นิพนธ์ต้นฉบับ • Original Article

การหนาตัวผิดปกติของเยื่อบุโพรงมดลูกในผู้ป่วยมะเร็งเต้านมที่อยู่ในวัยหมดระดู

สุพัชญ์ สีนะวัฒน์, ทวีศิลป์ ไชยบุตร
ภาควิชาสูติศาสตร์และนรีเวชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

Abnormally Thickened Endometrium in Postmenopausal Breast Cancer Patients

Supat Sinawat, Taweesilp Chiyabutra
Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, 40002, Thailand

หลักการและเหตุผล: มะเร็งเต้านมเป็นมะเร็งที่พบเป็นอันดับต้นๆ ในสตรี มีการศึกษาหลายรายงานที่พบปัจจัยบางประการ เช่น ความอ้วน หรือภาวะที่มีฮอร์โมนเอสโตรเจนในร่างกายสูง อาจกระตุ้นให้เกิดทั้งมะเร็งเต้านมและมะเร็งของเยื่อบุโพรงมดลูกได้ จึงควรจะได้มีการศึกษาเป็นอย่างยิ่งว่าผู้ป่วยมะเร็งเต้านมที่อยู่ในวัยหมดระดูและมารับการรักษาในโรงพยาบาลศรีนครินทร์ มีการหนาตัวที่ผิดปกติของเยื่อบุโพรงมดลูก ตลอดจนความผิดปกติอื่นๆ ของอวัยวะสืบพันธุ์หรือไม่

วัตถุประสงค์: เพื่อศึกษาความชุกของการหนาตัวผิดปกติของเยื่อบุโพรงมดลูกในผู้ป่วยมะเร็งเต้านมที่อยู่ในวัยหมดระดู

รูปแบบการศึกษา: เป็นการศึกษาเชิงพรรณนาแบบตัดขวาง (Cross-sectional descriptive study)

สถานที่ทำการศึกษา: โรงพยาบาลศรีนครินทร์ มหาวิทยาลัยขอนแก่น

กลุ่มตัวอย่าง: ผู้ป่วยมะเร็งเต้านมที่อยู่ในวัยหมดระดู และไม่ได้รับการรักษาด้วยฮอร์โมนใดๆ จำนวน 66 คน ซึ่งมารับการตรวจติดตามหลังการผ่าตัดรักษาที่โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ระหว่างวันที่ 1 กรกฎาคม 2542 ถึง 31 สิงหาคม 2543

การวัดผล: ผู้ป่วยทุกรายที่เข้าร่วมในการวิจัยนี้จะได้รับการซักประวัติ ตรวจร่างกายและตรวจคลื่นเสียงความถี่สูงทางช่องคลอด ความหนาของเยื่อบุโพรงมดลูกจะถูกวัดเป็นมิลลิเมตร และบันทึกในแบบบันทึกข้อมูล ร่วมกับความผิดปกติอื่นๆ ของอวัยวะสืบพันธุ์ที่ตรวจพบจากการตรวจคลื่นเสียงความถี่สูงทางช่องคลอด

ผลการวิจัย: การศึกษานี้พบว่าผู้ป่วยที่เข้าร่วมในการศึกษามีอายุเฉลี่ย 54.97 ปี มีน้ำหนักเฉลี่ย 57.95 กิโลกรัม และมีดัชนีมวลกายเฉลี่ย 24.48 กิโลกรัม/ตารางเมตร ผู้ป่วยมีอายุเฉลี่ยขณะ

Background: Breast cancer is among the commonest malignancies found in women. Several studies indicated that there are some factors that might co-incidentally give rise to the development of both breast cancer and endometrial cancer. These factors include obesity, prolong reproductive phase and excess estrogen level. It is interesting, therefore, to investigate whether postmenopausal breast cancer patients treated in Srinagarind hospital have thickened endometrium or other abnormalities of reproductive organs.

Objective: To determine the prevalence of endometrial thickening in postmenopausal breast cancer patients.

Design: Cross-sectional descriptive study.

Setting: Srinagarind hospital, Faculty of Medicine, Khon Kaen University.

Subjects: 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 have been treated with hormones such as estrogen, progesterone or tamoxifen are excluded from the study.

Measurements: Thorough history taking and physical examination as well as transvaginal ultrasonography were conducted in all patients.

Results: Among the 66 patients included in this study, the mean age was 54.97 years. The mean body weight and mean body mass index was 57.95 kg and 24.48 kg/m^2, respectively. The mean age at diagnosis of breast cancer was 51.62 years. The majority of patients (75.76%) had

ได้รับการวินิจฉัยมะเร็งเต้านม 51.62 ปี ผู้ป่วยส่วนใหญ่ (75.76%) เป็นมะเร็งเต้านมระยะที่สอง ค่าเฉลี่ย ± ส่วนเบี่ยงเบนมาตรฐาน ของเยื่อบุโพรงมดลูกเท่ากับ 3.55 ± 1.72 มิลลิเมตร ความชุกของความหนาตัวผิดปกติของเยื่อบุโพรงมดลูก (มากกว่า 5 มิลลิเมตร จากการตรวจด้วยคลื่นเสียงความถี่สูงทางช่องคลอด) เท่ากับ 10.60% การศึกษานี้ยังพบความผิดปกติอื่นๆ ร่วมด้วย กล่าวคือ พบเนื้องอกมดลูก (myoma uteri) 4.55% และก้อนที่รังไข่ 1.52%

สรุป: พบความชุกของการหนาตัวผิดปกติของเยื่อบุโพรงมดลูกค่อนข้างสูง ในผู้ป่วยมะเร็งเต้านมที่อยู่ในวัยหมดระดูที่มารับการตรวจรักษาในโรงพยาบาลศรีนครินทร์ ผู้ป่วยในกลุ่มนี้จึงควรได้รับการตรวจประเมินทางนรีเวช เพื่อสืบค้นหาความผิดปกติของเยื่อบุโพรงมดลูกที่อาจพบร่วมได้กับมะเร็งเต้านม

stage II disease. The mean ± SD of endometrial thickness found in this study was 3.55 ± 1.72 mm. The prevalence of thickened endometrium (defined as ET > 5mm from TVS) was 10.60%. Other pelvic pathologies detected by ultrasonography were myoma uteri (4.55%) and ovarian mass (1.52%).

Conclusion: The prevalence of thickened endometrium in postmenopausal breast cancer patients found in this study was interestingly high. It thus seems justified to propose that thorough pelvic examination as well as transvaginal ultrasound scan should be done in all postmenopausal patients diagnosed with breast cancer in order to detect endometrial and other pelvic pathologies that could arise in such cases.

ศรีนครินทร์เวชสาร 2547; 19(1), 2-6 • Srinagarind Med J 2004; 19(1), 2-6

Introduction

Breast cancer is one of the most common malignancies found in women. In western countries it accounts for approximately one-third of all cancer 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 excess 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 in hope that this screening method will provide some measures to detect or even prevent endometrial abnormalities co-incidentally arise in such patients.

Material and Method

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. 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. Patients were informed of their results at the end of the screening process.

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/m2, 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).

Table 1. Patient characteristics

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

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 I, III and IV of breast cancer were made in 4.55 %, 18.18% and 1.51 % of patients, respectively (Table 2).

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 %)**

The findings obtained from transvaginal ultrasonography conducted in the study patients revealed that the mean ± SD of endometrial thickness was 3.55 ± 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). 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.

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 %)**

Discussion

Breast cancer is among the commonest malignancies in women. In western world, this 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 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 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 were not obese and had normal length of reproductive phase. Breast cancer 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 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 66 study patients were found to have advanced disease (stage IV).

It is widely accepted that several factors play important role in the pathogenesis of both breast cancer and endometrial cancer. These factors include prolong exposure or 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 prevent endometrial abnormalities that could co-arise with breast cancer. Transvaginal ultrasonography was used in this study as a screening method for endometrial thickening and other pelvic abnormalities since it is generally accepted that in postmenopausal 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 without hormonal replacement therapy is associated with increase chance for endometrial pathologies[9-10]. The Nordic multicenter study evaluating 1,168 women with postmenopausal bleeding revealed that the prevalence of endometrial abnormalities in women whose endometrail thickness was found to be greater than 5 mmonj TVS was 64.85 %. These abnormalities vary from benign condition such as endometrial polyps (24.25 %) to pre-neoplastic (19.55 %) and neoplastic changes such as endometrial cancer (21.05 %).[9] To date, there are two prospective studies that 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 endometrium thickness greater than 4 mm or abnormal hysteroscopic findings. The results of our 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 %. The high prevalence of thickened endometrium observed in this study implies that associated endometrial abnormalities could be found in postmenopausal patients with breast cancer. In addition to detection of thickened endometrium, this 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 form such conditions. Since histological studies of the thickened endometrium detected by TVS was not performed in this study, precise conclusion could not be made whether the thickened endometrium detected by this study was associated with significant endometrial abnormalities or not. Further prospective study evaluating the thickened endometrium by histological examination is suggested before any precise recommendation could be drawn regarding the value of TVS screening in postmenopausal patients diagnosed with breast cancer.

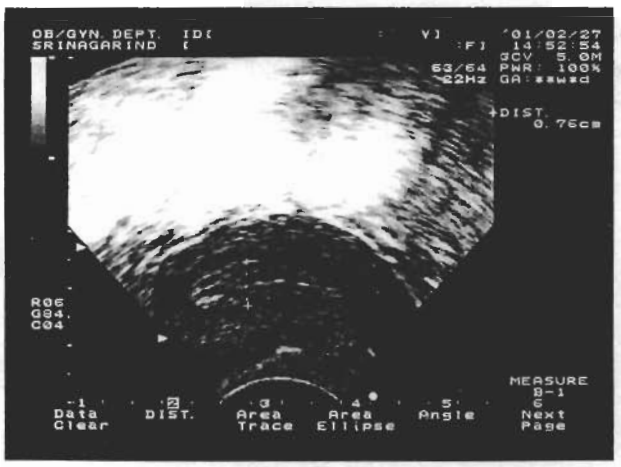

Figure 1. Thickened endometrium demonstrated by transvaginal ultrasonograpgy

References

1. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics. CA Cancer J Clin 1996; 46: 5-27.
2. Berliere M, Charles A, Galant C, Donnez J. Uterine side effects of tamoxifen: A need for systematic pretreatment screening. Obstet Gynecol 1998; 91: 40-4
3. Fleischer AC, Kalemaris GC, Machin JE, Entman SS, James AE Jr. Sonographic depiction of normal and abnormal endometrium with histopathologic correlation. J Ultrasound Med 1986; 5: 445-52.
4. Fleischer AC, Kalemaris GC, Entman SS. Sonographic depiction of endometrium during normal cycles. Ultrasound Med Biol 1986; 12:271-7.
5. Jemal A, Thomas A, Murray T, Thon M. Cancer statistics. CA Cancer J Clin 2002; 52 23-47.
6. Giuliano AE. Breast cancer. In: Berek JS, Adashi EY, Hillard PA, editors. Novakis Gynecology. 12th ed. Baltimore. Williams & Wilkins 1996:1283-302.
7. Pike MC, Krailo MD, Henderson BE, Casagrande JY, Hoel DG. 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. Nature 1983; 303:767-70.
8. Nora DT, Giuliano AE. Breast cancer. In: Berek JS, editor. Novak's Gynecology.13th ed. Philadelphia. Lippincott Williams & Wilkins 2002:1375-98.
9. Karlsson B, Granberg S,Wikland M., Ylostalo P, Torvid K, Marsal K, et al.Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding- a Nordic multicenter trial. Am J Obtset Gynecol 1995; 172: 1488-94.
10. Ferrazzi E, Torri V, Trio D, Zannoni E, Filiberto S, Dordoni D. Sonographic endometrial thickness: a useful test to predict atrophy in patients with postmenopausal bleeding: an Italian multi-center study. Ultrasound Obstet Gynecol 1996; 7:315-21.
11. Neven P, De Muylder X, Van Belle Y, Vanderick G, De Muylder E. Hysteroscopic follow-up during tamoxifen treatment. Eur J Obstet Gynecol Reprod Biol 1990; 35: 235-8.
12. Gal D, Kopel S, Bashevkin M, Lebowicz J, Lev R, Tancer ML. Oncogenic potential of tamoxifen on endometria of postmenopausal women with breast cancer -- preliminary report. Gynecol Oncol 1991; 42: 120-3.