Prevalence of Endometrial Proliferation in Pipelle Biopsies in Tamoxifen-Treated Postmenopausal Women with Breast Cancer in Kuwait

M. Al-Azemi^{a,b} N.S. Labib^b M.M.M. Motawy^c L. Temmim^c
M.A.A. Moussa^d A.E. Omu^{a,b}

^aDepartment of Obstetrics and Gynecology, Faculty of Medicine, Kuwait University, ^bMaternity Hospital,

^cKuwait Cancer Control Center, ^dDepartment of Community Medicine, Faculty of Medicine, Kuwait University, Kuwait

Key Words

Breast cancer · Tamoxifen · Screening · Endometrial pathology

Abstract

Objective: To determine the prevalence of pathologic changes in the endometrium of tamoxifen-treated asymptomatic postmenopausal patients with breast cancer. **Subjects and Methods:** Fifty postmenopausal asymptomatic breast cancer patients with positive estrogen receptor status were treated with 20 mg of tamoxifen daily for a period of 5–60 months. The control group consisted of 30 asymptomatic postmenopausal breast cancer patients who were negative for estrogen receptor and therefore did not receive tamoxifen. Endometrial biopsies were performed using Pipelle endometrial suction curette at least 5 months after the study began. The endometrium was classified as atrophic (negative finding) and proliferative or hyperplastic (positive findings). The study and control groups were compared for demographic characteristics, risk factors for endometrial cancer, histological findings and the duration of tamoxifen

treatment. **Results:** A significantly greater prevalence of endometrial abnormalities existed among the tamoxifen-treated than control patients (76 vs. 33%, $p < 0.001$). The abnormal endometrial changes were further demarcated in both groups into proliferative (54 vs. 26.7%, $p = 0.02$) and hyperplastic (22 vs. 6.6%, $p = \text{NS}$). In the study group, 63.6% of hyperplastic endometrium was simple hyperplasia and 36.4% was complex/no atypia hyperplasia, while in the control group all the cases were simple hyperplasia. No endometrial cancer was detected in either group. In addition, there was a positive association between the duration of tamoxifen exposure (< 1 year vs. ≥ 1 year) and the endometrial abnormalities (46.6 vs. 88.6%, $p = 0.003$; proliferative 57.1 vs. 74.1%, $p = 0.015$; hyperplastic 42.8 vs. 25.8%, $p = \text{NS}$). **Conclusion:** The adjuvant use of tamoxifen is associated with significant time-dependent abnormal endometrial changes among patients with cancer of the breast.

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Majedah Al-Azemi, Assistant Professor
Department of Obstetrics and Gynecology
Faculty of Medicine, PO Box 24923
KW-13110 Safat (Kuwait)
Tel. +965 5319601, Fax +965 5338906, E-Mail alazemimajda@hsc.kuniv.edu.kw

Introduction

With an incidence of 15.1 per 100,000 women, breast cancer is the most common malignant tumor among women in Kuwait and accounts for 27.6% of all female cancers [1]. Tamoxifen, a nonsteroidal triphenylethylene derivative, is widely used as adjuvant therapy for breast cancer in postmenopausal patients [2]. It has agonist and antagonist effects depending on the target tissues. The predominant antiestrogen activity is on the breast, while it produces estrogenic stimulatory effects on the endometrium, such as hyperplasia, endometrial polyps, and endometrial carcinoma [2–9]. It has been shown that tamoxifen-treated patients have an increased risk (1.3–7.5) of developing endometrial cancer [10]. In the National Surgical Adjuvant Breast Project Trial [4], women with stage I breast cancer who received adjuvant tamoxifen treatment at 20 mg daily for up to 5 years and women at high risk but with no malignancy in chemoprevention trials were shown to be at approximately 7 times greater risk for endometrial cancer than controls.

The long-term endometrial sequelae of tamoxifen treatment have raised concerns about monitoring the endometrium of all women receiving the drug [11, 12]. However, there is considerable uncertainty about the most effective and acceptable method of monitoring the endometrium. The techniques most frequently advocated are transvaginal sonography and hysteroscopy, supplemented by endometrial biopsy [13]. Transvaginal sonography may not be sensitive enough to detect endometrial polyps without additional procedures such as intracavity saline instillation. Hysteroscopy is valuable for detection of focal lesions, but less so in the evaluation of generalized endometrial hyperplasia and obtaining a representative biopsy by curettage [14]. Pipelle endometrial suction is a simple and remarkably less expensive method than both transvaginal sonography and hysteroscopy. Hence, we decided to use Pipelle endometrial suction to determine the incidence of pathologic changes in the endometrium of postmenopausal breast cancer patients treated with tamoxifen.

Subjects and Methods

Between October 1997 and October 1999, 80 breast cancer patients being treated at the Kuwait Cancer Control Center (KCCC) agreed to participate in this study. Breast cancer is managed at the KCCC using a standard protocol, according to T (size of the primary tumor), N (regional lymph node involvement) and M (distant metastasis) classification [15], and also according to the estrogen- and pro-

gesterone-receptor status. The study group consisted of 50 asymptomatic postmenopausal breast cancer patients with positive estrogen receptor status who were treated with 20 mg of tamoxifen daily for a period of 5–60 months (mean of 20.2 ± 15.8 months). The control group consisted of 30 asymptomatic postmenopausal breast cancer patients who were negative for estrogen receptor and therefore were not given tamoxifen treatment. The study was approved by the Ethics Committee at KCCC, and informed consent was obtained from each patient after full explanation of the objectives of the study.

All patients underwent endometrial biopsy using Pipelle endometrial suction curette, at least 5 months after entering the study. Endometrial biopsy was prepared by initial fixation in 10% formalin for 24 h, processed in 'Path-Shandon', and embedded in the 'Shandon Histocenter' (Shandon, Runcorn, Cheshire, UK) to make paraffin blocks. Cutting was performed in 5- μ m slides, followed by staining in hematoxylin and eosin. A minimum set of 3 slides was given to the pathologist for examination. All biopsies were evaluated histologically by 2 senior oncological pathologists at the KCCC. Tissue fragments were examined under light microscopy and the endometrium was classified as atrophic, proliferative, or hyperplastic. In postmenopausal women, the endometrium is expected to be atrophic due to the absence of estrogen effect. Therefore, atrophic endometrium was regarded as a negative finding. Proliferative and hyperplastic endometrium were considered as positive findings because these changes reflect an estrogenic effect on the endometrium.

The study and control groups were compared for the following: demographic characteristics, risk factors for endometrial cancer (age, parity, hypertension, diabetes, body mass index (BMI), histological findings and the duration of tamoxifen treatment.

Statistical Analysis

The normal-Z test was used to assess the significance for the difference between two proportions. The cutoff level for the statistical significance was $p < 0.05$. The results were analyzed with Mann-Whitney nonparametric methods.

Results

The demographic characteristics and risk factors for endometrial cancer are compared in table 1. There were no statistically significant differences between the groups in age (55 ± 9.1 vs. 51.8 ± 7.2 years) or incidence of the known endometrial cancer risk factors of parity, hypertension, diabetes mellitus, and obesity (BMI evaluation).

As shown in table 2, 38 women (76%) in the tamoxifen-treated group had positive endometrial pathology compared to 10 (33.3%) in the untreated group and the difference was statistically significant ($p < 0.001$). Further breakdown of the positive results into proliferative and hyperplastic endometrium revealed a significant difference in the occurrence of proliferative endometrium between the two groups ($p < 0.05$), with 27 (54%) treated compared to 8 (26.7%) untreated patients. However, although more patients (22%) in the treatment group

compared to the untreated group (6.6%) had hyperplastic endometrium, the difference was not statistically significant ($p = 0.07$). Of the 11 cases of hyperplastic endometrium in the study group, 7 were simple hyperplasia while 4 were complex/no atypia. The control group had 2 cases of simple hyperplasia and no complex hyperplasia. No endometrial cancer was detected in either group.

A comparison between the duration of tamoxifen treatment and the frequency of endometrial pathology

was conducted after subdividing the tamoxifen-treated group into those treated for less than 1 year and those for 1 year or longer (table 3). There was a significant time-dependent increase in positive endometrial finding: 7/15 (46.6%) for less than 1 year, compared to 31/35 (88.8%, $p = 0.003$) after more than 1 year of treatment. There was a statistically significant difference in the proliferative endometrium between less than (4/7) and more than (23/31) 1 year of treatment ($p = 0.015$), while the hyperplastic endometrium did not show any significant difference. Of the 3 cases of hyperplasia in patients treated with tamoxifen for less than 1 year, 2 were simple hyperplasia and 1 complex/no atypia, while in those treated for more than 1 year, 5 were simple hyperplasia and 3 were complex/no atypia.

Table 1. Demographic characteristics and risk factors for breast cancer patients treated (study group) and not treated (control group) with tamoxifen

Demographic characteristics	Study group (n = 50)	Control group (n = 30)	p value
Age, years			
<50	7	2	NS
50–60	35	17	NS
>60	8	11	NS
Means $\pm$ SD	55 $\pm$ 9.1	51.8 $\pm$ 7.2	NS
Parity			
0	7	2	NS
1–3	38	20	NS
>4	5	8	NS
Hypertension	10	4	NS
Diabetes	8	4	NS
BMI			
18–25	7	3	NS
26–30	30	18	NS
>30	13	9	NS
Means $\pm$ SD	34 $\pm$ 5.2	33.2 $\pm$ 4.3	NS

NS = Not significant; $p > 0.05$.

Discussion

In this study, although there was generally a higher incidence of endometrial pathology in the tamoxifen-treated (76%) than in the untreated (33%) group of patients, endometrial cancer was not detected in either group. Since Pipelle endometrial suction may not pick up all of the polyps and some of them might harbor endometrial cancer, the clinical utility of screening tamoxifen-treated patients with routine office biopsy becomes questionable, as pointed out by Barakat et al. [16]. Hence, it is necessary that other methods like hysteroscopy and directed endometrial sampling be carried out in patients who are symptomatic with vaginal bleeding and discharge [12, 14].

The statistically significant difference in the frequency of positive histological endometrial changes among the

Table 2. Histopathological (HP) analysis of the endometrium from patients treated (study group) and not treated (control group) with tamoxifen

HP diagnosis	Study group (n = 50)	Control group (n = 30)	Odds ratio	95% CI	p value
Negative (atrophic)	12 (24%)	20 (66.7%)	0.16	0.06–0.43	<0.001
Positive	38 (76%)	10 (33.3%)	6.33	2.33–17.19	<0.001
Proliferative	27 (54%)	8 (26.7%)	3.23	1.21–8.62	0.021
Hyperplastic	11 (22%)	2 (6.6%)	3.95	0.81–19.23	NS
Simple	7 (63.6%)	2 (100%)			
Complex	4 (36.4%)	0			
No atypia	4	0			
With atypia	0	0			

NS = Not significant; $p < 0.05$.

Table 3. Comparison between tamoxifen exposure and abnormalities detected in the study group

HP diagnosis	< 1 year exposure (n = 15)	≥ 1 year exposure (n = 35)	Odds ratio	95% CI	p value
Negative (atrophic)	8 (53.4%)	4 (11.4%)	8.86	2.07–37.9	0.003
Positive	7 (46.6%)	31 (88.6%)	0.11	0.03–0.48	0.003
Proliferative	4 (57.1%)	23 (74.1%)	0.19	0.05–0.72	0.015
Hyperplastic	3 (42.8%)	8 (25.8%)	0.84	0.19–3.75	NS
Simple	2 (66.6%)	5 (62.5%)			
Complex	1 (33.3%)	3 (37.5%)			
No atypia	1	3			
With atypia	0	0			

NS = Not significant; p < 0.05.

tamoxifen-treated patients compared to the nontreated group ($p < 0.001$) supports the idea that tamoxifen treatment induces endometrial proliferation, consistent with previous studies [14, 17–19]. Ismail [14] identified a dose-dependent effect in a subgroup of patients who took more than 35 g of tamoxifen and were at increased risk of developing endometrial cancer. He postulated that the spectrum of pathological findings in these patients suggested that the drug promotes endometrial growth and the formation of endometrial polyps, which might be an intermediate step in endometrial carcinogenesis due to estrogenic agonist activity in the endometrium. Also in accordance with our findings is a study by Cohen et al. [19], in which the prevalence of endometrial pathological findings was found to be high among asymptomatic postmenopausal breast cancer patients treated with tamoxifen (35.5%), compared with nontreated patients (20%).

An important finding in the present study is the time-dependent nature of endometrial proliferation in women treated with tamoxifen. Decensi et al. [20] demonstrated the same time-dependent proliferative effect of tamoxifen on the endometrium in an analysis of the stromal:epithelial ratio, assessment of DNA ploidy and proliferation by flow cytometry in 33 women who received 20 mg of tamoxifen as adjuvant breast cancer treatment, as compared to 37 controls.

Although there was a high incidence of endometrial pathology in the present study, especially in tamoxifen-treated women, most of the changes were endometrial proliferation, and no case of endometrial cancer was detected, which may be because the endometrial screening was conducted over a relatively short time. The findings of the present study are in accordance with the assertion that the net benefits induced by tamoxifen in breast

cancer chemoprevention [21] outweigh the risk of endometrial changes. Adjuvant tamoxifen therapy lengthens disease-free survival, increases overall survival and reduces the risk of developing breast cancer in the contralateral breast [10].

A principal limitation of this study is the lack of baseline endometrial biopsy, which could have been helpful for evaluating the sensitivity and specificity of the use of the Pipelle suction curettage method for screening endometrial changes induced by tamoxifen treatment. Such a study has already been advocated [14], and we hope to embark on it in the future.

Conclusion

The adjuvant use of tamoxifen is associated with significant abnormal endometrial changes among breast cancer patients with positive estrogen receptor status. Pipelle suction curettage is a useful method for monitoring endometrial changes.

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