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The Relationship Between Endometrial Thickness and Endometrial Pathology Results in Tamoxifen Users

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ABSTRACT

Background & Objective: As the selective estrogen receptor modulator tamoxifen plays a major role in treating breast cancer, the most common cancer among women globally. Proliferative alterations in the endometrium are among the side effects of tamoxifen therapy. Our study was aimed to evaluate the relationship between endometrial thickness and endometrial pathology results in tamoxifen users.

Materials & Methods: This cross-sectional study was conducted at Isfahan between 2022 and 2023. Asymptomatic patients with positive history of breast cancer and tamoxifen usage, underwent vaginal ultrasound and sampling. Samples were sent to pathology laboratory and results were analyzed.

Results: A total of 135 females with breast cancer who were taking tamoxifen, participated in this study. According to our findings, there was a significant difference (p=0.015) in the endometrial thickness between the normal group and the two groups of individuals with endometrial cancer and hyperplasia. Also, our data showed that in breast cancer patients, the endometrial thickness with a cut-off of “>14 mm” can significantly predict the risk of endometrial cancer.

Conclusion: Our findings indicate that patients with both endometrial cancer and hyperplasia had considerably higher endometrial thickness. Additionally, endometrial thickness with a cut-off of ">14 mm" is a strong predictor of endometrial cancer risk.

Keywords: Breast Neoplasms, Endometrial Neoplasms, Ultrasonography, Tamoxifen

1. Introduction

Breast cancer is the most frequent disease among women worldwide **(1)**. Tamoxifen, a revolutionary drug in the field of oncology, has been used as adjuvant therapy for the treatment of estrogen receptor-positive breast cancer for the past forty year **(2, 3)**. Tamoxifen use is extended from 5 to 10 years after the ATLAS study **(4)** because it successfully reduces the recurrence and progression of the disease. Tamoxifen is a selective estrogen receptor modulator that exhibits agonistic effects on the endometrium but competitive antagonistic effects for estrogens in breast tissue **(5)**. Tamoxifen inhibits breast tissue from proliferating, while it alters the endometrium's ability to proliferate **(6)**. Tamoxifen users have a higher incidence of endometrial cancer (1.26 per 1,000 patient-years); this is approximately twice as likely as those who do not use the drug **(7, 8)**. It is critical to identify risk groups with a high probability of developing endometrial disease. There is still disagreement over the frequency and methods of endometrial surveillance, even after many years of experience **(9)**. Additionally, debatable is the use of ultrasonography to assess the endometrium because tamoxifen-induced sub-endometrial hypertrophy can complicate the assessment **(10, 11)**. While research has been done on the connection between inflammation and endometrial diseases, it has not examined this problem in tamoxifen users. Investigating the connection between endometrial thickness and endometrial pathology outcomes in tamoxifen users was the goal of this investigation.

2. Materials and Methods

This cross-sectional study was conducted at Shahid Beheshti hospital, Isfahan between 2022 and 2023. After obtaining informed consent, we enrolled patients with ages of 30-80, who had breast cancer, history of 2 to 10 years of tamoxifen use. Patients with positive history of endometrial cancer or patients with hysterectomy were excluded. Afterward, patients were subjected to vaginal ultrasound examination. If the tissue was homogenous, they were subjected to Pipelle, and if it was non-homogeneous, they were subjected to hysteroscopy or D&C. Patients who had amenorrhea and polyps were determined as normal pathology.

All pathological slides were sent to the pathology laboratory, and results were analyzed using SPSS version 26 (IBM, USA). This study was approved at Isfahan University of Medical Science Ethics Committee (IR.ARI.MUI.REC.1401.133) and was conducted based on the Helsinki declaration.

3. Results

A total of 135 female breast cancer patients taking tamoxifen participated in this study. The mean ± SD age of the participants was 49.41 ± 7.52 years (ranged 30 to 80 years). Also, the duration of tamoxifen use in patients was evaluated, and the results showed that the mean±SD duration of tamoxifen use was 4.56 ± 2.44 years, with a range of 2 to 10 years. In addition, the mean ±SD of endometrial thickness was 13.28 ± 6.03 mm (ranged 5 to 40 mm). In this study, 15 patients (11.1 %) were diagnosed with endometrial cancer and 4 patients (3 %) had hyperplasia (Table 1). The descriptive data are shown in Table 1.

Table1. Descriptive characteristics of patients participating in the study

Variable	Mean	SD
Age [year]	49.41	7.52
Age of breast cancer diagnosis [year]	44.48	7.13
Duration of tamoxifen use [year]	4.56	2.44
Endometrial thickness [mm]	13.28	6.03
Age category	**N**	**%**
<45 years	34	25.2
45-54 years	73	54.1
≥55 years	28	20.7
Tamoxifen duration category		
2-3 years	56	41.5
4-6 years	61	45.2
≥ 7 years	18	13.3
Endometrial cancer pathology results		
Normal	116	85.9
Cancer	15	11.1
Hyperplasia	4	3
Underling disease		
Diabetes*	14	10.4
High blood pressure*	13	9.6

***Positive case**

The relationship between endometrial pathology and endometrial thickness was evaluated, and the results showed that the endometrial thickness was significantly lower in the normal group than in the two groups of people diagnosed with endometrial cancer and hyperplasia (p=0.015) (Table 2). Also, in patients aged 45 years and older, the thickness of the endometrium in the group of people with endometrial cancer and hyperplasia was significantly higher than the normal group (Table 2).

Also, in patients who took tamoxifen for 4 years or more, the thickness of the endometrium was significantly higher in the group of people with endometrial cancer and hyperplasia than in the normal group (Table 2). This result was also observed in patients who did not have diabetes or hypertension. While the results show that in people with high blood pressure, the thickness of the endometrium in normal group is a little higher than in people with endometrial

cancer. But this difference was not statistically significant (P=0.932) (Table 2).

Table 2. Correlation between endometrial pathology and endometrial thickness according to the studied variables

Group	Endometrial pathology			P-value
	Normal	Cancer	Hyperplasia	
	mean ± SD of endometrial thickness			
All patients	12.71 ± 5.67	16.27 ± 4.25	17.75 ± 14.5	P=0.015
Age category				
<45 years	13.12 ± 5.55	-	10 ± -	P=0.645
45-54 years	12.65 ± 6.06	16.75 ± 2.98	19.67 ± 15.25	P=0.045
≥55 years	12.12 ± 4.4	16.09 ± 4.74	-	P=0.032
Tamoxifen duration category				
2-3 years	12.42 ± 6.19	13.17 ± 4.95	-	P=0.778
4-6 years	12.87 ± 5.52	17.75 ± 2.06	12.5 ± 4.95	P=0.044
≥ 7 years	13.18 ± 4.04	18.8 ± 2.16	20 ± 18.21	P=0.036
Diabetes				
No	12.64 ± 5.76	16.55 ± 3.69	17.75 ± 14.5	P=0.017
Yes	13.4 ± 4.71	15.5 ± 6.13	-	P=0.395
High blood pressure				
No	12.58 ± 5.81	16.92 ± 3.72	17.75 ± 14.5	P=0.008
Yes	14 ± 3.77	13.67 ± 6.11	-	P=0.932

Also, association between the pathology of the endometrial and potential risk factors was evaluated. The results of univariate analysis show that increasing age and increasing the time of taking tamoxifen have a significant relationship with increasing the chance of developing cancer (or hyperplasia). Conversely, having diabetes and high blood pressure does not show a significant correlation with the risk of cancer development. These results were the same in multivariate analysis (Table 3).

Table 3. Association between the pathology of the endometrial (chance of developing cancer or the type of hyperplasia) and potential risk factors

Variables	Crude				Adjust[&]			
	OR	P-value	95% CI		OR	P-value	95% CI	
			lower	Upper			lower	Upper
Age	1.156	P<0.001	1.073	1.245	1.163	P<0.001	1.074	1.260
Tamoxifen duration	1.303	P=0.003	1.093	1.552	1.306	P=0.009	1.068	1.598
Diabetes*	2.827	P=0.111	0.786	10.16	1.464	P=0.658	0.271	7.902
High blood pressure*	1.987	P=0.334	0.493	8.00	2.368	P=0.342	0.400	14.01

***Yes** [&] **adjusted for age and duration of tamoxifen use**

In addition, the results of this study show that in breast cancer patients, the endometrial thickness with a cut-off of ">14 mm" can significantly predict the risk of endometrial cancer. (AUC=0.725, P=0.001, sensitivity=0.80, specificity=0.64.7) (Figure 1).

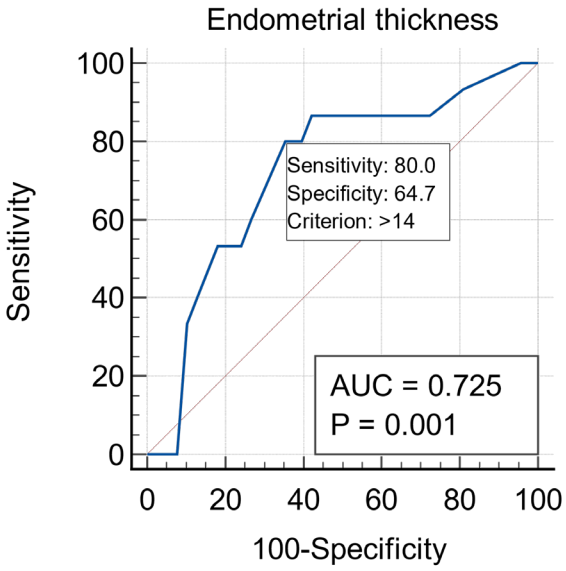

Figure 1. Prediction of endometrial cancer risk by endometrial thickness

Additionally, the duration of tamoxifen use was compared across the three groups. The findings revealed that the duration of tamoxifen use was 8.5, 5.67, and 4.28 years in hyperplasia, cancer, and normal groups, respectively. A notable disparity was evident between the hyperplasia and normal groups (P=0.002). In addition, the relationship between endometrial thickness and duration of tamoxifen use was evaluated. The results showed that there is no significant relationship between the duration of tamoxifen use and endometrial thickness (Spearman's correlation coefficient=0.160, P=0.065). Also, the mean of endometrial thickness was evaluated in three categories of tamoxifen consumption time and results showed that the thickness of the endometrium increases with the increase in the time of taking Tamoxifen. But it was not statistically significant (P=0.113) (Table 4).

Table 4. Association between tamoxifen duration of use and endometrial thickness

Tamoxifen duration of use	Endometrial thickness		P-value
	Mean	SD	
2-3 years	12.5	6.03	P=0.113
4-6 years	13.18	5.43	
≥ 7 years	14.65	4.42	

4. Discussion

The objective of this study was to assess the correlation between endometrial thickness and endometrial pathology outcomes in individuals using tamoxifen. Our findings demonstrated that, when compared to groups of individuals with endometrial cancer and hyperplasia, endometrial thickness was much smaller in normal patients. Additionally, the thickness of the endometrium was considerably larger in the group of patients with endometrial cancer and hyperplasia than in the normal group among patients who used tamoxifen for four years or longer. Additionally, our research indicates that endometrial thickness, with a cut-off of ">14 mm," can strongly predict the risk of endometrial cancer in women with breast cancer. Two cases of high-grade papillary serous carcinoma comprised the 15 total cancer cases; the remaining cases were endometrioid cancer, with grades of 1 (50%), 2(30%), and 3(20%). Additionally, all four of the hyperplasia cases are of the usual type. 53 patients with a history of breast carcinoma who later developed a malignant tumor of the uterine corpus were found using a computer search study of the Yale-New Haven Hospital Tumor Registry between 1980 and 1990. Of these patients, fifteen took tamoxifen for their breast carcinoma, while the remaining 38 did not. The two groups' mean ages did not differ appreciably. In the tamoxifen group, the mean time between the identification of endometrial and breast malignancies was five years, but in the nontreated group, it was 12 years. When comparing the patients in the tamoxifen group to the nontreated group, the former group had 24% more patients with poorly differentiated endometrioid carcinomas (including adenosquamous carcinoma) or carcinomas associated with poor outcome (uterine papillary serous carcinoma, clear-cell carcinoma, or mixed Müllerian tumor). Individuals on tamoxifen had a significantly higher risk of dying from endometrial cancer **(12)**. Our findings are in line with

earlier studies that demonstrate tamoxifen increases the incidence of uterine sarcoma, polyps, endometrial proliferation, hyperplasia, and invasive carcinoma in a dose- and time-dependent way **(13-17)**.

Endometrial thickness evaluation by ultrasonography is the most often used approach for gynecologic surveillance in patients with breast cancer treated with tamoxifen; nevertheless, even with a cut-off value of 10 mm, this method's diagnostic accuracy is not particularly high **(18-20)**. The appearance of the endometrium varies with the menstrual cycle, making it difficult to determine an appropriate cut-off value in premenopausal women. Therefore, when performing gynecologic surveillance in women treated with tamoxifen, endometrial appearance or the presence of abnormal uterine bleeding should be taken into account in addition to endometrial thickness.

A related study including fifty breast cancer patients receiving tamoxifen treatment was conducted by Jindal, Mohi **(19)**. According to their findings, 35 patients (or70%) exhibited endometrial thicknesses up to 5 mm on ultrasonography. The endometrial thickness was greater than 5 mm in 15 individuals. Of them, two patients, or 4% of the total, had endometrial thicknesses above 20 mm, while 11 patients, or 22% of the total, had endometrial thicknesses between 5.1 and 10 mm. We performed hysteroscopy on eleven patients. Three of these individuals had aberrant hysteroscopic pictures, whereas the remaining eight had normal hysteroscopic appearances. They came to the conclusion that there was a correlation between the length of tamoxifen therapy and the patients' symptom level ($P < 0.0001$) as well as a relationship between the duration of tamoxifen medication and the incidence of endometrial cancer ($P < 0.0001$). Another observational longitudinal cohort study found a high association between hysteroscopic suspicion of endometrial atypia, which was verified by histology, and a history of irregular uterine bleeding, with or without endometrial thickening. In order to diagnose endometrial atypia, hysteroscopy exhibited 83.3% sensitivity, 99% specificity, 83.3% positive predictive value (PPV), and 99% negative predictive value (NPV). Histological atypia and endometrial thickening to a depth of more than 0.5 mm without bleeding did not significantly correlate, according to the findings. Likewise, there was no correlation between the length of treatment and histological atypia or endometrial thickening. Histology revealed endometrial stromal hyperplasia in 70.5% of patients, with endometrial thickness measures between 5 and 10 mm. On the other hand, when endometrial thickness was less than 5 mm, no atypia was found. When endometrial thickness was measured with ultrasound, a 5-mm cut-off threshold produced 100% sensitivity, 15% specificity, 4% PPV, and 100% NPV for endometrial atypia detection; a 10-mm cut-off threshold produced 84% sensitivity, 69% specificity, 10% PPV, and 99% NPV. The authors came to the conclusion that people taking low-risk tamoxifen do not need to undergo different endometrial surveillance than people in general **(18)**. In a different study, Weaver et al demonstrated that measuring endometrial thickness with transvaginal ultrasound using a 5 mm cut-off is a highly accurate way to rule out endometrial disease in symptomatic women taking tamoxifen. Unless symptoms return, this may eliminate the need for additional diagnostic testing in women. Additional testing is required since a positive transvaginal ultrasonography result is not very meaningful **(21)**. Our study wasn't without limitation. Most important one, was our relatively small sample size, which would makes us unable to drive meaningful conclusions.

5. Conclusion

We conducted a cross-sectional study to evaluate the relationship between endometrial thickness and endometrial pathology results in tamoxifen users. We showed that endometrial thickness was significantly higher in patients with endometrial cancer and hyperplasia. Furthermore, our data shows that in breast cancer patients, the endometrial thickness with a cut-off of ">14 mm" can significantly predict the risk of endometrial cancer.

6. Declarations

Acknowledgments

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Ethical Considerations

This study was approved at Isfahan University of Medical Science Ethics Committee (IR.ARI.MUI.REC.1401.133) and was conducted based on the Helsinki declaration.

Authors' Contributions

Maryam Shirini wrote the first manuscript. Leila Mousavi Seresht gathered the data. Fatemeh Zahrasadat Allameh and Fariba Behnamfar revised the manuscript. Fahimeh Sabet review data analysis. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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Informed consent

All patients provided informed consent prior to participation in this study.

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