Endometrial Abnormalities in Postmenopausal Breast Cancer Patients

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Objective : *To determine the prevalence of endometrial thickening and pelvic pathologies in postmenopausal breast cancer patients.*

Material and Method : *A total of 66 postmenopausal breast cancer patients receiving treatment at Srinagarind Hospital from 1 July 1999 to 31 August 2000 were included in the study. Patients who had been treated with hormones such as tamoxifen or progestins were not eligible for this study. Thorough history taking and physical examination as well as transvaginal ultrasonography were conducted in all study patients. Fractional curettage was carried out and the specimens obtained were sent for pathological examination in all patients whose endometrial thickness was found to be greater than 5 mm on the ultrasound scan.*

Results : *Among the 66 patients included in this study, the mean age was 54.97 years. The majority of patients (75.76%) had stage II disease. The mean $\pm$ SD of endometrial thickness found in this study was 3.55 $\pm$ 1.72 mm. The prevalence of thickened endometrium (defined as ET > 5mm from TVS) was 10.60% (7 from 66 cases). Other pelvic pathologies detected by ultrasonography were myoma uteri (4.55%) and ovarian mass (1.52%). Among the seven patients whose endometrial thickness was found to be greater than 5 mm, results of curettage specimens revealed inadequate tissue obtained (42.85%), atrophic endometrium (28.57%), active endometrial gland (14.29%), and scanty stromal cell (14.29%).*

Conclusion : *The prevalence of thickened endometrium in postmenopausal breast cancer patients found in this study was interestingly high. The pathological results of such cases, however, turned out to be negative for neoplastic changes in all cases. Further study, thus, is needed before precise recommendation could be made regarding the value of TVS screening in breast cancer patients not taking tamoxifen.*

Keywords : *Endometrium, Menopuase, Breast cancer*

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The global picture indicates that 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 are involved in the pathogenesis of breast cancer. Prolonged exposure or an excess level of estrogen could also give rise to neoplastic changes of the endometrium. A 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, endometrial pathologies as well as other pelvic abnormalities in postmenopausal patients diagnosed with breast cancer in the hope that this screening method will provide some measures to detect or even prevent endometrial abnormalities which co-incidentally arise in such patients.

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Material and Method

A total of 66 asymptomatic postmenopausal women with intact uteri were recruited from breast cancer patients undergoing regular post-surgical

therapy follow-up at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. Women who had symptoms of postmenopausal bleeding, who had taken tamoxifen, or who had taken additional hormone therapies such as progesterone were excluded from the study. 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. Fractional curettage was conducted in all patients whose endometrial thickness was found to be greater than 5 mm on TVS. The specimens obtained from the curettage procedures were then sent for pathological examinations. Assessments of endometrial thickness by TVS were performed by the same clinician and the same pathologist examined all endometrial samples taken from curettage procedure. Patients were informed of their results during their follow-up visit 1-month after fractional curettage was conducted.

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

Results

Sixty-six women were recruited to this study. The mean age of the study subjects was 54.97 years while the mean body weight and body mass index was 57.95 kg and 24.48 kg/m^2, respectively. The mean age at menarche and age at menopause of the patients was 16.12 and 48.11 years, respectively. The mean age when breast cancer initially recognised was 51.62 years. This study demonstrated that breast cancer was diagnosed approximately 3.51 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 (75.76%) had stage II disease. The diagnosis of stage III, I, and IV of breast cancer were made in 18.18%, 4.55%, and 1.51% of patients, respectively (Table 2).

The findings obtained from transvaginal ultrasonography conducted in the study patients revealed that the mean $\pm$ SD of endometrial thickness was 3.55 $\pm$ 1.72 mm. The prevalence of abnormally thick endometrium (defined as endometrial thickness greater than 5 mm by TVS) was 10.60% (7 from the total of 66 cases). Among these seven patients whose endometrial thickness was greater than 5 mm on TVS, the majority (6 from 7 cases or 85.71%) had breast cancer stage II while the rest (14.29%) were diagnosed initially with stage III breast cancer. Other pelvic abnormalities detected by ultrasonography were myoma uteri (4.55%), multiple hypoechogenic areas in the endometrium (1.52%), and ovarian mass (1.52%) as shown in Table 3.

Among seven patients whose fractional curettage was conducted, the pathological results revealed inadequate tissue for pathological evaluation in 3 patients (42.85%), while the rest of the cases demonstrated atrophic endometrium (28.57%), active endometrial gland (14.29%), and scanty stromal gland (14.29%) as shown in Table 4. The patient whose curettage specimen turned out as scanty stromal cell had stage III breast cancer while the rest of the patients having fractional curettage performed were found to have stage II of breast cancer at the time of recruitment to the study. There was no neoplastic endometrium detected among the patients whose endometrial thickness was greater than 5 mm on TVS in this study.

Table 1. Patient characteristics

Characteristics	Mean $\pm$ SD (n = 66)
Age (year)	54.97 $\pm$ 6.24
Weight (kg)	57.95 $\pm$ 8.97
BMI (kg/m^2)	24.48 $\pm$ 3.54
Age at menarche (year)	16.12 $\pm$ 1.44
Age at menopause (year)	48.11 $\pm$ 3.65
Age at diagnosis of CA breast (year)	51.62 $\pm$ 6.74

Table 2. Staging of breast cancer in recruited patients

Stage	Number of patients (%) (n = 66)
I	3 (4.55 %)
II	50 (75.76 %)
III	12 (18.18 %)
IV	1 (1.51 %)
Total	66 (100 %)

Table 3. Other pelvic abnormalities detected by TVS

Findings	Number of cases (%)
Myoma uteri	3 (4.56 %)
Ovarian mass	1 (1.52 %)
Multiple hypoechogenic areas in endometrium	1 (1.52 %)
No abnormal finding detected	61 (92.42 %)
Total	66 (100 %)

Table 4. Pathological results of the curettage specimens

Pathological results	Number of cases (%)
Inadequate tissue for evaluation	3 (42.85%)
Atrophic endometrium	2 (28.57%)
Active endometrial gland	1 (14.29%)
Scanty stromal cell	1 (14.29%)
Total	7 (100%)

Discussion

Breast cancer is one of the most common malignancies detected in women. In the Western world, this cancer accounts for approximately 30% of all cancers in women and is second only to lung cancer as the leading cause of cancer death in women. According to estimates from the American Cancer Society, in the United States during 2002, there will be 203,500 new cases of breast cancer and 39,600 deaths from this disease[5]. During the past 50 years, the incidence of breast cancer in the US has increased significantly; nearly one in every eight American women will develop breast cancer.

Several risk factors have been claimed to be associated with the development of breast cancer. These include advancing age, family history of breast cancer, and a 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 compared to those who did not have such a disease[7]. This study, however, demonstrated that the majority of patients recruited were not obese and had a normal length of reproductive phase. Breast cancer was initially detected at approximately 3 years after menopause.

Breast cancer most commonly arises in the upper outer quadrant, where there is more breast tissue. Breast masses are more often discovered by the patient and less frequently by the physician during routine breast examination[8]. The increasing use of screening mammography has expanded the ability to detect nonpalpable abnormalities. After the diagnosis of breast cancer has been established, the clinical stage of disease is normally determined. The Columbia Clinical staging System was widely used for many years but has been replaced by the tumor-nodes-metastasis (TNM) system recommended by the International Union against Cancer (UICC) and the American Joint Committee on Cancer[8]. The proportion of patients detected in each stage varied from one center to another. This study demonstrated that three-fourths of the patients recruited were diagnosed with stage II breast cancer, whereas, only 1 out of 66 study patients were found to have advanced disease (stage IV).

It is widely accepted that several factors play an important role in the pathogenesis of both breast cancer and endometrial cancer. These factors include prolonged exposure or an excess level of estrogen and obesity[8]. It is, therefore, interesting to evaluate the endometrial status of patients diagnosed with breast cancer in order to detect or even prevent progression of endometrial abnormalities that could co-arise with breast cancer. Transvaginal ultrasonography was used in this study as a screening method for endometrial pathologies and other pelvic abnormalities since it is generally accepted that in postmenopuasal women the endometrium normally undergoes atrophic changes and thin endometrium is expected on ultrasound scan. It has been reported that endometrial thickness greater than 5 mm in postmenopausal women without hormonal replacement therapy is associated with an increased chance of endometrial pathologies[9,10]. These abnormalities vary from benign conditions such as endometrial polyps to pre-neoplastic and neoplastic changes. To date, there are two prospective studies that have assessed the baseline endometrial status before starting hormonal therapy in postmenopausal patients diagnosed with breast cancer[11,12]. 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 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 hystero-

scopic findings[2]. The results of the present study confirmed the finding previously reported by Berliere since the prevalence of abnormally thick endometrium (greater than 5 mm on TVS) detected by this study was 10.60%. Among the patients who had abnormally thick endometrium demonstrated in this study, most (85.71%) were diagnosed initially with breast cancer stage II. The relationship between breast cancer stage and the presence of abnormally thick endometrium, however, could not be precisely drawn using the results of this study since most of the study patients (75.76%) were having breast cancer stage II at the time of recruitment. A larger scale, and prospective study is thus needed before any precise conclusion can be proposed regarding the relationship between breast cancer stage and the presence of abnormally thick endometrium. The high prevalence of thickened endometrium observed in this study implies that associated endometrial abnormalities could be found in postmenopausal patients with breast cancer. The pathological results of curettage specimens, however, showed no neoplastic changes in such cases indicating the discrepancy between the thickened endometrium detected from TVS and endometrial pathologies. A larger scale prospective study is recommended to evalute the benefits of TVS as a screening method for endometrial abnormalities in breast cancer patients before precise conclusion can be made regarding the value of TVS screening in such cases.

In addition to the detection of thickened endometrium, the present study also demonstrated that other pelvic abnormalities such as myoma uteri and ovarian mass could be revealed using transvaginal ultrasound scan. Thorough pelvic examination as well as transvaginal ultrasonography could be the measures to uncover such abnormalities and hence, reduce morbidity or mortality that may result from such conditions.

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ความผิดปกติของเยื่อบุโพรงมดลูกในผู้ป่วยมะเร็งเต้านมที่อยู่ในวัยหมดระดู

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วัตถุประสงค์ *: เพื่อศึกษาความชุกของการหนาตัวอย่างผิดปกติของเยื่อบุโพรงมดลูกและพยาธิสภาพของอวัยวะในอุ้งเชิงกรานในผู้ป่วยมะเร็งเต้านมที่อยู่ในวัยหมดระดู*

กลุ่มตัวอย่างและวิธีการศึกษา *: ทำการศึกษาในผู้ป่วยมะเร็งเต้านมที่อยู่ในวัยหมดระดู และไม่ได้รับการรักษาด้วยฮอร์โมนใด ๆ จำนวน 66 คน ซึ่งมารับการตรวจติดตามหลังการผ่าตัดที่โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ระหว่างวันที่ 1 กรกฎาคม 2542 ถึง 31 สิงหาคม 2543 ผู้ป่วยทุกรายที่เข้าร่วมในการวิจัยนี้จะได้รับการซักประวัติ ตรวจร่างกายและตรวจคลื่นเสียงความถี่สูงทางช่องคลอด ผู้ป่วยที่มีความหนาของเยื่อบุโพรงมดลูกมากกว่า 5 มิลลิเมตรจะได้รับการขูดมดลูกแบบแยกส่วนแล้วส่งตรวจชิ้นเนื้อทางพยาธิวิทยาต่อไป*

ผลการวิจัย *: การศึกษานี้พบว่าผู้ป่วยที่เข้าร่วมในการวิจัยมีอายุเฉลี่ย 54.97 ปี ผู้ป่วยส่วนใหญ่ (75.76%) เป็นมะเร็งเต้านมระยะที่สอง ค่าเฉลี่ย ± ส่วนเบี่ยงเบนมาตรฐานของเยื่อบุโพรงมดลูกเท่ากับ 3.55 ± 1.72 มิลลิเมตร ความชุกของความหนาตัวอย่างผิดปกติของเยื่อบุโพรงมดลูก (มากกว่า 5 มิลลิเมตร จากการตรวจด้วยคลื่นเสียงความถี่สูงทางช่องคลอด) เท่ากับ 10.60% การศึกษานี้ยังพบความผิดปกติอื่นๆร่วมด้วย กล่าวคือพบเนื้องอกมดลูก (myoma uteri) 4.55% และก้อนที่รังไข่ 1.52% สำหรับผู้ป่วย 7 รายที่ได้รับการขูดมดลูกแบบแยกส่วนนั้นผลการตรวจทางพยาธิวิทยาพบว่ามีชิ้นเนื้อไม่เพียงพอต่อการแปลผล 42.85%, พบเยื่อบุโพรงมดลูกบางตัว 28.57%, พบต่อมของเยื่อบุโพรงมดลูก 14.29% และพบเซลล์สโตรมา 14.29%*

สรุป *: พบความชุกของการหนาตัวอย่างผิดปกติของเยื่อบุโพรงมดลูกค่อนข้างสูงในผู้ป่วยมะเร็งเต้านมที่อยู่ในวัยหมดระดูที่มารับการตรวจรักษาในโรงพยาบาลศรีนครินทร์ แต่ไม่พบความผิดปกติทางพยาธิวิทยาของเยื่อบุโพรงมดลูกในผู้ป่วยกลุ่มดังกล่าว การศึกษาต่อไปในอนาคตจึงมีความจำเป็นก่อนที่จะสามารถสรุปได้ว่าการตรวจคัดกรองโดยใช้คลื่นเสียงความถี่สูงทางนรีเวชมีความจำเป็นหรือไม่ในผู้ป่วยมะเร็งเต้านมที่ไม่ได้รับประทานยาทาม็อกซิเฟน*