Endometrial Thickening in Postmenopausal Breast Cancer Patients Taking Tamoxifen: A Cross-Sectional Study

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Objective: *To determine the prevalence of endometrial thickening (endometrial thickness > 5 mm) in postmenopausal breast cancer patients taking tamoxifen.*
Design: *Cross-sectional descriptive study*
Settings: *Srinagarind Hospital, Faculty of Medicine, Khon Kaen University.*
Subjects : *Total of 37 postmenopausal breast cancer patients receiving 20-40 mg/day of tamoxifen treatment for at least 6 months were included in the study.*
Method: *Thorough history taking and physical examination as well as transvaginal ultrasonography (TVS) were conducted in all patients.*
Results : *Among the 37 patients included in this study, the mean age was 56.35 years. The mean body weight and mean body mass index was 60.88 kg and 26.03 kg/m^2, respectively. The mean age at diagnosis of breast cancer was 51.84 years. The majority of patients (75.68%) had stage II disease while the rest of patients were diagnosed with stage III (16.22%), I (5.40%) and IV (2.70%), respectively. The mean $\pm$ SD of endometrial thickness (ET) found in this study was 7.53 $\pm$ 5.16 mm. The prevalence of thickened endometrium (defined as ET > 5mm from TVS) was 59.46%. Other pelvic pathologies detected by ultrasonography were multiple small hypoechogenic areas in the endometrium (32.43%), and myoma uteri (5.41%).*
Conclusion: *The prevalence of thickened endometrium in postmenopausal breast cancer patients taking tamoxifen found in this study was extraordinarily high. Therefore it seems to be justified to propose a transvaginal ultrasound screening in all postmenopausal breast cancer patients taking tamoxifen to detect endometrial thickening and possibly pathologies which could be resulted from tamoxifen treatment*

Keywords: *Tamoxifen, Postmenopause women, Breast cancer.*

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Breast cancer is one of the most common malignancies found in women. In western countries it accounts for approximately one-third of all cancers found in women and the incidence has been found to be increasing globally[1]. It is widely accepted that several hormones, especially estrogen, involve in the pathogenesis of breast cancer. Prolong exposure or excessive level of estrogen could also give rise to neoplastic changes of the endometrium. Recent report by Berliere M and his colleagues demonstrated that 17 % of postmenopausal breast cancer patients were found to have abnormally thick endometrium (greater than 4 mm on transvaginal ultrasound scan) before initiation of tamoxifen therapy[2]. Moreover, up to 74% of these patients with thickened endometrium revealed abnormal pathological findings upon biopsy. It is thus interesting to assess the prevalence of thickened endometrium as well as other pelvic abnormalities in postmenopausal patients diagnosed with breast cancer, currently on tamoxifen therapy, to detect endometrial abnormalities that may co-incidentally arise in such patients.

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Material and Method

Between July 1999 to August 2000, 37 asymptomatic postmenopausal (more than 12 months

of amenorrhea) breast cancer patients with intact uteri who had taken 20-40 mg/day of tamoxifen for at least 6 months and undergoing regular post-surgical therapy follow-up at Srinagarind hospital, Faculty of Medicine, Khon Kaen University were recruited to the study. Women who had symptoms of postmenopausal bleeding, or who had taken other hormone therapies such as progesterone were excluded. All patients gave written informed consent to the screening procedures. 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 hypoehogenic halo was excluded, as this is believed to represent the compact inner layers of vascular myometrium[3,4]. Other structural pelvic abnormalities identified by TVS were documented. Assessments of endometrial thickness by TVS were performed by the same clinician. Endometrial thickening is defined as endometrial thickness greater than 5 mm by transvaginal ultrasound scan.

This research was approved by the Faculty of Medicine, Khon Kaen University Ethical Committee as part of the clinical study (HE 42026).

Results

Thirty-seven women were recruited to this study. The mean age of the study subjects was 56.35 years while the mean body weight and body mass index was 60.88 kg and 26.03 kg/m^2, respectively. The mean age at menarche and age at menopause of the patients was 15.51 and 48.11 years, respectively. The mean age when breast cancer initially recognised was 51.84 years. This study demonstrated that breast cancer was diagnosed approximately 3.73 years after patients approached menopause (Table 1).

Regarding the staging of breast cancer in the recruited cases, this study showed that the majority of patients (75.68 %) had stage II disease. The diagnosis of stage III, I, and IV of breast cancers were made in 16.22 %, 5.40 %, and 2.70 % of patients, respectively (Table 2).

The findings obtained from transvaginal ultrasonography conducted in this study revealed that the mean $\pm$ SD of endometrial thickness was 7.53 $\pm$ 5.16 mm. The prevalence of abnormally thick endometrium (defined as endometrial thickness greater than 5 mm by TVS) was 59.46 % (22 from the total of 37 cases). Other pelvic abnormalities detected by ultrasonography were multiple hypoechogenic areas in the endometrium (32.43 %) and myoma uteri (5.41 %) as shown in Table 3.

Discussion

Breast cancer is among the commonest malignancies found in women. In western world, this cancer accounts for approximately one-third of all female cancers. According to estimates from the American Cancer Society, in the United States during 2002, there would be 203,500 new cases of breast cancer and 39,600 deaths from this disease[5]. The data from hospital-based cancer registry demonstrated that there were over 1800 breast cancer patients being treated in Srinagarind hospital during the last decade

Table 1. Patient characteristics

Characteristics	Mean $\pm$ SD (n = 37)
Age (year)	56.35 $\pm$ 7.48
Weight (kg)	60.88 $\pm$ 8.81
BMI (kg/m^2)	26.03 $\pm$ 4.10
Age at menarche (year)	15.51 $\pm$ 2.01
Age at menopause (year)	48.11 $\pm$ 4.19
Age at diagnosis of CA breast (year)	51.84 $\pm$ 8.17

Table 2. Staging of breast cancer in recruited patients

Stage	Number of patients (%) (n = 37)
I	2 (5.40 %)
II	28 (75.68 %)
III	6 (16.22 %)
IV	1 (2.70 %)
Total	37 (100 %)

Table 3. Other pelvic abnormalities detected by TVS

Findings	Number of cases (%)
Multiple hypoechogenic areas in endometrium	12 (32.43 %)
Myoma uteri	2 (5.41 %)
No abnormal finding detected	23 (62.16%)
Total	37 (100 %)

and this cancer was ranked as the third common cancer in female patients.

Several factors have been claimed to be associated with the development of breast cancer. These include advancing age, family history of breast cancer, and the long reproductive phase[6]. The study by Pike MC et al revealed that the median age at menarche was lower for women who developed breast cancer comparing to those who did not have such disease[7]. This study, however, demonstrated that the majority of patients recruited had normal length of reproductive phase. Breast cancer initially detected at approximately 3 years after menopause.

After the diagnosis of breast cancer had been established, the clinical stage of disease was determined by the tumor-nodes-metastasis (TNM) system recommended by the International Union against Cancer (UICC) and the American Joint Committee on Cancer[8].The proportions of patients detected in each stage varied from one center to the others. This study demonstrated that three-fourth of the patients recruited were diagnosed with stage II breast cancer whereas only 1 out of 37 study patients were found to have advanced disease (stage IV).

Tamoxifen is a nonsteroidal antiestrogen. It 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 worldwide are now using tamoxifen to reduce the risk of recurrent breast cancers[9]. It has been clear that tamoxifen provides several beneficial effects to breast cancer patients both in terms of the disease itself and to general health status (e.g. the decrease in coronary event). 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.

The adverse effects of tamoxifen on reproductive tract can be categorized into two groups, the first of which is benign alterations such as the development of endometrial polyp, endometrial hyperplasia, adenofibroma of endometrium, ovarian cyst and the progress in the size of uterine fibroid[10-12]. The second change associated with tamoxifen use is malignant transformation such as endometrial carcinoma, uterine sarcoma, and malignant mixed tumor of the uterus[12,13]. 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[14]. 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[15].

Due to these drawbacks of tamoxifen on reproductive tract, especially in association with the development of endometrial abnormalities, it is thus justified for gynecologists to provide a reliable screening method to early detect the changes in endometrium associated with tamoxifen use.

During the past decade several screening methods have been proposed. These include endometrial sampling, ultrasonography, sonohysterography, doppler studies and office hysteroscopy[12]. Several studies have examined the use of ultrasonography followed by endometrial biopsy in patients taking tamoxifen since it is generally accepted that in postmenopuasal women endometrium will undergo atrophic changes and thin endometrium is expected on ultrasound scan. It is reported that endometrial thickness of greater than 5 mm in postmenopausal women is associated with increase chance for endometrial abnormalities[16,17]. These abnormalities vary from benign condition such as endometrial polyps to pre-neoplastic and neoplastic change. Kedar and collegues demonstrated that among postmenopausal women receiving 20 mg/day of tamoxifen for 24 months, 49 % were found to have abnormally thick endometrium on transvaginal ultrasound scan (endometrium thickness greater than 5 mm). The incidence of premalignant and malignant changes in this study was 16% and the author concluded that the endometrial thickness greater than 8 mm on ultrasonography had a 100% positive predictive value for endometrial diseases[18].

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[19,20]. These studies revealed normal or atrophic endometrium upon biopsy before initiation of tamoxifen treatment. Berliere et al., however, revealed a high prevalence of baseline endometrial abnormalities in asymptomatic postmenopausal women with breast cancer (46 of the 246 women, 17.4 %). The abnormal endometium mentioned in this study was defined by endometrial

thickness greater than 4 mm or abnormal hysteroscopic findings.

The endometrial thickness greater than 5 mm on TVS was considered abnormally thick in the present study. This was due to several previous studies which indicated that endometrial thickness greater than 5 mm in postmenopausal women without hormonal replacement therapy was associated with increase chance for endometrial pathologies[16,17]. The results of the present study demonstrated that the prevalence of abnormally thick endometrium (more than 5 mm on TVS) was extraordinary high (59.46%) among post-menopausal breast cancer patients receiving tamoxifen treatment for more than 6 months. This high prevalence agreed with the findings previously reported by Kedar et al[16]. This implies that associated endometrial abnormalities could be found in post-menopausal breast cancer patients undertaken tamoxifen treatment. Moreover this study could also demonstrate other common pelvic abnormalities such as myoma uteri. This confirmed that transvaginal ultrasonography could be a screening method to uncover such abnormalities and probably can prevent the morbidity or mortality thereafter. However the cause-effect association between tamoxifen treatment and thickened endometrium could not be properly proposed in this study. Further prospective study evaluating the endometrial status prior to tamoxifen treatment as well as the histological studies which can confirm the value of TVS measurement is needed. Other limitations arisen in this study were the small number of the patients recruited and the lack of intra-observer reproducibility assessment. Nevertheless, this study leads to conclude that TVS screening during tamoxifen treatment should not be overlooked.

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ภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติในสตรีวัยหมดระดูที่เป็นมะเร็งเต้านมและได้รับการรักษาด้วยยาทาม็อกซิเฟน: การศึกษาแบบตัดขวาง

สุพัชญ์ สีนะวัฒน์, ทวีศิลป์ ไชยบุตร

วัตถุประสงค์ *: เพื่อประเมินความชุกของภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติ (>5 ม.ม.) ในสตรีวัยหมดระดูที่เป็นมะเร็งเต้านม และได้รับการรักษาด้วยยาทาม็อกซิเฟน*

รูปแบบการวิจัย *: การศึกษาแบบตัดขวาง*

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ประชากรที่ศึกษา *: สตรีวัยหมดระดูจำนวน 37 คน ที่ได้รับการวินิจฉัยเป็นมะเร็งเต้านมและได้รับการรักษาด้วยยาทาม็อกซิเฟน ในขนาด 20-40 มิลลิกรัม ต่อวันเป็น เวลาอย่างน้อย 6 เดือน*

วิธีการทำวิจัย *: ผู้ป่วยทุกคนที่เข้าร่วมโครงการวิจัยจะได้รับการซักประวัติ ตรวจร่างกายและทำการตรวจคลื่นความถี่สูงทางช่องคลอดเพื่อประเมินความหนาของเยื่อบุโพรงมดลูก*

ผลการวิจัย *: การศึกษานี้พบว่าในจำนวนผู้ป่วยทั้ง 37 คนมีอายุเฉลี่ย 56.35 ปี มีน้ำหนักเฉลี่ย 60.88 กิโลกรัมและมีดัชนีมวลกายเฉลี่ย 26.03 กิโลกรัมต่อตารางเมตร อายุเฉลี่ยขณะที่ผู้ป่วยได้รับการวินิจฉัยว่าเป็นมะเร็งเต้านมคือ 51.84 ปี ผู้ป่วยส่วนใหญ่ (75.68%) เป็นมะเร็งเต้านมระยะที่ 2 ผู้ป่วยส่วนที่เหลือได้รับการวินิจฉัยเป็นมะเร็งเต้านมระยะที่ 3 (16.22%) ระยะที่ 1 (5.40%) และระยะที่ 4 (2.70%) การศึกษานี้พบว่าค่าเฉลี่ย $\pm$ ส่วนเบี่ยงเบนมาตรฐานของเยื่อบุโพรงมดลูกของผู้ป่วยมีค่าเท่ากับ 7.53 $\pm$ 5.16 มิลลิเมตร พบความชุกของภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติ (> 5 ม.ม.) เท่ากับ 59.46% ความผิดปกติทางนรีเวชอื่นๆ ที่ตรวจพบด้วยคลื่นเสียงความถี่สูง ได้แก่การตรวจพบบริเวณที่มีความเข้มของคลื่นเสียงต่ำกระจายทั่วไปในเยื่อบุโพรงมดลูก (32.43%) และเนื้องอกกล้ามเนื้อมดลูก (5.41%)*

สรุป *: การศึกษานี้แสดงให้เห็นว่าผู้ป่วยมะเร็งเต้านมที่อยู่ในวัยหมดระดูและได้รับการรักษาด้วยยาทาม็อกซิเฟนมีความชุกของภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติที่สูงมาก ผู้ป่วยกลุ่มนี้จึงควรได้รับการตรวจกรองด้วยคลื่นเสียงความถี่สูงทางช่องคลอด เพื่อประเมินความหนาของเยื่อบุโพรงมดลูกและวินิจฉัยพยาธิสภาพอื่น ๆ ในอุ้งเชิงกรานที่อาจเกิดขึ้นจากการรักษาด้วยยาทาม็อกซิเฟน*