

# Increased Risk of Endometrial Abnormalities in Breast Cancer Patients Taking Tamoxifen: The Need for Gynaecologic Surveillance

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### Abstract

**Objective:** To evaluate the risk of abnormally thickened endometrium associated with tamoxifen treatment in postmenopausal breast cancer patients.

**Methods:** Two groups of asymptomatic postmenopausal breast cancer patients were recruited in the study. The first consisted of 70 patients taking 20mg/day of tamoxifen for at least 6 months. The second group included 140 patients without tamoxifen treatment. Endometrial evaluation using transvaginal ultrasonography (TVS) was conducted for all patients. Fractional curettage was carried out for patients whose endometrial thickness was greater than 5 mm on TVS.

**Results:** The prevalence of abnormally thickened endometrium (greater than 5 mm on TVS) was significantly higher in patients receiving tamoxifen (58.57% VS 10.71 %,  $P = 0.0001$ ). Patients undergoing tamoxifen treatment had a 5.61 relative risk of developing abnormally thickened endometrium (95% CI= 2.65 -11.86).

**Conclusion:** Tamoxifen significantly increases the risk of developing abnormally thickened endometrium in postmenopausal breast cancer patients. There is, thus, a true need for gynaecologic surveillance in such patients to early detect neoplastic change of endometrium that may arise as a result of tamoxifen use.

**Key Words:** Breast cancer - tamoxifen - endometrial cancer - surveillance

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### Introduction

It is reported that over one million women worldwide are using tamoxifen to reduce the risk of recurrence of breast cancer. Tamoxifen therapy in early-stage breast cancer was introduced in 1980s, and has been shown to improve disease-free survival and overall survival for women older than 50 years (Benshushan and Brezezinski, 1999). In developed world breast cancer accounts for approximately one-third of all malignancies found in women and the incidence has been increasing globally (Parker et al., 1996). In Thailand, breast cancer has also become one of the leading causes of cancer deaths among female patients. Although tamoxifen provides several beneficial effects to breast cancer patients, reports have been made regarding its adverse effects on female reproductive tract (Baldini et al., 1996, Kenedy et al., 1999, Sinawat et al., 2001). A recent report from our group in Thailand revealed a high prevalence (59.46 %) of thickened endometrium in postmenopausal breast cancer patients receiving more than 6 months of tamoxifen

treatment (Sinawat et al., 2003). Most of the previously published studies, including ours, were descriptive and thus any association between endometrial abnormalities and exposure to tamoxifen could not be precisely defined. The present investigation was thus designed to overcome the limitation of the previously published studies by assessing the risk of developing abnormally thickened endometrium in postmenopausal breast cancer patients exposed to tamoxifen compared to those without tamoxifen treatment.

### Materials and Methods

Between July 1999 to July 2002, two groups of asymptomatic postmenopausal breast cancer patients with intact uteri who underwent regular post-surgical therapy follow-up at Srinagarind hospital, Faculty of Medicine, Khon Kaen University were recruited to the study. The first group consisted of patients who had been treated with 20 mg/day of tamoxifen for at least 6 months. The second group were those who had not received tamoxifen. All patients gave

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**Table 1. Patient Characteristics<sup>a</sup>**

Characteristics	Tamoxifen treated (N = 70)	Tamoxifen untreated (N = 140)	P value
Age (year)	56.23 ± 6.28	54.92 ± 6.18	0.351
Weight (kg)	60.76 ± 7.23	58.81 ± 5.94	0.121
BMI (kg/m <sup>2</sup> )	26.21 ± 4.23	24.54 ± 3.61	0.062
Age at menarche (year)	15.48 ± 1.85	16.07 ± 1.63	0.118
Age at menopause (year)	48.21 ± 4.29	48.22 ± 3.54	0.985
Age at diagnosis (year)	51.63 ± 7.87	51.56 ± 6.64	0.892

<sup>a</sup>Data are presented as mean ± SD

**Table 2. Staging of Breast Cancer in Recruited Patients<sup>b</sup>**

Stage	Tamoxifen treated (N = 70)	Tamoxifen untreated (N = 140)
I	4 (5.71 %)	5 (3.57 %)
II	54 (77.14 %)	114 (81.43 %)
III	11 (15.72 %)	20 (14.29 %)
IV	1 (1.43 %)	1 (0.71 %)
Total	70 (100 %)	140 (100 %)

<sup>b</sup>Data are presented as N (%).

written informed consent to the procedures involved in the study. Besides careful history taking and thorough physical examinations, patients were screened by transvaginal ultrasonography (TVS) using an Aloka SSD-2000 ultrasound machine with a 5-7.5 MHz mechanical sector transducer vaginal probe. The uterus was imaged in both longitudinal and transverse planes with maximum endometrial thickness measured in the longitudinal plane across the endometrial cavity, between the endometrial-myometrial junction. Thus, a double endometrial thickness was measured. The surrounding hypoechoic halo was excluded, as this is believed to represent the compact inner layers of vascular myometrium (Fleischer et al., 1986). Fractional curettage was conducted in all patients whose endometrial thickness was greater than 5 mm on TVS. Assessments of endometrial thickness by TVS were performed by the same clinician. Both the ultrasonologist and the pathologists were not aware of the information regarding the group in which each study patient belonged to. Patients were informed of their results during the follow-up visit.

This research was approved by the Faculty of Medicine, Khon Kaen University Ethical Committee. Statistical analysis was performed with Epi Info statistical package. Continuous variables were analysed with Student t-test. Categorical variables were analysed by Chi square. At all

times a P value of < 0.05 was considered statistically significant.

## Results

The demographic characteristics and health habits of the patients in tamoxifen treated and untreated groups are shown in Table 1. No statistically significant differences were found between the two groups with regard to weight, body mass index, age, age at menarche, age at menopause, and age at diagnosis of breast cancer.

The distribution of breast cancer staging in tamoxifen treated group was similar to that of untreated group. Most of the patients in both groups were diagnosed with stage II breast cancer and less than 2 % of patients in either group was found to have advanced stage breast cancer (Table 2).

The mean ± SD of endometrial thickness in tamoxifen treated and untreated patients were 7.56 ± 4.23 mm and 3.47 ± 1.65 mm, respectively. Statistical analysis demonstrated that endometrium in tamoxifen treated patients was significantly thicker than that of the untreated group (P = 0.0001). The prevalence of thickened endometrium (defined as endometrial thickness greater than 5 mm by TVS) was significantly higher in tamoxifen exposed group (58.57 % VS 10.71 %, P = 0.0001) as shown in Table 3. This study revealed that tamoxifen was associated with a 5.61 relative risk in developing thickened endometrium (95% CI = 2.65 – 11.86).

All patients in both the control and tamoxifen-treated groups who were found to have thickened endometrium on TVS proceeded for fractional curettage. The pathological results of all patients in tamoxifen untreated group turned out negative for pre-neoplastic or neoplastic changes of endometrium. The findings from tamoxifen treated patients, however, revealed a 2.44 % prevalence of endometrial adenocarcinoma (Table 4).

**Table 3. Endometrial Assessments by TVS in Recruited Patients<sup>c</sup>**

	Treated group (N = 70)	Untreated group (N = 140)	P value
Mean endometrial thickness (mm)	7.56 ± 4.23	3.47 ± 1.65	0.0001
Prevalence of thickened endometrium (%)	58.57	10.71	0.0001

<sup>c</sup>Data are presented as mean + SD or %.

**Table 4. Pathological Results of the Curettage Specimens<sup>d</sup>**

Pathological results	Treated group (N =41)	Untreated group (N = 15)
Inadequate tissue for evaluation	30 (73.17%)	6 (40.00%)
Atrophic endometrium	6 (14.63%)	5 (33.33%)
Unremarkable	4 (9.76%)	4 (26.67%)
Endometriod adenocarcinoma	1 (2.44%)	-
Total	41 (100%)	15 (100%)

<sup>d</sup>Data are presented as N (%)

## Discussion

In western world, breast cancer accounts for approximately one-third of all cancers in women and is second only to lung cancer as the leading cause of cancer death in female patients (Jemal et al., 2002). The data from hospital-based cancer registry demonstrated that there were over 1800 breast cancer patients being treated in our centre during the last decade. Among these patients, approximately 400 cases are currently undertaking tamoxifen treatment. Tamoxifen was approved by the American Food and Drug Administration (FDA) to be used as an adjuvant therapy in all stages of breast cancer. It is estimated that over one million women world-wide are now using tamoxifen to reduce the risk of breast cancer recurrence (Nora et al., 2002). Tamoxifen provides several beneficial effects to breast cancer patients both in terms of the disease itself and to general health status. Tamoxifen prolongs disease-free survival and reduces mortality rate due to breast cancer. In addition, it provides a 30 to 50 % reduction in the development of contralateral breast cancer. Besides its wide ranges of benefits, tamoxifen also exhibits several drawbacks mostly involving reproductive organs. Several studies previously suggested that long term tamoxifen use was associated with endometrial abnormalities such as endometrial polyp, endometrial hyperplasia or even endometrial cancer (Baldini et al., 1996; Neven et al., 1990; Neven, 2003).

This study was designed to investigate the risk of developing abnormally thickened endometrium associated with tamoxifen use in postmenopausal breast cancer patients. Transvaginal ultrasonography was used as a method to evaluate endometrial status. The cut-off value of 5 mm on TVS was used to designate abnormally thickened endometrium since there have been several reports indicating that endometrial thickness greater than 5 mm in postmenopausal women is associated with increase chance for endometrial abnormalities (Karlson et al., 1995; Ferrazzi et al., 1996).

This study revealed no statistically significant differences in demographic data between the tamoxifen treated and untreated groups. Tamoxifen is associated with a significant increase in the prevalence of abnormally thickened endometrium (58.57 % VS 10.71 %, P = 0.0001). Moreover, endometrium was significantly thicker in breast cancer

patients treated with tamoxifen than in those without tamoxifen treatment ( $7.56 \pm 4.23$  VS  $3.47 \pm 1.65$  mm, P = 0.0001). These results were comparable to the findings previously reported by other investigators (Elizabeth et al., 1999; Kedar et al., 1994). Kedar RP demonstrated that among postmenopausal women receiving 20 mg/day of tamoxifen for 24 months, 49 % were found to have abnormally thick (>5mm) endometrium on transvaginal ultrasound scan (Kedar et al., 1994). The information revealed in our study confirmed this finding. When statistical analysis was applied the present study demonstrated that tamoxifen use in postmenopausal breast cancer patients was associated with a 5.61 relative risk of developing abnormally thickened endometrium.

Eventhough the prevalence of abnormally thickened endometrium detected in this study was significantly higher in tamoxifen treated group, a discrepancy was found regarding the correlation between abnormally thickened endometrium detected by TVS and endometrial abnormalities revealed pathologically. The prevalence of neoplastic changes of endometrium in tamoxifen treated group was 2.44 % or thirty-time lower than the prevalence of abnormally thickened endometrium. In most cases histology of curettage specimen turned out as atrophic endometrium or inadequate tissue for evaluation implying that there was only scant amount of endometrium covering uterine cavity. The lack of correlation between ultrasonography and histology of endometrium demonstrated in this study was comparable to the results presented by other studies (Berliere et al., 1998; Chen et al., 1997; Uziely et al., 1993; Sinawat et al., 2003). Cohen et al. have suggested that, in postmenopausal patients taking tamoxifen, a thicker endometrium sonographic image does not necessarily correlate with pathological endometrial findings (Cohen et al., 1993). This discrepancy could be explained by the fact that tamoxifen results in cystically dilatation of endometrial glands surrounded by dense endometrial stroma and lined with atrophic epithelium (Decensi et al., 1996; Ismail., 1994; Mourits et al., 1999). The cystic endometrial gland dilatation and dense stroma correspond with the thickened endometrium appeared on TVS: the dense stroma causing the echogenicity and the fluid-filled cysts the echolucent areas of the ultrasonographic picture. Since the superficial layer of endometium in tamoxifen treated patients was atrophic, the curettage specimens thus revealed atrophic or

scant endometrium histologically.

This study also revealed that among asymptomatic tamoxifen-treated patients with thickened endometrium, the prevalence of endometrial adenocarcinoma was 2.44 %. This finding is very important as it represents the value of transvaginal ultrasonography in early detection of endometrial neoplasia prior to the presence of gynaecologic symptoms.

Over the past decade, it has been reported that postmenopausal breast cancer patients who have been treated for more than 12 months with tamoxifen are at increased risk of endometrial carcinoma (Van Leewen et al., 1994). The incidence of endometrial cancer during postmenopausal tamoxifen therapy is estimated to be approximately 2 per 1000 annually and the relative risk of developing endometrial cancer in this group of patients was 1.3 to 7.5 compared to the age-matched tamoxifen non-exposing group (Daniel et al., 1996). Due to these drawbacks of tamoxifen on reproductive tract, a reliable surveillance method thus seems justified to early detect the changes in endometrium associated with tamoxifen use. Several methods have been proposed as the screening tools to detect endometrial pathologies in breast cancer patients taking tamoxifen. These include endometrial sampling, ultrasonography, sonohysterography, doppler studies and office hysteroscopy (Sinawat, 2002). A recent report by our group in Khon Kaen, Thailand revealed a 5.26 % prevalence of endometrial cancer in postmenopausal breast cancer patients taking more than 6 months of tamoxifen (Sinawat et al., 2003). This result together with the findings demonstrating in the present study confirms the true need for gynaecologic surveillance in postmenopausal breast cancer patients taking long term tamoxifen therapy.

One limitation of this study is that there was no baseline information of endometrial status prior to the beginning of tamoxifen treatment and hence precise conclusion could not be drawn regarding the association of tamoxifen use and endometrial thickening detected in this study. To date, there are two prospective studies that assessed the baseline endometrial status before starting adjuvant hormonal therapy in postmenopausal patients diagnosed with breast cancer (Neven et al., 1990; Gal et al., 1991). In these two studies all patients revealed normal or atrophic endometrium upon biopsy before initiation of tamoxifen treatment. Transvaginal ultrasonography, however, was not conducted in these studies thus baseline endometrial thickness could not be demonstrated. In contrast to these reports, a study by Berliere et al. (Berliere et al., 1998) revealed a high prevalence of baseline endometrial abnormalities in asymptomatic postmenopausal women with breast cancer (46 of the 246 women, 17.4 %). The abnormal endometrium mentioned in this study was defined by endometrial thickness greater than 4 mm or abnormal hysteroscopic findings. Berliere et al. also demonstrated that after three years follow-up, the incidence of atypical endometrial lesions was significantly higher in women with lesions initially than in those without. These investigators proposed

that pre-treatment evaluation could be one measure to identify patients at risk of later development of endometrial lesions (Beliere et al., 1998).

The data from the present study, together with those previously reported demonstrated that long term use of tamoxifen in postmenopausal patients significantly increased risk of abnormally thickened endometrium, and possibly neoplastic changes of the endometrium. The appropriate surveillance methods, therefore, is required to prevent morbidity and mortality associated with endometrial pathologies that could arise from tamoxifen therapy.

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