Tamoxifen use and risk of endometrial pathology in breast cancer patients:

A Prospective cohort study

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Submission: 10 February 2026 | **Acceptance**: 20 March 2026 | **Publication**: 15 April 2026,

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Abstract

Background:

There is significant evidence implicating the association of tamoxifen with endometrial pathologies leading to various gynecological symptoms. Therefore surveillance is needed for possible adverse effects of tamoxifen therapy on uterus but data regarding surveillance of endometrial symptoms is scarce.

Objective:

To investigate the effects of tamoxifen on uterine endometrium in preventive setting.

Methods:

This prospective cohort study conducted at Mayo Hospital , Lahore between November 2019 to November 2024 that included female breast cancer patients who underwent mastectomy, aged 30-70 years undergoing tamoxifen therapy.Self- administered questionnaire was used for data collection. A non-probability consecutive sampling technique was used to recruit eligible patients. Baseline demographic data, gynecological symptoms, and endometrial thickness measurements were collected at 2.5 years and 5 years. Statistical analyses were conducted using SPSS (version 25), with $p < 0.05$ considered statistically significant.

Results :

The mean age of the patients was 55 years and mean BMI was 27kg/m^2. The mean endometrial thickness at 2.5 years and 5 years was 6 mm and 4.3 mm respectively. The p-value for endometrial thickness at 2.5 years and 5 years was 1 and 0.0001, respectively.
Endometrial samples were taken in 160(30.4%) patients,
and the average duration for referral was 2.5 years.
Hysterectomy was performed on 3(0.4%) patients and none of them had endometrial carcinoma on biopsy.

Conclusion:

Our study reinforces the need for individualized monitoring strategies for tamoxifen-treated breast cancer patients, particularly premenopausal women. While routine gynecological assessments remain the standard of care, clinicians should recognize the potential for increased endometrial pathology in this population

Keywords:

Frequency, gynecological symptoms, breast cancer, tamoxifen.

Introduction

Breast cancer is one of the most prevalent cancer in women worldwide. The majority of the patients present with end-stage disease because of the social taboo of the illness, and the incidence of patients with early-stage cancer hasn't changed since two decades . However, diagnosis and prompt treatment have mitigated the death rate significantly by 38% in the recent times . The touchstones for breast cancer management include surgery, chemotherapy, ionizing radiotherapy, endocrine therapy, and targeted therapy [1,2,3,4].

Endocrine therapy or hormonal therapy is considered the preliminary systemic treatment for Hormonal Receptor (HR) positive breast cancer. Tamoxifen (TAM) is a selective estrogen receptor modulator (SERM) that inhibits estrogen attachment to estrogen receptors, and tamoxifen therapy is helpful in pre-and postmenopausal women.

The five-year-recurrence of breast cancer has declined by 50% because of tamoxifen therapy in HR-positive breast cancer. Therefore, TAM therapy for a longer life span is recommended [5,6]

Estrogen receptors (ER) are indispensable for many functions, affecting cardiovascular, musculoskeletal, and reproductive systems. Moreover, it is also responsible for breast cancer progression; about 70-80% of the patients are ER-positive [7].

TAM users can experience various gynecological effects, including vasomotor symptoms(hot flushes, sweating, vaginal dryness), cyst occurrence, leiomyoma, vaginal bleeding, and high chances of endometrial pathologies . Moreover, it also affects menstruation ranging from no alteration to complete cessation of menses. However, the exact pathophysiology is unknown; it is believed that higher plasma estrogen levels impede the hypothalamus-pituitary and ovarian axis [8, 9].

According to another study , there is a significant relationship between tamoxifen and endometrial thickening. The imminence of endometrial hyperplasia and polyps has increased 2 to 4 times, especially in pre and early postmenopausal women [10].

This study aims to dig up the impact of tamoxifen on endometrium. So that various pharmacological interventions can be made to improve the quality of life for these survivors. We are standing on the verge of an era in which millions of patients will take this drug for life long, and many of them may have remained clinically disease-free. It is a dire need of the hour to get more information about tamoxifen's long-term effects on endometrium. Due to the increase in the use of TAM, there is a significant decrease in the recurrence of breast cancer in the contralateral breast, due to which it has a vital stance in prevention. We have to check the risk versus benefit ratio, and in this case, risk belongs to endometrial anomalies; because of that, continuous paradoxical monitoring is needed. Although there are well-documented data regarding the effects of TAM on the endometrium, there is a need for more exploration in this aspect, which resulted in planning this study to probe the effects of TAM therapy in preventive settings on endometrium.

Methodology

This was a prospective cohort study conducted at West Surgical ward, Mayo Hospital from November 2019 to November 2024. The study was approved by the Institutional Review Board (IRB)of KEMU with approval number 152/RC/KEMU. Written informed consent was obtained from all participants before enrollment, ensuring confidentiality and adherence to ethical guidelines.

Female patients aged 30-70 years diagnosed with breast cancer, who underwent mastectomy and had completed at least six months of tamoxifen therapy were included in the study whereaspatients with a history of endometrial hyperplasia or endometrial carcinoma before tamoxifen therapy, patients on concurrent hormonal therapy (e.g., aromatase inhibitors), patients with pre-existing gynecological disorders affecting the endometrium, pregnant or lactating women and patients who discontinued tamoxifen therapy before six months of follow-up were excluded from the study. Self-administered questionnaire wasused to collect data.

The sample size was calculated based on an expected prevalence of gynecological symptoms in tamoxifen-treated patients. Using a confidence level of 95%, a margin of error of 5%, and accounting for a dropout rate of 30%, a minimum of 750 patients were required for adequate statistical power [12].

A non-probability consecutive sampling technique was used. All eligible patients presenting to the oncology and gynecology clinics during the study period were recruited until the required sample size was achieved.

Baseline demographic data (age, BMI, socioeconomic and educational status) and gynecological outcome in terms of irregular vaginal bleeding, endometrial thickness, hysterectomy were recorded. Endometrial thickness was measured via transvaginal ultrasound (TVUS) at 2.5 years and 5 years of tamoxifen therapy. Data were collected using structured case report forms (CRFs) and entered into SPSS (version 25) for statistical analysis

Descriptive statistics were used to present the data as mean ± standard deviation (SD) for continuous variables and frequency/percentages for categorical variables.

Inferential statistics applied, **t-test to assess the change in endometrial thickness over time**.

A p-value < 0.05 was considered statistically significant.

Primary outcome was frequency of gynecological signs and symptoms (e.g., vaginal bleeding, thickened endometrium, hysterectomy.

Results

Out of 750 breast carcinoma patients, the discontinuation rate after the beginning of tamoxifen was 30%(n=225) and the meantime for the drug use was 18 months among the drop outs**.**

70% of the patients in this study were postmenopausal, while 30% were premenopausal and the total patients that completed surveillance were 525. These patients were put on surveillance through endometrial thickness and symptoms like irregular per vaginal bleeding. Cut off of endometrial thickness was 5 mm among postmenopausal and 13 mm among pre menopausal female that warranted sampling..

The socio-demographic details of study participants are shown in Table No. 1.

Table No. 1: Socio-demographic details

Variable	Category	Frequency N=(mention number of subjects)	Percentage
Age	**Upto 50**	**157**	**29.91%**
	Above 50	**368**	**70.09%**
Education	**Illiterate**	**150**	**28.5%**
	Primary	**100**	**19.04%**
	Up to matric	**130**	**24.7%**
	Intermediate & above	**145**	**27.6%**

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Patients fulfilling the inclusion criteria and after excluding the dropouts total of 525 were put on surveillance through transvaginal ultrasound and symptom diary.The mean endometrial thickness at 2.5 years and 5 years is shown in **Table 2**. The p-value for endometrial thickness at 2.5 yearswas 1 and at 5 years was 0.0001 that was statistically significant**.** These findings were irrespective of the menopausal status**.**

Table No. 2: Mean endometrial thickness in Patients taking Tamoxifen

Timeline	Mean ± SD	T test Value	P value
2.5 years N=525	6+1	0	1
5 years N=525	4.3+1	6.87	.0001

Out of 525 patients 73(13.9%) patients had irregular vaginal bleeding and 87 (16.5%) had increased endometrial thickness for which endometrial sampling was performed. So endometrial samples were taken in 160 (30.4%) patients, and the rest of the cohort 365(69.5%) were put on surveillance through the aforementioned methods.

Hysterectomy was performed on 3(0.4%) patients and none of them were proved to be endometrial carcinoma on biopsy.

Discussion

Our study provides valuable insights on effects of tamoxifen therapy on endometrium in breast , particularly among premenopausal women—a population often underrepresented in earlier Western research. Contrary to the prevailing evidence suggesting a heightened risk of endometrial pathology with tamoxifen, we found no statistically significant increase in the incidence of endometrial hyperplasia, polyps, or malignancies in our cohort. However, this absence of a strong association should not be interpreted as a lack of risk. Rather, it underscores the importance of continued vigilance and individualized monitoring in all women undergoing tamoxifen therapy, regardless of menopausal status.

Tamoxifen, a selective estrogen receptor modulator (SERM), exerts dual agonist-antagonist effects depending on tissue type. While it inhibits estrogen activity in breast tissue, its partial agonist effect on the endometrium can stimulate proliferation, leading to abnormal uterine bleeding (AUB) and structural abnormalities. In our study, 14.1% of women reported irregular per vaginal bleeding (PVB), consistent with findings by Kim et al. and Chai et al., who also documented increased rates of endometrial pathology among tamoxifen users. This highlights the clinical relevance of patient-reported symptoms, which may serve as early indicators of underlying endometrial changes, even when imaging or histology remains inconclusive.

Several studies have described an increased risk of endometrial hyperplasia and polyps in tamoxifen users, conditions that, although benign, often necessitate further diagnostic procedures such as transvaginal sonography, hysteroscopy, and biopsy. These interventions contribute to increased healthcare burden, both financially and psychologically, especially in premenopausal women who may already be coping with the implications of breast cancer. Moreover, the cumulative exposure to invasive procedures in this younger population further emphasizes the need for more precise risk stratification and monitoring protocols tailored to age and reproductive status. [15,16.17, 18]

Interestingly, our study demonstrated a **statistically significant decrease in mean endometrial thickness**, from 6 mm at 2.5 years to 4.3 mm at 5 years of tamoxifen therapy. While this contrasts with the widely held notion that tamoxifen leads to progressive endometrial thickening, it may reflect a plateau or regression effect over time, potentially influenced by individual hormonal profiles, genetic factors, or intermittent withdrawal from therapy. Prior literature, including studies by Park et al. (2019) and Huang et al. (2021), predominantly focused on postmenopausal cohorts, thereby missing critical trends in younger

populations. Our findings add to the growing body of evidence that the endometrial response to tamoxifen is neither linear nor uniform, and may be influenced by ethnicity, duration of therapy, and baseline endometrial histology.[19, 20, 21]

Another noteworthy outcome in our cohort was the **low hysterectomy rate of 0.4%**, which aligns with rates reported in general population studies. This suggests that while gynecological symptoms are common during tamoxifen therapy, they do not necessarily culminate in surgical intervention for most patients. However, it is essential to recognize the rare but serious association of tamoxifen with aggressive uterine malignancies such as endometrial stromal sarcoma and malignant mixed Müllerian tumors. As such, the decision to pursue hysterectomy should be guided by the severity of symptoms, persistence of abnormal bleeding, histopathological findings, and patient preference, rather than by symptom presence alone.[22,23]

Importantly, existing guidelines from the American College of Obstetricians and Gynecologists (ACOG) recommend routine gynecological follow-up without additional surveillance for premenopausal women on tamoxifen. However, recent data from East Asian populations challenge this generalization. Several studies report that **younger women in these regions are experiencing increased incidences of tamoxifen-related endometrial abnormalities**, thereby calling for a re-evaluation of standard surveillance protocols. Considering that Asian women tend to be diagnosed with breast cancer at a **younger median age** compared to their Western counterparts, the risk profile for endometrial pathology may be significantly different in this population. Therefore, region-specific surveillance strategies—incorporating clinical, ultrasonographic, and, when indicated, histologic evaluation—may be more appropriate to ensure timely identification and management of endometrial changes.[13, 23, 24, 25]

Conclusion

Our study reinforces the need for heightened awareness and individualized monitoring strategies for tamoxifen-treated breast cancer patients, particularly premenopausal women. While routine gynecological assessments remain the standard of care, clinicians should recognize the potential for increased endometrial pathology in this population.

Study Limitations

Several limitations should be considered when interpreting these results. The study's observational design may introduce selection bias, and the reliance on ultrasound measurements for ET could be subject to inter-observer variability. Additionally, the high dropout rate (30%) may affect the generalizability of the findings, although statistical analyses accounted for this attrition.

Future direction:

Future studies should aim to recruit a larger sample size and extend the follow up period to better evaluate the long-termeffects of tamoxifen therapy on gynecological symptoms.

Sources of funding: None
Conflict of interest: No conflict of interest is declared

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