European Journal of Gynaecological Oncology

Eur. J. Gynaecol. Oncol. **2022**; 43(2): 169–174
http://doi.org/10.31083/j.ejgo4302022

Original Research

Is screening for endometrial cancer necessary in asymptomatic women treated with tamoxifen for breast cancer?

U Chul Ju[1,†], Woo Dae Kang[1,†], Seok Mo Kim[1,*]

[1]Department of Obstetrics and Gynecology, Chonnam National University Medical School, 61469 Gwangju, Republic of Korea
*Correspondence: seokmo2001@hanmail.net (Seok Mo Kim)
[†]These authors contributed equally.

Academic Editor: Enrique Hernandez
Submitted: 9 December 2021 Revised: 17 January 2022 Accepted: 20 January 2022 Published: 15 April 2022

Abstract

Objective: This study aimed to investigate the endometrial pathology findings and to determine the appropriate diagnostic approach to assess for potential endometrial malignancy or premalignant pathology in women treated with tamoxifen for breast cancer. **Methods**: We retrospectively reviewed the medical records of 162 patients taking tamoxifen and who underwent endometrial biopsy. We compared the clinical features of the patients with endometrial intraepithelial neoplasia or cancer (EIN/EC group) and the patients with other pathologic results (others group). **Results**: EIN or EC was found in ten patients (6.2%). While 70.0% of EIN/EC group received tamoxifen treatment for more than 3 years, 71.7% of the others group received less than 3 years ($p < 0.001$). Regardless of the presence of vaginal bleeding, EIN/EC was not found in patients with endometrial thickness (ET) <5 mm on transvaginal ultrasonography (TV-US). When ET was ≥5 mm, the incidence rates of EIN/EC were only 2.9% in asymptomatic patients and 11.6% in symptomatic patients, respectively ($p = 0.002$). When ET was ≥8 mm, the incidence rates of EIN/EC were 3.8% in asymptomatic patients and 12.0% in symptomatic patients, respectively ($p = 0.002$). When ET was <8 mm, EIN/EC was not found in patients without vaginal bleeding, while EIN/EC was found in 7.1% of patients with vaginal bleeding. **Conclusions**: Indiscriminate endometrial evaluation should be avoided in women treated with tamoxifen for breast cancer. Patients taking tamoxifen who experience vaginal bleeding and have a thick endometrium (≥5 mm) on TV-US, they should undergo endometrial biopsy.

Keywords: breast cancer; tamoxifen; endometrial pathology; vaginal bleeding; endometrial thickness

1. Introduction

Breast cancer is the second most common cancer affecting women in South Korea and the disease's mortality shows constant increasing trends [1]. Tamoxifen, a selective estrogen receptor modulator (SERM), is widely used adjuvant therapy to reduce the risk of recurrence and the mortality of breast cancer [2]. Because tamoxifen stimulates the proliferation of the uterine endometrium, however, the use of the drug can increase the risk of endometrial pathologic change such as endometrial polyp, hyperplasia and cancer [3,4].

Several studies on the relationship between the use of tamoxifen and endometrial pathologic change have reported the importance of early and optimal diagnostic approach [5–7]. The aims of this study were to investigate the results of endometrial pathologic change and to determine the appropriate diagnostic approach to endometrial pathologic change in women treated with tamoxifen for breast cancer.

2. Materials and methods

This study was retrospectively performed in single center after the approval of the Institutional Review Board of Chonnam National University Hospital (CNUH), Gwangju, Korea (approval number: HTMP-2021-086). The clinical data were obtained from medical records of women treated for breast cancer at CNUH between June 2004 and December 2019. Total 278 patients visited outpatient clinic of gynecology for presenting vaginal bleeding or gynecologic checkup without vaginal bleeding. Of these, 116 patients who were treated with aromatase inhibitors, chemotherapy, radiation or only surgery without the use of tamoxifen were excluded. Remaining 162 patients were finally included in this study. They were taking oral 20 mg tamoxifen per day or had taken.

At the time of visit, all patients underwent transvaginal-ultrasonography (TV-US), cervical cytology by pap smear, and endometrial biopsy. Endometrial thickness (ET) was measured in the largest anteroposterior dimension on the midline sagittal scan by TV-US. Doppler modes measuring endometrial vascularity was not used in this study. ET ≥4 or 5 mm by TV-US has been generally considered the indication of endometrial biopsy, especially for women with vaginal bleeding. Based on this, ET ≥5 mm was used as the first useful cut-off value in predicting endometrial intraepithelial neoplasia (EIN) or endometrial cancer (EC) in this study. In addition, receiver operating characteristics (ROC) curve was used to determine the most useful ET in predicting EIN or EC, and ET ≥8 mm was shown to have the most predictive power. ET ≥8 or 10 mm was used as a cut-off threshold in previous reports, which supported this result.

Endometrial biopsy was performed by catheter, curettage and hysteroscopy. Catheter biopsy was used when ET was relatively thin and no suspicious lesion in uterine cavity by TV-US. Curettage biopsy was applied to thick endometrium. Biopsy using hysteroscopy was performed when there were suspicious lesions in uterine cavity on TV-US. The pathologic results of endometrial biopsy were described as normal, inactive atrophy, hormonal effect, endometrial polyp, typical endometrial hyperplasia, EIN and EC. All analyses of pathology were confirmed by a single gynecologic pathologist of our institution. Duration of tamoxifen use was defined as the period from the month of the first tamoxifen administration to the month of the last tamoxifen treatment or endometrial biopsy. We compared the clinical features of the patients with EIN or EC (EIN/EC group) with those of the patients with other pathologic results (others group).

All the variables were described for each of the two groups and statistically compared using the Chi-squared or Fisher's exact test as required. All p values reported were 2-tailed and p values of 0.05 or less were considered to be statistically significant. All data were analyzed using Statistical Package Service Solution (SPSS) software for Windows version 23.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Of total 162 women, EIN and EC were found in four (2.5%) and six (3.7%), respectively (Table 1). The incidence of EIN or EC was 6.2% in this study. Table 2 shows the comparison of clinical characteristics of the patients in the two groups. There was no significant difference in the age at diagnosis of breast cancer and the age at endometrial biopsy. However, all patients diagnosed with EIN/EC started the use of tamoxifen before the age of 50 years. The EIN/EC group more commonly presented with vaginal bleeding than the others group (80.0% *vs* 46.1%) ($p < 0.001$). All patients in the EIN/EC group had ET $\geq$5 mm. ET $\geq$5 mm had 100% of sensitivity, 11.3% of specificity, 6.7% of positive predictive value (PPV) and 100% of negative predictive value (NPV) in the detection of EIN or EC. ET $\geq$8 mm had 80.0% of sensitivity, 38.2% of specificity, 7.8% of PPV and 96.7% of NPV in the detection of EIN or EC. On cervical cytology, atypical glandular cells (AGC) or adenocarcinoma was very rare (1.2%). However, all patietns with these cytologic diagnoses were diagnosed with EIN or EC on biopsy. There was no significant difference based on the methods used to obtain the endometrial sample. The duration of tamoxifen treatment in the EIN/EC group was longer than in the others group ($p < 0.001$). While 70.0% of the EIN/EC group received tamoxifen treatment for more than 3 years, 71.7% of the others group received the treatment for less than 3 years.

The clinical and pathological details of EIN/EC group are shown in Table 3. Endometrial cancers developed in six patients, including five endometrioid adenocarcinomas and one of clear cell adenocarcinoma. Nine patients diagnosed with EIN or EC, except one who refused a treatment, received the proper treatments including a surgery. After a surgery, four patients were staged as IA, one was staged as IIIA (metastasis to fallopian tube), and one was staged as IIIC2 (metastasis to para-aortic lymph nodes) by the International Federation of Gynecology and Obstetrics (FIGO) system.

Table 4 shows the relationship of patient's symptom (vaginal bleeding), ET by TV-US, and endometrial pathology. Regardless of the presence of vaginal bleeding, EIN or EC was not found in patients with ET $<$5 mm. While the incidence rate of EIN or EC was only 2.6% in asymptomatic patients with ET $\geq$5 mm, it was 11.6% in symptomatic patients with ET $\geq$5 mm ($p = 0.002$). Even if ET $\geq$8 mm is taken as the cut-off threshold, there was no significant change in the incidence rates of EIN or EC according to the presence of vaginal bleeding. The incidence rates of EIN or EC were 3.8% in asymptomatic patients with ET $\geq$8 mm and 12.0% in symptomatic patients with ET $\geq$8 mm, respectively ($p = 0.002$). When ET was $<$8 mm, EIN or EC was not found in patients without vaginal bleeding, whereas EIN or EC was found in 7.1% of patients with vaginal bleeding.

4. Discussion

The major systemic treatment for breast cancer with estrogen receptor is endocrine therapy with tamoxifen [2]. Many women usingtamoxifen present gynecological symptoms such as vaginal bleeding. Among the adverse effects of tamoxifen, the most important gynecologic effect is endometrial pathologic change such as endometrial proliferation, hyperplasia, polyp formation, invasive carcinoma and uterine sarcoma [3,4]. As the use of tamoxifen has significant correlation with endometrial pathologic changes, the importance of early and proper diagnosis has been emphasized. There are various opinions on the indication, method, and interval of endometrial evaluation. Although there are no clearly defined guidelines for endometrial examination, TV-US, immediate endometrial biopsy and hysteroscopy have been often performed.

The 2014 American College of Obstetricians and Gynecologists (ACOG) committee opinion concluded that premenopausal women treated with tamoxifen have no increased risk of uterine cancer [3]. In the present study, however, all patients with EIN or EC were diagnosed with breast cancer and started tamoxifen treatment before the age of 50 years. Premenopausal tamoxifen users should undergo endometrial evaluation, if they experinced vaginal bleeding. Endometrial pathology is known to be more likely diagnosed in gynecological symptomatic women than in asymptomatic women [7].

Some studies showed a weak relationship between ultrasonographic measurements of ET and abnormal endometrial pathology in asymptomatic tamoxifen users because of

Table 1. Endometrial pathologic results in patients treated with tamoxifen for breast cancer.

Item	Normal	Inactive atrophy	Hormonal effect	Polyp	Typical hyperplasia	EIN	EC	Total
N = 162	88	9	9	44	2	4	6	162
%	54.3	5.6	5.6	27.2	1.2	2.5	3.7	100

EIN, endometrial intraepithelial neoplasia; EC, endometrial cancer.

Table 2. Comparison of clinical characteristics of patients treated with tamoxifen for breast cancer according to the pathologic result of endometrial biopsy.

Characteristics	Total (N = 162)	EIN/EC (N = 10)	Others (N = 152)	*p* value
	N (%)	N (%)	N (%)	
Age at diagnosis of breast cancer				
Median (range), years	44 (27–67)	44 (36–49)	44 (27–67)	0.269
>50	19 (11.7)	0 (0)	19 (12.5)	
≤50	143 (88.3)	10 (100)	133 (87.5)	
Age at endometrial biopsy				
Median (range), years	47 (27–69)	49 (41–53)	47 (27–69)	0.304
>50	48 (29.6)	4 (40.0)	44 (28.9)	
≤50	114 (70.4)	6 (60.0)	108 (71.1)	
BMI				
Median (range), kg/m^2	22 (17–35)	21 (20–23)	22 (17–35)	0.147
≥25	33 (20.4)	1 (10.0)	32 (21.1)	
<25	129 (79.6)	9 (90.0)	120 (78.9)	
Symptom				<0.001
Vaginal bleeding	78 (48.2)	8 (80.0)	70 (46.1)	
No	84 (51.8)	2 (20.0)	82 (53.9)	
ET by TV-US				
≥5 mm	146 (90.1)	10 (100)	136 (89.5)	0.285
<5 mm	16 (9.9)	0 (0)	16 (10.5)	
≥8 mm	102 (63.0)	8 (80.0)	94 (61.8)	0.175
<8 mm	60 (37.0)	2 (20.0)	58 (38.2)	
Results of cervical cytology				0.003
AGC/adenocarcinoma	2 (1.2)	2 (20.0)	0 (0)	
Negative/others	104 (64.2)	4 (40.0)	100 (65.8)	
Not checked	56 (34.6)	4 (40.0)	52 (34.2)	
Endometrial biopsy instruments				0.887
Catheter	67 (41.3)	4 (40.0)	63 (41.4)	
Curettage	45 (27.8)	2 (20.0)	43 (28.3)	
Hysteroscopy	50 (30.9)	4 (40.0)	46 (30.3)	
Duration of treatment with tamoxifen, months				<0.001
>6, <12	38 (23.5)	0 (0)	38 (25.0)	
≥12, <24	36 (22.2)	2 (20.0)	34 (22.4)	
≥24, <36	38 (23.5)	1 (10.0)	37 (24.3)	
≥36, <48	20 (12.3)	3 (30.0)	17 (11.2)	
≥48, <60	20 (12.3)	3 (30.0)	17 (11.2)	
≥60	10 (6.2)	1 (10.0)	9 (5.9)	

EIN, endometrial intraepithelial neoplasia; EC, endometrial cancer; BMI, body mass index; ET, endometrial thickness; TV-US, transvaginal-ultrasonography; AGC, atypical glandular cells.

Table 3. Clinical and pathological details of patients diagnosed with endometrial intraepithelial neoplasia (EIN) or endometrial cancer (EC) (N = 10).

Case	Pathology	FIGO stage	Age at endometrial biopsy	Duration of tamoxifen (months)	Symptom	ET (mm)	Result of cervical cytology	Treatment
1	EIN		42	13	Bleeding	5	Not	TLH BSO
2	EIN		52	42	Bleeding	5	Negative	Not
3	EIN		45	50	Bleeding	19	Not	TLH BSO
4	EIN		48	52	Bleeding	13	Not	TLH BSO
5	Endometrioid G1	IA	51	18	Bleeding	8	Negative	TLH BSO
6	Endometrioid G1	IA	49	28	Bleeding	9	Not	TLHBSO
7	Endometrioid G1	IA	52	40	No	24	Negative	TLH BSO
8	Endometrioid G1	IIIA (tube)	41	43	No	28	Negative	TLH BSO PLND + chemotherapy
9	Endometrioid G2	IA	49	57	Bleeding	12	AGC	TLH BSO
10	Clear cell	IIIC2 (PALN)	53	75	Bleeding	20	Adenocarcinoma	TAH BSO PLND + chemotherapy

FIGO, the International Federation of Gynecology and Obstetrics; ET, endometrial thickness, EIN, endometrial intraepithelial neoplasia; PALN, para-aortic lymph node; TLH, total laparoscopic hysterectomy; BSO, bilateral salpingo-oophorectomy; PLND, pelvic lymph node dissection; TAH, total abdominal hysterectomy.

tamoxifen-induced subepithelial stromal hypertrophy [6,8]. On the other hand, other studies reported a significant relationship between ET by TV-US and endometrial pathology, regardless of the presence of symptoms [5,9]. Kedar *et al.* [9] found that PPV of ET $\geq$8 mm was 100% for the detection of EIN. Saccardi *et al.* [5] reported that an ET of $\geq$5 mm resulted in 100% sensitivity, 15% specificity, 4% PPV and 100% NPV, and ET of $\geq$10 mm resulted in 84% sensitivity, 69% specificity, 10% PPV and 99% NPV, in detecting EIN. In the present study, ET $\geq$5 mm on TV-US had 100% sensitivity and 100% NPV in the detection of EIN or EC. ET $\geq$8 mm had 80.0% sensitivity for detecting EIN or EC and 100% sensitivity for detecting EC. Although 90% of patients showed ET of $\geq$5 mm in this study, ET $\geq$5 mm without vaginal bleeding was less likely related to EIN or EC. In contrast, the risk of EIN or EC increased in patients with vaginal bleeding. Similar to this result, in patients with ET $\geq$8 mm, the risk of EIN or EC increased in patients with vaginal bleeding. EIN or EC was not found in asymptomatic patients with ET $<$8 mm. Although the relationship between thick endometrium and endometrial pathology is weak, in that the majority of tamoxifen users show thick endometrium ($\geq$5 mm), EIN/EC is more likely diagnosed in women with a thick endometrium and vaginal bleeding than in asymptomatic women. TV-US could help determine the need for endometrial biopsy, especially in symptomatic patients on tamoxifen therapy.

Both dose and duration of tamoxifen are known to be associated with endometrial pathologic changes [10,11]. The higher dose and the longer duration more likely lead to endometrial pathologic changes than lower dose and shorter duration. In the current study, patients treated with the same dose of tamoxifen showed an association of length of use with malignant or pre-malignant endometrial pathology. There is controversy about how often patients on tamoxifen should undergo evaluation of the endometrium. Peters-Engl *et al.* [12] recommended annual follow-up of patients on tamoxifen. Katase *et al.* [13] concluded that tamoxifen did not appear to increase subsequent endometrial cancer in patients with breast cancer who underwent annual screening. Other studies have demonstrated no benefit of screening women on tamoxifen if they are asymptomatic [6,14]. Our study did not address how often the endometrium should be evaluated in women taking tamoxifen. However, our findings suggest thet it is more appropriate to evaluate the endoemtrium when the patient presents vaginal bleeding than to undergo regular screening. Even when the patient presents with vaginal bleeding, if the patient has thin and non-specific endometrium, endometrial biopsy may be unnecessary.

There are several limitations to this study. This is a retrospective study with a small number of cases from a single institution. In addition, patients did not undergo evaluation of the endometrium before starting tamoxifen treatment. It is possible that in some cases the abnormal pathology was present before the initiation of tamoxifen. Nonetheless, this study revealed an association of ET by TV-US with risk of EIN or EC according to the presence of vaginal bleeding in women taking tamoxifen. This finding suggests that an endometrial biopsy could be avoided in women on tamoxifen who have a hick endometrium but no vaginal bleeding. A large-scale prospective study is needed for evaluating endometrial pathologic changes and risk factors and for deciding proper screening methods and follow-up intervals of the endometrium of women with a history of tamoxifen treatment.

Table 4. Endometrial pathologic results according to patient's symptom and endometrial thickness (ET) by transvaginal-ultrasonography (TV-US).

Symptom	N (%)	TV-US	N (%)	Pathology	N (%)
No	84 (51.8)	ET <5 mm	7 (8.3%)	EIN/EC	0 (0%)
				Others	7 (100%)
		ET ≥5 mm	77 (91.7%)	EIN/EC	2 (2.6%)
				Others	75 (97.4%)
		ET <8 mm	32 (38.1%)	EIN/EC	0 (0%)
				Others	32 (100%)
		ET ≥8 mm	52 (61.9%)	EIN/EC	2 (3.8%)
				Others	50 (96.2%)
Vaginal bleeding	78 (48.2)	ET <5 mm	9 (11.5%)	EIN/EC	0 (0%)
				Others	9 (100%)
		ET ≥5 mm	69 (88.5%)	EIN/EC	8 (11.6%)
				Others	61 (88.4%)
		ET <8 mm	28 (35.9%)	EIN/EC	2 (7.1%)
				Others	26 (92.9%)
		ET ≥8 mm	50 (64.1%)	EIN/EC	6 (12.0%)
				Others	44 (88.0%)

TV-US, transvaginal-ultrasonography; ET, endometrial thickness; EIN, endometrial intraepithelial neoplasia; EC, endometrial cancer.

5. Conclusions

Regular endometrial screening including pelvic ultrasound for oncologic endometrial change may not be necessary in all women on tamoxifen treatment for breast cancer. Indiscriminate endometrial evaluation might be avoided in patients without vaginal bleeding regardless of the duration of tamoxifen use. When patients on tamoxifen have abnormal vaginal bleeding, TV-US can be a good method of endometrial evaluation and a screening tool before endometrial biopsy. If the endometrium is thin (≤5 mm) on TV-US, endometrial biopsy is unnecessary. When women on tamoxifen need to undergo endometrial biopsy if they have vaginal bleeding and a thick endometrium on TV-US.

Author contributions

UCJ, WDK and SMK designed the research study. UCJ and WDK performed the research and analyzed the data. SMK provided help and advice on the data analyzation. UCJ and WDK wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The protocol was approved by the Institutional Review Board of Chonnam National University Hospital (CNUH) (approval number: HTMP-2021-086).

Acknowledgment

Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Jung K, Won Y, Kong H, Lee ES. Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2015. Cancer Research and Treatmen. 2018; 50: 303–316.

[2] Yarnold J. Early and Locally Advanced Breast Cancer: Diagnosis and Treatment National Institute for Health and Clinical Excellence Guideline 2009. Clinical Oncology. 2009; 21: 159–160.

[3] Committee Opinion No. 601: Tamoxifen and uterine cancer. Obstetrics and Gynecology. 2014;123: 1394–1397.

[4] Ismail SM. Pathology of endometrium treated with tamoxifen. Journal of Clinical Pathology. 1994; 47: 827–833.

[5] Saccardi C, Gizzo S, Patrelli TS, Ancona E, Anis O, Di Gangi S, *et al*. Endometrial surveillance in tamoxifen users: role, timing and accuracy of hysteroscopic investigation: observational longitudinal cohort study. Endocrine-Related Cancer. 2013; 20: 455–462.

[6] Fung MFK, Reid A, Faught W, Le T, Chenier C, Verma S, *et al*. Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. Gynecologic Oncology. 2003; 91: 154–159.

[7] Cohen I, Perel E, Flex D, Tepper R, Altaras MM, Cordoba M, *et al*. Endometrial pathology in postmenopausal tamoxifen treat-

ment: comparison between gynaecologically symptomatic and asymptomatic breast cancer patients. Journal of Clinical Pathology. 1999; 52: 278–282.

[8] Achiron R, Lipitz S, Sivan E, Goldenberg M, Horovitz A, Frenkel Y, *et al*. Changes mimicking endometrial neoplasia in postmenopausal, tamoxifen-treated women with breast cancer: a transvaginal Doppler study. Ultrasound in Obstetrics & Gynecology. 1995; 6: 116–120.

[9] Kedar RP, Bourne TH, Powles TJ, Collins WP, Ashley SE, Cosgrove DO, *et al*. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. Lancet. 1994; 343: 1318–1321.

[10] Schweikart KM, Eldridge SR, Safgren SL, Parman T, Reid JM, Ames MM, *et al*. Comparative uterotrophic effects of endoxifen and tamoxifen in ovariectomized Sprague-Dawley rats. Toxicologic Pathology. 2014; 42: 1188–1196.

[11] Marshall K, Senior J. A study on the effect of a single dose of tamoxifen on uterine hyperaemia and growth in the rat. British Journal of Pharmacology. 1987; 92: 429–435.

[12] Peters-Engl C, Frank W, Danmayr E, Friedl HP, Leodolter S, Medl M. Association between endometrial cancer and tamoxifen treatment of breast cancer. Breast Cancer Research and Treatment. 1999; 54: 255–260.

[13] Katase K, Sugiyama Y, Hasumi K, Yoshimoto M, Kasumi F. The incidence of subsequent endometrial carcinoma with tamoxifen use in patients with primary breast carcinoma. Cancer. 1998; 82: 1698–1703.

[14] Bertelli G, Venturini M, Mastro LD, Garrone O, Cosso M, Gustavino C, e*t al.* Tamoxifen and the endometrium: findings of pelvic ultrasound examination and endometrial biopsy in asymptomatic breast cancer patients. Breast Cancer Research and Treatment. 1998; 47: 41–46.