broadened to include long-term adjuvant therapy as well as preventative therapy for selected high-risk women. Consequently, a large number of women, including healthy, young patients with no history of cancer, will be subjected to the long-term effects of tamoxifen. In the NSABP P-1 trial, 13,338 women at increased risk for breast cancer were randomly assigned to tamoxifen versus placebo for 5 years⁽⁵⁾. Tamoxifen reduced the risk of both invasive and noninvasive breast cancer by 49% and 50%, respectively. The authors reported 33 cases of endometrial cancers in the tamoxifen-treated group compared with 14 in the control group (relative risk = 2.53). The cancers in the tamoxifen-treated group occurred predominantly in women over the age of 50. These cancers were diagnosed at an early stage and, therefore, did not result in any deaths as a result of

endometrial cancer. This study investigates the association between tamoxifen uses in breast cancer patients and associated uterine pathology.

Methods

This case control study was conducted from the beginning of March 2010 to the end of July 2011. Postmenopausal women with breast cancer who attended the oncology outpatient clinic at al-kadhmiya teaching hospital for regular control for their breast cancer were asked to participate in this study.

All patients were treated by primary breast surgery, Adjuvant radiotherapy and/or chemotherapy were included in the therapeutic plan, according to current guidelines of oncology department at Al-Kadhmiya Teaching Hospital. Postmenopausal status was defined as more than 12 months amenorrhea.

In total, 60 women with an intact uterus and without gynecologic symptoms (bleeding or discharge) took part in the current study.

Thirty women were receiving 20-40 mg of tamoxifen daily for a period of 6 to 60 months constitutes the case group, and a control group included 30 postmenopausal breast carcinoma patients who were not receiving tamoxifen.

Patient approval was obtained from each patient after the nature of the study was fully explained. None of the women in either group used hormone replacement therapy at the time of the investigation.

Age, body mass index, the years since menopause, history of hypertension, diabetes and smoking were recorded.

Transvaginal ultrasound

Transvaginal ultrasonographic measurements of the endometrial thickness was performed by senior sonographer using Siemens Versa (Germany) ultrasound machine with 6.3 MHz transducer as follows: Patients consent was obtained and following explanation of the technique, the women asked to empty her bladder and were placed in the dorsal lithotomy position, a small amount of gel is applied to transducer tip, and the tip and the shaft of the

probe covered with condom, apply a small amount of lubricant gel to allow easy insertion of the probe.

The Measurements of the endometrial thickness were performed in the thickest part in the longitudinal plane. The measurement included both endometrial layers. When the endometrial layers were separated by intracavity fluid, both layers were measured and the sum was recorded.

All the patients underwent endometrial sampling using Novak curette size 3mm without anesthesia and the curetting was sent for histopathological examination done in the pathology department in Al-Kadhimiya hospital. Slides were reviewed by senior pathologist.

Endometrial pathology was defined by the presence of one or more of the following histologic findings: proliferative endometrium, simple hyperplasia, complex hyperplasia with or without atypia, endometrial polyp, or endometrial carcinoma. The endometrium was considered as negative if no finding, other than atrophic endometrium, was diagnosed.

Statistical analysis

Data were analyzed using SPS version 16 & Microsoft office Excel 2007. Numeric data were presented as means±SD and nominal data were presented as number and percents. Numeric data were analysed using T test or ANOVA while nominal data were analysed using Chi-Square. P value <0.05 was considered significant.

Results

60 patients with carcinoma of breast were included in this study. 30 patients were on tamoxifen constitute the study group and 30 patients were without tamoxifen use constitute the control group.

The medium age of the on tamoxifen group was 57.17±5.71 and of the without treatment was 54.80±4.92.

Mean BMI for the study group was 30.73±3.09, and 29.40±4.19 for the control group. Mean parity was 3.40±2.12 and 4.20±3.02 respectively. Patients in study group were older, with higher BMI, but with lesser parity than the control group. The median duration of tamoxifen use was 3.31 years(range: 4.83-1.79).

The mean time since breast cancer diagnosis in months in study group was 48±17.57 and in control group was 32.73±13.00, the difference was statistically significant with longer duration in study group. The study group was associated with 11 endometrial pathologies while the control group was associated with only 3 pathologies. The p value was (0.015) so it was statistically significant. There was significant difference in endometrial thickness between study group (7.3±3.2 mm) and the control group (5.0±1.6mm) with p value 0.002. as shown in table 1. There is no difference in co morbid conditions(hypertention, DM) between the two groups.

Table 1. Comparison Between Patients On Tamoxifen Treatment And Those With No Tamoxifen Treatment

Characteristic	Patients on tamoxifen N = 30	Patients with no tamoxifen N = 30
Age (years)	57.17 ± 5.71	54.8 ± 4.92
BMI (Kg/m2)	30.73 ± 3.09	29.4 ± 4.19
Parity	3.4 ± 2.12	4.2 ± 3.02
Age at menopause (years)	48.4 ± 2.56	47.63 ± 2.32
Smoking	6	6
DM	8	7
Hypertension	8	5
Time since breast cancer diagnosis (months)	48.0 ± 17.57	32.73 ± 13.0***
Endometrial pathology	11	3*
Endometrial thickness (mm)	7.3 ± 3.2	5.0 ± 1.6**

* = P 0.05, ** = P 0.005, *** = P 0.001

Table 2: Relation of Endometrial Thickness and Frequency of Endometrial Pathology in Study Group

Endometrial thickness	No. of patients	%
< 5 mm	5	16%
5 mm	7	23.3%
> 5 mm	18	60%
<i>P</i> = 0.003		

In the study group, 5 patients (16%) showed endometrial thickness of less than 5 mm, while 7 (23%) showed endometrial thickness of 5 mm, 18 patients (60%) with endometrial thickness more than 5 mm. The mean endometrial thickness was 0.73 mm.

There is statistically significant relation between endometrial thickness and endometrial pathology (*p*=0.003). as shown in table 2.

Only patients with endometrial thickness of more than 5mm was associated with pathologies, 7 (38.8%) of the endometrial biopsies revealed normal endometrium, whereas, 11(61.1%) had endometrial pathology like hyperplasia, endometrial polyp or carcinoma. As endometrial thickness increased, the incidence of abnormal finding was increased. Endometrial pathology was present in three cases in the control group and all of them were in those with endometrial thickness of more than 5mm, as shown in table 3.

Table 3. Relation of endometrial thickness and frequency of endometrial pathology in control group.

Endometrial thickness	No. of patients	Percent %	endometrial pathology
< 5 mm	13	43.3	0
5 mm	8	26.6	0
> 5 mm	9	30	3
<i>P</i> = 0.02			

There were four cases of simple hyperplasia ,two cases of Complex atypical hyperplasia, two

cases of benign endometrial polyp and three cases with endometrial carcinoma in the study group. As shown in table 4.

There were only two cases of simple hyperplasia and one case with polyp in the control group. There was no endometrial carcinoma detected in control group. As shown in table 4, the incidence of total endometrial abnormalities in the tamoxifen group was greater than that in the control group (*P* < 0.015)

The three cases of endometrial carcinoma developed in those on tamoxifen were well differentiated stage I endometrioid adenocarcinoma.

Table 4. Type of pathologies of the endometrium for study and control groups.

Endometrial pathology	Tamoxifen		Total	P value
	Yes	No		
Negative	19	27	46	0.015
Simple hyperplasia	4	2	6	0.671
Complex atypical hyperplasia	2	0	2	0.492
Polyp	2	1	3	1.000
CA	3	0	3	0.237
Total	30	30	60	

There was significant relation between duration of treatment and endometrial thickness, after 3 years of treatment there is marked rise in number of patient with thickened endometrium. As shown in table 5.

Table 5. Relation between duration of use of tamoxifen and endometrial thickness

Duration of use	≤ 5 mm thickness	> 5 mm thickness
6 months – 1 year	2	1
1 year – 2 years	3	0
2 years – 3 years	4	3
3 years – 4 years	0	3
> 4 years	3	11
<i>P</i> = 0.036		

Table 6. The correlation between duration of tamoxifen exposure and the abnormalities detected in the study group

H/P diagnosis	≤1 year exposure N = 3	>1 year exposure N = 27	Odds ratio	95% CI	P value
Negative	2	17	1.17	(0.094-14.68)	1.000
(atrophic)	1	10	0.98	(0.77-1.25)	1.000
Positive	0	4	1.17	(1.00-1.37)	1.000
simple	0	2	1.08	(0.97-1.20)	1.000
complex hyperplasia polyp	1	1	0.1	(0.01-0.64)	0.18
endometrial carcinoma	0	3	1.12	(0.98-1.28)	1.000

Table 6 describes the distribution of endometrial pathologies with relation to duration of tamoxifen treatment, 3 (10%) patient were on tamoxifen for a duration of one year or less, 27(90 %) used it for a duration more than one year. The rate of endometrial pathologies considerably increase with increasing duration of treatment.

Three patient were on tamoxifen therapy (40 mg \day). One of them had carcinoma and the other have complex hyperplasia and one of normal endometrium. Twenty seven patients was on tamoxifen 20 mg \day, two had cancer, two with polyp, one with complex hyperplasia and four with simple hyperplasia, as shown in table 7.

Table 7. Comparison between different doses of tamoxifen regarding endometrial pathology in the study group

Dose	Negative	Positive pathology	Total
20	18	9	27
40	1	2	3
Total	19	11	30
<i>P</i> = 0.548			

Discussion

The oestrogen-receptor antagonist tamoxifen is effective in premenopausal, perimenopausal, and postmenopausal women with oestrogen-receptor positive breast, including hyperplasia, polyps, cancer, and uterine sarcoma reported; Tamoxifen users have a two fold to seven fold

increased risk of endometrial cancer, and the risk seems to be highest after long-term use (2-3/1000 women per year, during or after Tamoxifen therapy)^(6,7).

In our study there was statistical significant difference in number of pathologies between tamoxifen treated and control groups (*p*=0.015). Our findings are consistent with those of Cohen et al. They found a high rate of pathological endometrial changes among asymptomatic, postmenopausal patients who have been treated with tamoxifen for breast cancer, compared with non-treated patients. Twenty-two (29%) of the 77 postmenopausal women tested had positive histological findings in the endometrial biopsy⁽⁸⁾.

Mcgonigle *et al* failed to detect a single case of endometrial hyperplasia after tamoxifen therapy, in this study patients with thickened endometrium and significant endometrial pathologies prior to tamoxifen therapy were excluded. As such, the effects on the endometrium detected after tamoxifen therapy were unlikely to be preexisting but rather a true effect of tamoxifen. At baseline, 80% of patients had atrophic endometrium and 9% proliferative endometrium compared with 61% and 26% at 1 year, respectively. No cases of endometrial hyperplasia or adenocarcinoma were detected. Findings observed at 6 months persisted through 5 years of follow-up. They conclude that tamoxifen exerts a weak estrogenic effect on the vagina and uterus in pre-screened

postmenopausal women without preexisting endometrial pathology⁽⁹⁾.

We found a significant increase in endometrial thickness in tamoxifen treated group than in the control, and a highly significant positive correlation between the duration of tamoxifen treatment and endometrial thickness ($P=0.036$), and we found abnormal endometrial biopsy in 36.6% ($p = 0.015$) of women treated with tamoxifen and a significant relation between endometrial thickness and risk of endometrial pathology ($p=0.003$). Women with long-term use of tamoxifen (four or more years) were more likely to develop uterine pathology than nonusers.

The time-dependent nature of the development of endometrial pathology by women treated with tamoxifen (shown in our study) is in accordance with the report by Decensi et al that tamoxifen at 20 mg per day exerts a time-dependent proliferative effect on the endometrium⁽¹⁰⁾.

Kochar *et al* noticed a significant relation between endometrial thickness and duration of tamoxifen treatment ($P=0.025$) as in the present study and a significant linear relationship between the symptomatic status and duration of tamoxifen use ($P < 0.01$), and a significant linear relationship between endometrial thickness and duration of tamoxifen use⁽¹¹⁾.

The British Tamoxifen Second Cancer Study Group showed that the odds of endometrial cancer associated with tamoxifen use increased significantly with increasing duration of use up to 10 years ($P= 0.001$)⁽¹²⁾.

Fishman *et al* found that endometrial thickness increased with increasing duration of tamoxifen use at a rate of 0.75 mm/yr. The mean endometrial thickness after 5 years of tamoxifen use was 12 mm (range 6 to 21 mm). After discontinuation of tamoxifen treatment the endometrium decreased by 1.27 mm/yr⁽¹³⁾.

MIGNOTTE *et al* results clearly support the notion that tamoxifen increases the risk for endometrial cancer, with a significant crude overall risk, mainly dependent on the duration of treatment (relative risk 1.5 per year of

treatment) irrespective of the daily dose. estimates for the RRs for endometrial cancer associated with the duration of treatment at this dose 20 mg were particularly high after 3 years of treatment⁽¹⁴⁾.

Gerber *et al*, reported that mean endometrial thickness in tamoxifen- treated patients ranged from 7.2 ± 8.5 to 12.1 ± 12.4 mm, compared with 1.5 ± 4.3 to 5.4 ± 2.7 mm in controls⁽¹⁵⁾.

Nahari *et al* were unable to find a significant effect of the duration of tamoxifen exposure on the endometrial thickness, whereas other investigators have reported such a correlation⁽¹⁶⁾.

Ozsner *et al* have shown that tamoxifen use increases the risk of endometrial cancer and premalignant change. They also noticed significant relation between endometrial thickness and duration of tamoxifen treatment ($P=0.025$) as in our study⁽¹⁷⁾.

Bernstein *et al* in a case control study concluded that endometrial cancer associated with tamoxifen use and the risk increased with the duration of tamoxifen use⁽⁶⁾.

Leeuwen *et al* emphasized that there was a significant increasing risk of endometrial carcinoma with duration of tamoxifen use, and also with cumulative dose⁽⁷⁾.

Cohen I et al, reported that endometrial pathologies are associated with high cumulative doses of tamoxifen administered to postmenopausal breast cancer patients. Women who received 20 mg of tamoxifen daily developed endometrial pathologies after longer periods of treatment compared to those who were treated with 40 mg of tamoxifen daily⁽⁸⁾.

This is not consistent with our result since we fail to demonstrate any association between dose of tamoxifen and endometrial pathologies, perhaps because of small size of our sample.

The National Surgical Adjuvant Breast and Bowel Project study suggested that the incidence of uterine malignancies is increased in women taking tamoxifen⁽⁴⁾.

Magriples, et al. reviewed 53 patients diagnosed with breast cancer who subsequently developed uterine malignancy and found that 67% of

tamoxifen users developed a uterine cancer of high risk histologic type as compared to 24% of tamoxifen non-users, $p=0.03$ ⁽¹⁸⁾.

The Stockholm Trial showed a continued divergence of the cumulative incidence curves of endometrial cancer for the tamoxifen treated and control groups even several years after cessation of tamoxifen treatment⁽¹⁹⁾.

Katase et al concluded that tamoxifen does not appear to increase subsequent endometrial carcinoma in patients with primary breast carcinoma who underwent annual screening for gynaecologic cancer⁽²⁰⁾.

Long-term tamoxifen exposure, obesity, and prior estrogen replacement therapy older menopausal age, and longer duration of breast disease may increase the risk of tamoxifen-associated endometrial pathology.

In our study we found no difference in age, BMI, parity, age at menopause, DM and HT comorbidity in both treatment and control group.

We found no difference in these variables between patient with pathology after tamoxifen treatment and patient without pathology. Therefore, it was impossible to predict which of these women would have developed pathological endometrial changes.

Bland et al find There were no significant differences in age, BMI, or medical comorbidities or other demographic variables that they identified between tamoxifen users and non-users⁽²¹⁾.

Mandana et al. find that, patient-related risk factors for endometrial cancer including age, history of unopposed estrogen use, and comorbid conditions such as obesity, hypertension, and diabetes were similar between the tamoxifen treated and non tamoxifen groups⁽²²⁾.

Cohen *et al* could find no risk factors nor any high risk subgroup among the women in their study There was only a statistical tendency of lower mean age or those patients with positive histological findings when compared to those with negative findings ($P = 0.0510$)⁽⁸⁾.

Patients should be told of the small risk of endometrial cancer (even after stopping the use

of the drug), and encouraged to report relevant symptoms early. They can, however, be reassured that the clinical benefits of treatment far outweigh the risks.

Women using tamoxifen should seek prompt medical attention and prompt investigation required if abnormal vaginal bleeding including menstrual irregularities, vaginal discharge, and pelvic pain or pressure in those receiving (or who have received) tamoxifen.

Seoud et al concluded that the value of routine screening for endometrial pathology in patients on tamoxifen is controversial. They found that all patients who developed an abnormal endometrium had abnormal vaginal bleeding⁽²³⁾. Peters-Engl et al demonstrated that clinical benefits of tamoxifen greatly outweigh the risk. They recommended annual follow up of patients on tamoxifen⁽²⁴⁾.

The etiology of endometrial cancer in tamoxifen-treated patients has been theorized to be related to estrogenic effects on the endometrium, and randomized studies have been undertaken to determine if oral or intrauterine progestins can reduce the negative effects of tamoxifen on the uterus^(25,26).

Depending on the specific clinical situation, recent data suggest equal or superior efficacy of selective estrogen receptor modulators and new antiestrogens compared with tamoxifen for women with breast cancer^(27,28).

Despite the introduction of these newer hormonal therapies, tamoxifen remains the standard initial adjuvant therapy for women with hormone receptor-positive breast cancer and is still the most common hormonal therapy used for breast cancer patients. The clinician must keep in mind, however, that tamoxifen is highly effective in reducing recurrence and deaths from breast cancer, and the risk to the patient of developing endometrial cancer while taking this drug is no worse than that of unopposed estrogen administration.

The most recent American College of Obstetricians and Gynecologists guideline for tamoxifen use and endometrial cancer risk has several recommendations for postmenopausal

women: Routine endometrial screening is not recommended for women taking tamoxifen because of the costs incurred and risk of unnecessary further investigation. Instead, women should be educated regarding the symptoms of endometrial cancer and instructed to consult their doctor if they develop any spotting or postmenopausal bleeding. If a woman develops endometrial hyperplasia, the use of tamoxifen should be re-assessed⁽²⁹⁾.

The present study has shown that long term use of tamoxifen as adjuvant therapy for carcinoma of the breast is associated with increased frequency of endometrial pathology. Endometrial thickness is increased in such patients and is related to the duration of tamoxifen use. All patients on long term tamoxifen should be annually screened for endometrial pathology.

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