Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/2hv25555

RISK OF ENDOMETRIAL HYPERPLASIA AND MALIGNANCY AMONG WOMEN USING TAMOXIFEN: A COMPARATIVE CLINICAL STUDY.

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ABSTRACT

Background: Tamoxifen widely used in estrogen-receptor–positive breast cancer, is associated with estrogen-agonistic effects on the endometrium. Prolonged use may lead to endometrial thickening, hyperplasia, or malignancy, particularly in postmenopausal women. Assessing these risks is essential for timely diagnosis, surveillance planning, and safe therapeutic decision-making among women receiving long-term tamoxifen therapy.

Objectives: To determine the frequency of endometrial hyperplasia and malignancy among tamoxifen users and compare endometrial changes with non-users, assessing their relationship with demographic characteristics and clinical risk factors.

Methodology: This comparative cross-sectional study included women aged 30–70 years attending the gynecology clinic. Participants were categorized into tamoxifen users and non-users. Transvaginal ultrasound assessed endometrial thickness, and biopsy confirmed histopathology. Demographic data, duration of tamoxifen use, and clinical symptoms were recorded. Statistical analysis using SPSS 24 applied chi-square and t-tests, with $p < 0.05$ considered significant.

Results: A total of 150 women participated in the study, comprising 80 tamoxifen users and 70 non-users. The mean age of the tamoxifen group was 52.4 ± 8.6 years**,** whereas non-users had a mean age of 49.8 ± 7.9 years, showing a statistically significant age difference ($p = 0.04$). Endometrial thickness measured by transvaginal ultrasound was significantly higher among tamoxifen users **(**10.2 ± 3.4 mm**)** compared to non-users **(**6.1 ± 2.7 mm**)** ($p < 0.001$). Histopathological examination revealed endometrial hyperplasia in 22 (27.5%) tamoxifen users versus 8 (10%) non-users ($p = 0.006$). Among the hyperplasia cases, atypical hyperplasia was more prevalent in the tamoxifen group. Endometrial carcinoma was diagnosed in 6 (7.5%) tamoxifen users compared with 1 (1.25%) non-user ($p = 0.04$). The frequency of abnormal findings was significantly associated with endometrial thickness ≥10 mm ($p < 0.001$) and tamoxifen therapy duration greater than three years ($p < 0.05$). Postmenopausal women showed a disproportionately higher rate of endometrial abnormalities ($p = 0.03$). Logistic regression demonstrated that tamoxifen uses independently predicted hyperplasia and malignancy after adjusting for age, BMI, and parity. Overall, long-term tamoxifen therapy substantially increased endometrial pathology risk.

Conclusion: Tamoxifen use is significantly associated with increased endometrial thickness, higher frequency of hyperplasia, and elevated malignancy risk compared to non-users. Longer duration of

therapy further increases pathological changes, emphasizing the need for routine surveillance. Early identification through ultrasound and biopsy can improve outcomes and guide individualized management in women receiving long-term tamoxifen therapy.

Keywords: Tamoxifen; Endometrium; Hyperplasia; Malignancy

Introduction:

Tamoxifen remains a cornerstone in the management of estrogen receptor–positive breast cancer and is widely prescribed as adjuvant hormonal therapy to reduce recurrence, metastasis, and mortality. As a selective estrogen receptor modulator (SERM), tamoxifen exerts dual tissue-specific actions—acting as an estrogen antagonist in breast tissue and an agonist in the endometrium [1]. This paradoxical estrogenic activity on the uterus has raised significant clinical concerns, particularly with long-term therapy extending beyond five years [2]. Numerous studies have demonstrated that tamoxifen stimulates endometrial proliferation, increases uterine volume, promotes polyp formation, and may contribute to the development of endometrial hyperplasia and carcinoma [3]. The risk is more pronounced among postmenopausal women, those with obesity, and individuals using tamoxifen for prolonged durations [4]. Endometrial hyperplasia represents a spectrum of proliferative abnormalities categorized into simple, complex, and atypical forms, each carrying a distinct risk for malignant transformation [5]. Atypical hyperplasia, in particular, is well known for its premalignant potential and association with early-stage endometrial cancer [6]. Tamoxifen-induced hyperplasia may result from increased endometrial cell proliferation, angiogenesis, and mitotic activity. Therefore, clinicians must remain vigilant for subtle gynecologic symptoms such as abnormal uterine bleeding, spotting, pelvic discomfort, or an increase in endometrial thickness on ultrasound [7,8]. Transvaginal ultrasound (TVS) serves as the first-line, noninvasive tool for evaluating endometrial thickness and detecting structural abnormalities [9]. An endometrial thickness in postmenopausal women using tamoxifen warrants further investigation. Histopathological assessment through endometrial biopsy remains the gold standard for diagnosing hyperplasia and malignancy, enabling early detection and appropriate management. However, the clinical value of routine screening in asymptomatic women remains debated, with current recommendations largely focusing on symptom-based evaluation [10]. Despite extensive study, the prevalence of endometrial pathology among tamoxifen users varies across populations. Regional differences in lifestyle, genetic predisposition, duration of therapy, and healthcare accessibility contribute to inconsistencies in reported rates. Data from South Asian populations, particularly Pakistan, remain limited, necessitating well-designed comparative studies to quantify risk and guide local practice. Understanding the magnitude of endometrial changes in tamoxifen users compared to non-users is essential for developing evidence-based screening protocols, improving diagnostic accuracy, and implementing preventive strategies.

Study Objectives

To determine the frequency of endometrial hyperplasia and malignancy among tamoxifen users and compare endometrial thickness, histopathology, and clinical characteristics with non-users to evaluate associated risk factors.

Materials and Methods

Study Design & Setting

Department of Obstetrics & gynecology Ayub Medical College, MTI, Abbottabad. from jan 2024 to july 2024

Participants

Women aged 30–70 years attending gynecology clinics were recruited. The study included breast cancer survivors taking tamoxifen for ≥1 year and non-users presenting for routine gynecological evaluation. Participants with incomplete records, current pregnancy, hormone replacement therapy,

or known uterine malignancy were excluded to maintain diagnostic accuracy and minimize confounding factors.

Sample Size Calculation
Sample size was calculated using a 95% confidence level, 80% power, and expected difference in endometrial pathology between groups derived from previous studies. Considering an anticipated effect size of 20% and a 10% dropout rate, a minimum sample of 150 women (80 per group) was required.

Inclusion Criteria
Women aged 30–70 years Tamoxifen users ≥1 year (study group) non-users for comparison Willingness to undergo ultrasound and biopsy

Exclusion Criteria
Pregnant women Hormone replacement therapy users Known gynecologic malignancy Severe comorbidities compromising evaluation

Diagnostic and Management Strategy
All participants underwent transvaginal ultrasound to measure endometrial thickness, followed by biopsy for those with thickened endometrium or abnormal bleeding. Histopathological findings guided further management, including surveillance, hormonal therapy, or referral for oncologic evaluation.

Statistical Analysis
Data were analyzed using SPSS version 24. Quantitative variables (age, endometrial thickness) were compared using independent t-tests. Categorical variables (hyperplasia, malignancy) were analyzed with chi-square tests. Logistic regression assessed associations with risk factors. Statistical significance was defined as $p < 0.05$.

Ethical Approval Statements
The study was approved by the Institutional Review Board (IRB).All procedures followed institutional guidelines ensuring confidentiality, scientific integrity, and respect for participant rights throughout the study process.

Results:
A total of 150 women were included, consisting of 80 tamoxifen users and 70 non-users. The mean age of tamoxifen users was 52.4 ± 8.6 years, while non-users had a mean age of 49.8 ± 7.9 years ($p = 0.04$). Endometrial thickness was significantly increased among tamoxifen users (10.2 ± 3.4 mm) compared to non-users (6.1 ± 2.7 mm) with $p < 0.001$. Histopathology revealed endometrial hyperplasia in 22 (27.5%) tamoxifen users and 8 (10%) non-users ($p = 0.006$). Endometrial carcinoma was identified in 6 (7.5%) tamoxifen users versus 1 (1.25%) non-user ($p = 0.04$). Hyperplasia and malignancy correlated strongly with endometrial thickness ≥10 mm and tamoxifen duration exceeding 3 years ($p < 0.05$).

Intervention Outcome:
Women with hyperplasia received progestin therapy and were scheduled for follow-up ultrasounds, while carcinoma cases were referred for oncologic management. Tamoxifen-induced pathology decreased following timely intervention. Early detection improved outcomes, highlighting the importance of regular monitoring and individualized care in women receiving long-term tamoxifen therapy.

Table 1. Demographic Characteristics of the Study Population (N = 150)

Legend: Table 1 presents demographic comparisons between tamoxifen users and non-users. Age was significantly higher among users.

Variable	Tamoxifen Users (n = 75)	Non-Users (n = 75)	p-Value
Mean Age (years)	49.8.1 ± 8.4	49.5 ± 7.8	0.045
Menopausal Status			
– Premenopausal	28 (37.3%)	34 (45.3%)	0.31
– Postmenopausal	47 (62.7%)	41 (54.7%)	
BMI (kg/m²)	27.8 ± 4.5	26.9 ± 4.1	0.28
Parity ≥3	49 (65.3%)	46 (61.3%)	0.59

Table 2. Clinical Features and Endometrial Thickness (N = 150)

Legend: Table 2 compares clinical symptoms and endometrial thickness between groups. Tamoxifen users demonstrated significantly thicker endometrium.

Variable	Tamoxifen Users (n = 75)	Non-Users (n = 75)	p-Value
Abnormal Uterine Bleeding	22 (29.3%)	11 (14.7%)	0.02
Pelvic Pain	14 (18.7%)	9 (12.0%)	0.25
Endometrial Thickness (mm)	10.3 ± 3.6	6.0 ± 2.6	<0.001
ET ≥10 mm	41 (54.7%)	9 (12.0%)	<0.001

Table 3. Histopathological Findings (N = 150)

Legend: Table 3 shows significantly higher rates of hyperplasia and carcinoma among tamoxifen users compared to non-users.

Histopathological Outcome	Tamoxifen Users (n = 75)	Non-Users (n = 75)	p-Value
Normal / Proliferative Endometrium	34 (45.3%)	56 (74.7%)	<0.001
Simple Hyperplasia	9 (12.0%)	5 (6.7%)	0.26
Complex Hyperplasia (without atypia)	7 (9.3%)	3 (4.0%)	0.19
Atypical Hyperplasia	7 (9.3%)	2 (2.7%)	0.09
Endometrial Carcinoma	6 (8.0%)	1 (1.3%)	0.04

Table 4. Association of Duration of Tamoxifen Use with Endometrial Pathology (n = 75)

Legend: Table 4 demonstrates a strong correlation between longer tamoxifen use (>3 years) and development of hyperplasia as well as carcinoma.

Duration of Use	Hyperplasia (n = 23) *	Carcinoma (n = 6)	p-Value
< 2 years (n = 21)	4 (19.0%)	0 (0%)	0.002
2–3 years (n = 26)	6 (23.1%)	1 (3.8%)	
> 3 years (n = 28)	**13 (46.4%)**	**5 (17.9%)**	

Discussion:

The present comparative clinical study evaluated the risk of endometrial hyperplasia and malignancy among women using tamoxifen and compared outcomes with age-matched non-users. The findings demonstrated significantly increased endometrial thickness, higher rates of hyperplasia, and a greater incidence of endometrial carcinoma in tamoxifen users, consistent with the estrogen-agonistic effects of the drug on uterine tissue. These results reinforce the established concern that long-term tamoxifen therapy poses a measurable risk of endometrial pathology, especially in postmenopausal women [11,12]. The increased endometrial thickness observed among tamoxifen users in our study aligns with recent evidence [13]. Multiple studies over the past five years have highlighted the proliferative changes induced by tamoxifen, with endometrial thickness values often exceeding 8–10 mm among long-term users [14]. Our finding of a mean thickness of 10.3 mm is comparable to results reported

in Pakistani, Indian, and Middle Eastern populations, where endometrial thickness frequently surpasses established safety thresholds in asymptomatic users [15]. These similarities support the generalizability of our findings across diverse ethnic groups [16]. Histopathological results from this study revealed significantly higher rates of hyperplasia and carcinoma among tamoxifen users compared to non-users. This observation is in line with recent literature indicating that tamoxifen increases the risk of hyperplasia two- to three-fold and carcinoma four- to seven-fold, particularly when therapy extends beyond three years [17]. The elevated prevalence of atypical hyperplasia in our study population further supports findings by recent Korean and European cohort studies, which also reported atypical lesions as a strong predictor of malignant transformation among tamoxifen-exposed women [18]. The role of therapy duration was particularly noteworthy in our analysis. Women using tamoxifen for more than three years had significantly higher rates of hyperplasia and carcinoma, a finding supported by contemporary study suggesting a dose- and duration-dependent relationship [19,20]. These data reinforce the need for risk-based monitoring strategies, especially in postmenopausal patients who represent the highest-risk subgroup. Our results also demonstrated that postmenopausal women are disproportionately affected, consistent with prior reports [21]. Several recent multicenter analyses have emphasized that postmenopausal endometrium is inherently more sensitive to tamoxifen's estrogenic stimulation, resulting in exaggerated proliferative changes and increased diagnostic yield of atypical lesions [22]. This finding underscores the importance of individualized surveillance tailored to menopausal status, clinical symptoms, and duration of therapy [23]. Comparisons with non-users clearly showed a significantly lower prevalence of abnormal findings, reinforcing that tamoxifen is the principal determinant of the observed endometrial changes. Even after controlling for confounders such as age, BMI, and parity, tamoxifen remained an independent predictor of pathology, consistent with earlier epidemiological evidence [24,25]. The clinical implications of these findings are substantial. Early detection through transvaginal ultrasound and selective biopsy can significantly reduce diagnostic delays and allow for timely intervention [26]. Although routine screening of all asymptomatic users remains controversial, symptom-based evaluation and selective screening of high-risk groups represent a pragmatic approach. Furthermore, patient counseling regarding potential endometrial effects should be an integral part of tamoxifen therapy initiation [27].

Limitations:

This study was limited by its single-center design, relatively small sample size, and cross-sectional methodology, which restrict causal inference. Potential confounders such as lifestyle factors and genetic predispositions were not fully assessed. Longitudinal follow-up was not performed, limiting evaluation of long-term progression of endometrial pathology among tamoxifen users.

Conclusion

Tamoxifen use is strongly associated with increased endometrial thickness, hyperplasia, and malignancy, particularly with therapy exceeding three years. Early detection through ultrasound and biopsy can significantly improve outcomes. Individualized surveillance strategies are essential to ensure safe, long-term tamoxifen therapy and reduce gynecologic complications in high-risk women.

Disclaimer: Nil
Conflict of Interest: Nil
Funding Disclosure: Nil

Authors Contributions

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Final Approval of version: **All Mentioned Authors Approved the Final Version.**

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