RESEARCH COMMUNICATION

Surveillance for Endometrial Cancer in Postmenopausal Breast Cancer Patients Taking Tamoxifen

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Abstract

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

Materials and Methods: A total of 37 postmenopausal breast cancer patients receiving 20 mg/day of tamoxifen treatment for at least 6 months at Srinagarind hospital were included in the study. Thorough history taking and physical examination as well as transvaginal ultrasonography were conducted for all patients. Fractional curettage was carried out in those whose endometrial thickness was found to be greater than 5 mm.

Results: Among 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 majority of patients (75.68%) had stage II disease. The mean $\pm$ SD of endometrial thickness 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%. Among the 19 patients for whom fractional curettage was conducted, the majority (73.69%) exhibited inadequate endometrium for evaluation. Atrophic endometrium and other unremarkable changes were found in 21.05% of patients and it is important to note that endometrial adenocarcinoma was detected in 1 case (5.26%).

Conclusion: The prevalence of thickened endometrium in postmenopausal breast cancer patients taking tamoxifen found in this study was extraordinarily high. These is, however, a discrepancy between the value and that for endometrial abnormalities detected histologically.

Key Words: Endometrial cancer - high risk - tamoxifen - surveillance

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Introduction

Breast cancer is one of the most common malignancies found in women. In western countries it accounts for approximately one-third of all female cancers and the incidence appears to be increasing globally (Parker et al., 1996). It is widely accepted that several hormones, especially estrogen, are involved in the pathogenesis of breast cancer. Prolong exposure or excess level of estrogens could also give rise to neoplastic changes of the endometrium. In a recent report by Berliere and his colleagues,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 (Berliere et al., 1998). 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 and endometrial pathologies, as well as other pelvic abnormalities in postmenopausal patients diagnosed with breast cancer, currently on tamoxifen therapy, in hope that this screening method will provide some measures to detect or even prevent endometrial abnormalities which coincidentally arise in such patients.

Materials and Methods

Between July 1999 to August 2000, 37 asymptomatic postmenopausal breast cancer patients with intact uteri who had taken 20 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

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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 (Fleischer et al., 1986; Fleischer et al., 1986). 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 and the specimens obtained were sent for pathological examination. Assessment of endometrial thickness by TVS was performed by the same clinician and the same pathologist examined all endometrial samples taken at curettage procedures. Patients were informed of their results during their follow-up visit a few weeks after fractional curettage was conducted.

This research was approved by the Faculty of Medicine Khon Kaen University Ethical Committee as part of a clinical study.

Results

Thirty-seven women were recruited. The mean age of the study subjects was 56.35 years while the mean body weight and body mass index were 60.88 kg and 26.03 kg/m^2, respectively. The mean ages at menarche and at menopause of the patients were 15.51 and 48.11 years, respectively. The mean age when breast cancer was 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 cancer were made in 16.22 %, 5.40 %, and 2.70 % of patients, respectively (Table 2).

The findings obtained from transvaginal ultrasonography conducted in the study patients revealed that the mean $\pm$ SD for 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 %), myoma uteri (5.41 %) as shown in table 3.

Among the 22 patients whose endometrial thickness was found to be greater than 5 mm on TVS, 19 cases allowed fractional curettage to be carried out. The pathological results of these 19 cases revealed inadequate tissue for evaluation in 14 cases (73.68%), atrophic endometrium in 2 cases (10.53%), unremarkable endometrium in 1 case (5.26%), fibrous stroma with basal layer of endometrial gland in 1 case (5.26%) and endometriod adenocarcinoma in 1 case (5.26%) as shown in table 4.

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)	5.51 $\pm$ 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 %)

Discussion

Breast cancer is among the commonest malignancies found in women. In western world, this cancer accounts for approximately one-third of all cancers in women and is

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 %)

Table 4. Pathological Results of the Curettage Specimens

Pathological results	Number of cases (%)
Inadequate tissue for evaluation	14(73.69%)
Atrophic endometrium	2(10.53%)
Unremarkable	1(5.26%)
Fibrous stroma with basal layer of endometrium	1(5.26%)
Endometriod adenocarcinoma	1(5.26%)
Total	19(100%)

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 (Jemal et al., 2002). 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 during her lifetime.

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 (Giuliano, 1996). 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 (Pike et al., 1983). 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 (Nora and Giuliano, 2002). 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 (Nora and Giuliano, 2002). 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 world-wide are now using tamoxifen to reduce the risk of breast cancer recurrence (Fisher and Constantino, 1989). 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. 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 (Baldini et al., 1996; Huang et al., 1996; Sinawat, 2002). The second change associated with tamoxifen use is malignant transformation such as endometrial carcinoma, uterine sarcoma, and malignant mixed tumor of the uterus (Kennedy et al., 1999; Sinawat, 2002). 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, especially in association with the development of endometrial abnormalities, it is thus justified for gynaecologists to provide a reliable surveillance method to early detect the changes in endometrium associated with tamoxifen use.

During the past decade 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). Several studies have examined the use of ultrasonography followed by endometrial biopsy in patients taking tamoxifen. Kedar and collegues demonstrated that among postmenopausal women receiving 20 mg/day of tamoxifen for 24 months, 49 % were found to have abnormally thick (> 5 mm)endometrium on transvaginal ultrasound scan. 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 (Kedar et al., 1994).

Transvaginal ultrasonography was used in this study as a screening method for endometrial thickening, endometrial pathologies and other pelvic abnormalities since it is generally accepted that in postmenopuasal women endometrium normally undergoes 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 (Karlson et al., 1995; Ferrazzi et al., 1996). These abnormalities vary from benign condition such as endometrial polyps to pre-neoplastic and neoplastic change. 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 tamoxiofen 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 hysteroscopic findings (Berliere et al., 1998).

This study demonstrated that, among postmenopausal breast cancer patients receiving tamoxifen treatment for more than 6 months, the prevalence of abnormally thick endometrium (more than 5 mm on TVS) was extraordinary high (59.46%). This finding confirmed the data previously reported by Kedar (Kedar et al., 1994). The high prevalence of thickened endometrium observed in this study implies that associated endometrial abnormalities could possibly be found in postmenopausal breast cancer patients undertaking long term tamoxifen treatment and thus fractional curettage was performed in such cases. The results of pathological evaluation demonstrated a malignancy prevalence of 5.26 % in patients who had thickened endometrium on TVS. This figure, though not extremely high, is comparable to the results of several studies previously reported (Van et al., 1994; Daniel et al., 1996; Kedar et al., 1994). The result from this study, together with those reported earlier indicated that long term tamoxifen treatment, especially in postmenopausal patients, is associated with thickened endometrium as well as endometrial pathologies such as endometrial cancer. We thus suggest that a reliable surveillance method for endometrial abnormalities shall be offered to all asymptomatic postmenopausal breast cancer patients undertaking long term tamoxifen treatment.

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