

Determining a Treatment Threshold Value for Endometrial Thickness in Women with Breast Cancer Receiving Tamoxifen

Lurong Huang*, Ye Lu*, Yanhui Chen*, Hongli Liu, Jian An 

Department of Gynecology, Department of Obstetrics and Gynecology, Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen, 361000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hongli Liu; Jian An, Department of Gynecology, Department of Obstetrics and Gynecology, Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen, 361000, People's Republic of China, Email doc79924763@163.com; anjian1994@foxmail.com

Background: Breast cancer is a prevalent malignancy in women that often requires endocrine treatment, such as tamoxifen, which is known to affect endometrial thickness and pose risks of endometrial pathologies.

Objective: This study aimed to determine a clinically relevant threshold for transvaginal ultrasound-measured endometrial thickness in breast cancer patients receiving tamoxifen therapy and assess its predictive value for endometrial pathologies.

Methods: We analyzed a total of 205 endometrial biopsies from women dichotomized into premenopausal and postmenopausal groups. We assessed the clinical and pathological characteristics in relation to the presence of endometrial pathologies, employing receiver operating characteristic (ROC) curves to evaluate the predictive value of endometrial thickness as a diagnostic marker.

Results: Among the study cohort, 11.71% of patients were diagnosed with endometrial hyperplasia, and 3.90% had endometrial cancer. Our findings indicate that women with endometrial pathologies exhibited significantly greater endometrial thickness ($P < 0.001$) in both premenopausal and postmenopausal cohorts. Notably, demographic and clinical factors including age, body mass index, gravidity, parity, comorbidities, duration of tamoxifen use, and abnormal vaginal bleeding did not differ significantly between groups with or without pathology. The ROC analysis yielded an area under the curve (AUC) of 0.845 for premenopausal and 0.759 for postmenopausal patients, establishing cutoff values of 0.95 cm and 0.55 cm, respectively.

Conclusion: Our research confirms that endometrial thickness serves as a significant clinical indicator for diagnosing endometrial pathologies in breast cancer patients receiving tamoxifen therapy, underscoring the necessity for risk-based strategies to monitor patients with thickened endometria and advocating for timely hysteroscopic intervention when warranted.

Keywords: endometrial pathology, breast cancer, endometrium, cutoff, menopause

Introduction

Breast cancer is one of the most common malignancies affecting women globally, highlighting the need for ongoing research to improve treatment effectiveness and patient outcomes. Among the various therapeutic agents available, tamoxifen is widely used as a selective estrogen receptor modulator (SERM) for managing hormone receptor-positive breast cancer. However, concerns have been raised regarding its impact on endometrial health, particularly the potential increase in endometrial thickness, which is linked to a greater risk of endometrial hyperplasia and malignancy.¹ At the standard dosage of 20 mg/day, tamoxifen use for ≥ 2 years is associated with a 2–7-fold increased risk of endometrial hyperplasia and a 2–4-fold higher risk of endometrial cancer, particularly in postmenopausal women who lack the protective effects of cyclical progesterone secretion.^{2–4} The risk of endometrial pathology escalates with prolonged use. Studies report that 5–10 years of tamoxifen therapy further elevates the incidence of endometrial cancer to 1.5–2.3 per 1000 women annually, compared to 0.7 per 1,000 in non-users.⁵ This risk is disproportionately higher in postmenopausal

women due to their unopposed endometrial estrogen exposure, whereas premenopausal women experience partial mitigation through endogenous progesterone.⁶ Notably, endometrial changes—including polyps (30–50% of users), hyperplasia (10–20%), and malignancy (1–2%)—often manifest asymptotically, underscoring the need for proactive surveillance.^{7–9} This condition presents not only a clinical challenge but also significant emotional and economic burdens for patients, as they cope with the complexities of cancer treatment while managing the risks of secondary malignancies.

Current guidelines diverge on screening protocols. The American Society of Clinical Oncology (ASCO) recommends annual gynecologic evaluation and prompt investigation of abnormal vaginal bleeding but does not advocate routine ultrasound screening.¹⁰ In contrast, the European Society for Medical Oncology (ESMO) suggests transvaginal ultrasound (TVUS) monitoring for postmenopausal women after 2–3 years of tamoxifen use, with hysteroscopy reserved for endometrial thickness >4–5 mm.¹¹ Despite these recommendations, evidence-based thresholds for intervention remain contentious, especially in premenopausal women where cyclical hormonal fluctuations complicate interpretation. Traditional diagnostic methods, such as ultrasound and biopsy, often have limitations, including variability in interpretation and invasiveness.¹² Prior studies have shown that tamoxifen can induce significant changes in endometrial morphology, with evidence indicating an increase in endometrial thickness that may serve as a phenotypic marker for endometrial cancer risk.^{1,12} Consequently, there is an urgent need for research to establish standardized thresholds for endometrial thickness that can guide clinical decision-making and improve patient outcomes during tamoxifen therapy.^{12,13} Thus, this study aims to establish endometrial thickness thresholds to guide clinical decisions for tamoxifen-treated patients. With rising breast cancer incidence and increasing tamoxifen use, identifying high-risk patients is critical to prevent endometrial complications. Our findings will provide a framework for personalized monitoring, improving patient outcomes while balancing tamoxifen's benefits and risks.

Materials and Methods

Study Design

This retrospective study included breast cancer patients undergoing hysteroscopic endometrial biopsy while receiving tamoxifen therapy at Women and Children's Hospital, School of Medicine, Xiamen University, between December 2012 and March 2024. This study was reviewed and approved by the Research Ethics Committee of Xiamen Women and Children's Hospital (No: KY-2025-007-K01), which waived the requirement for informed consent due to the retrospective nature of the study. We extracted data from the database and deidentified through anonymity to keep data confidentiality. This study was performed in compliance with the "Declaration of Helsinki." We excluded patients who met any of the following criteria: (1) age <25 years, (2) received tamoxifen at doses exceeding 20 mg per day, (3) stopped taking tamoxifen more than three months prior to the biopsy, (4) had a history of endometrial pathology before starting tamoxifen, (5) had unknown results from endometrial biopsies, (6) had a family history of malignant tumors such as colorectal, endometrial, or ovarian cancers, (7) were currently taking anticoagulant or antiplatelet drugs or had blood disorders, or (8) had missing data related to clinical characteristics or ultrasonography. The primary objective of this study was to determine menopausal-specific threshold values for endometrial thickness that can effectively predict pathological findings in breast cancer patients undergoing tamoxifen therapy. And the secondary objectives was to assessing potential correlations between endometrial thickness and the duration of tamoxifen treatment.

Clinicopathological Data

We collected the clinicopathological data for all patients, which included patient age, body mass index (BMI), gravidity and parity, pathology and stage of breast cancer, comorbid conditions, menopausal status, duration of tamoxifen use, presence of abnormal vaginal bleeding, transvaginal ultrasonography report upon admission, and endometrial pathology reports. Ultrasonography was performed routinely, and endometrial thickness was measured from the anterior endometrial-myometrial interface to the posterior in the sagittal plane. Histological examination was carried out on tissue samples obtained through hysteroscopy and dilation and curettage. Final pathologic diagnoses were made by pathologists at our center using consistent criteria, classifying cases as normal endometrium, endometrial polyp, adenomyomatous polyp, hyperplasia without atypia, atypical hyperplasia, or endometrial cancer. We divided the study population into

premenopausal and postmenopausal cohorts. Each cohort was further grouped into normal endometrium and pathological endometrium based on pathology results.

Statistical Analysis

Continuous variables were reported as median (interquartile range, IQR) and compared using the Mann–Whitney test. Categorical variables were presented as counts (percentage) and analyzed with the χ^2 -test. The correlation between endometrial thickness and the duration of tamoxifen therapy was assessed using a scatter plot and the Spearman correlation coefficient. Receiver operating characteristic (ROC) curves were plotted and evaluated using the area under the ROC curve (AUC) to determine the diagnostic power of endometrial thickness in various endometrial pathologies. Additionally, cut-off values for endometrial thickness were established in relation to hazard assessment. Restricted cubic splines (RCS) were utilized to visualize the relationship between continuous variables and pathological findings. All analyses and data visualizations were performed using R (version 4.4.1), with a two-sided p-value of less than 0.05 considered statistically significant.

Results

Clinical Features

A total of 205 individuals were identified from the database and included in our analysis. Among these, 89 individuals (43.41%) had a normal endometrium, while 116 individuals (56.59%) exhibited pathological findings. Specifically, 87 individuals (42.44%) had endometrial polyps, 8 individuals (3.90%) had adenomyomatous polyps, 20 individuals (9.76%) presented with hyperplasia without atypia, 4 individuals (1.95%) were diagnosed with atypical hyperplasia, and 8 individuals (3.90%) were diagnosed with endometrial cancer. The general clinical and pathological features of the 205 patients are summarized in Table 1.

Table 2 compares the characteristics of premenopausal patients with endometrial pathology to those with a normal endometrium. Endometrial thickness was significantly higher in women with pathology [1.3 (1.0, 1.8) cm vs 0.7 (0.5,

Table 1 Clinical and Pathological Characteristics of the Study Population

Variables	N=205
Age (year)	48 (44, 53)
Body mass index (kg/m ²)	22.68 (20.42, 24.81)
Gravidity	2 (2, 3)
Parity	1 (1, 2)
Menopause	64 (31.22)
Breast pathology	
In-situ carcinoma	39 (19.02)
Invasive carcinoma(NST)	127 (61.95)
Invasive carcinoma(ST)	12 (5.85)
Unknown	27 (13.17)
Breast cancer stage	
Stage 0	39 (19.02)
Stage I	55 (26.83)
Stage II	60 (29.27)
Stage III	23 (11.22)
Stage IV	1 (0.49)
Unknown	27 (13.17)
Diabetes mellitus	10 (4.87)
Hypertension	18 (8.78)

(Continued)

Table 1 (Continued).

Variables	N=205
Months of tamoxifen use	36 (17.5, 60)
Presence of bleeding symptom	74 (36.10)
Endometrial thickness (cm)	10 (0.65, 1.50)
Endometrial pathology	
Normal endometrium	89 (43.41)
Endometrial polyp	87 (42.44)
Adenomyomatous polyp	8 (3.90)
Hyperplasia without atypia	20 (9.76)
Atypical hyperplasia	4 (1.95)
Endometrial cancer	8 (3.90)

Abbreviations: NST, no special type; ST, special type.

Table 2 Comparisons of Characteristics Between Premenopausal Women with Endometrial Pathology and Normal Endometrium

Variables	Pathologic (N=85)	Normal (N=56)	P Value
Age (year)	45 (42.5, 48)	46.5 (42, 49)	0.615
Body mass index (kg/m ²)	21.33 (19.77, 24.34)	22.99 (20.32, 24.96)	0.145
Gravidity	2 (1, 3)	3 (2, 4)	0.111
Parity	1 (1, 2)	1 (1, 2)	0.603
Diabetes mellitus	4 (4.71)	2 (3.57)	
Hypertension	8 (9.42)	2 (3.57)	
Months of tamoxifen use	32 (15, 55)	32.5 (10, 52.75)	0.692
Presence of bleeding symptom	37 (43.53)	21 (37.50)	
Endometrial thickness (cm)	1.3 (1.0, 1.8)	0.7 (0.5, 0.98)	<0.001

0.98) cm, $P<0.001$]. No significant differences were observed regarding age, BMI, gravidity and parity, comorbid conditions, duration of tamoxifen use, or the presence of abnormal vaginal bleeding between the two groups of premenopausal patients. **Table 3** presents comparisons of the characteristics between postmenopausal patients with endometrial pathology and those with a normal endometrium. Endometrial thickness in women with pathology was significantly higher [1.2 (0.8, 1.8) cm vs 0.7 (0.35, 1.05) cm, $P<0.001$]. Interestingly, women with endometrial pathology had a shorter duration of tamoxifen use [33 (14, 57) months vs 55 (30.5, 86) months, $P=0.027$]. Additionally, no

Table 3 Comparisons of Characteristics Between Postmenopausal Women with Endometrial Pathology and Normal Endometrium

Variables	Pathologic (N=31)	Normal (N=33)	P Value
Age (year)	55 (51, 61)	55 (50, 60.5)	0.778
Body mass index (kg/m ²)	22.86 (21.16, 24.98)	24.03 (21.25, 26.46)	0.229
Gravidity	2 (2, 3)	2 (2, 3)	0.329
Parity	2 (1, 2)	2 (1, 2)	0.209
Diabetes mellitus	3 (9.68)	1 (3.03)	
Hypertension	3 (9.68)	5 (15.15)	
Months of tamoxifen use	33 (14, 57)	55 (30.5, 86)	0.027
Presence of bleeding symptom	6 (19.35)	10 (30.30)	
Endometrial thickness (cm)	1.2 (0.8, 1.8)	0.7 (0.35, 1.05)	<0.001

significant differences regarding age, BMI, gravidity and parity, comorbid conditions, or the presence of abnormal vaginal bleeding were found between the two groups. Additionally, a detailed description of the 8 patients with pathologically confirmed endometrial cancer is shown in [Table 4](#).

There Was No Significant Correlation Between Endometrial Thickness and the Duration of Tamoxifen Therapy

Duration of tamoxifen therapy ranged from 1–204 months (median: 36 months). The maximum observed endometrial thickness was 3.7 cm in postmenopausal patients after 36 months of therapy and 3.5 cm in premenopausal patients after 21 months of therapy. To illustrate the correlation between endometrial thickness and duration of tamoxifen use, we present scatter plots of endometrial thickness by tamoxifen duration, along with the results from Spearman correlation (see [Figure 1A](#) and [C](#)). However, we found no remarkable correlation between endometrial thickness and tamoxifen duration in both premenopausal and postmenopausal patients (Spearman correlation coefficient $R=0.2$, $P=0.015$ for premenopausal patients; Spearman correlation coefficient $R=-0.025$, $P=0.84$ for postmenopausal patients). We also employed restricted cubic splines (RCS) to visualize the relationship between the duration of tamoxifen use and pathological findings, and no association was found between the odds ratio of endometrial pathology and the duration of tamoxifen use (see [Figure 1B](#) and [D](#)).

Value of Endometrial Thickness in the Diagnosis of Endometrial Pathologies

To determine treatment threshold values for endometrial thickness in diagnosing endometrial pathologies, we presented the ROC curves in [Figure 1](#). In premenopausal patients, the area under the curve (AUC) for endometrial thickness in diagnosing endometrial pathologies was 0.845 (95% CI, 0.780–0.910), with a cut-off value of 0.95 cm, yielding a specificity of 0.750 and a sensitivity of 0.812 (see [Figure 2A](#)). For postmenopausal patients, the AUC for endometrial thickness was 0.759 (95% CI, 0.642–0.875), with a cut-off value of 0.55 cm, resulting in a specificity of 0.455 and a sensitivity of 0.968 (see [Figure 2B](#)). [Figure 3](#) shows no non-linear association between the odds ratio of endometrial pathologies and endometrial thickness among both premenopausal and postmenopausal patients, indicating that a thicker endometrium is correlated with a higher risk of developing endometrial complications in breast cancer patients undergoing tamoxifen therapy.

Discussion

Our study investigates the relationship between endometrial pathologies and endometrial thickness among breast cancer patients undergoing tamoxifen therapy, particularly highlighting the necessity of establishing clinical thresholds for intervention. This retrospective cohort analysis included 205 pre- and postmenopausal breast cancer patients, focusing on their ultrasound reports and clinicopathological characteristics. The findings indicate that regular monitoring of endometrial thickness is crucial for early detection of potential complications, as the results demonstrated that a thicker endometrium is correlated with a significant increase in the incidence of endometrial pathologies during tamoxifen therapy. Furthermore, cutoff values of 0.95 cm for premenopausal patients and 0.55 cm for postmenopausal patients were determined. It is essential that these findings are verified through further research.

Current recommendations suggest conducting a risk assessment for endometrial cancer prior to starting tamoxifen therapy, and monitoring for endometrial lesions when abnormal vaginal bleeding is present.¹⁴ However, there have not yet been consistent recommendations regarding treatment thresholds for the endometrium in tamoxifen-treated patients. Currently, the recommended duration of tamoxifen therapy has been extended from 5 years to 10 years.¹⁵ Clinically, opting for conservative or no treatment may lead to more anxiety regarding disease progression compared to medical interventions, especially considering the extended duration of tamoxifen use in breast cancer patients. Therefore, our findings hold significant clinical value, as establishing a treatment threshold for endometrial thickness may enhance clinical decision-making and improve patient outcomes by enabling timely interventions for those at increased risk of developing endometrial pathology.

Table 4 Characteristics of Patients with Endometrial Cancer

	Age (Year)	BMI (kg/m ²)	G	P	Menopause	Breastpathology	Breast Cancer Stage	Diabetes Mellitus	Hypertension	Months of Tamoxifen Use	Presence of Bleeding Symptom	Endometrial Thickness (cm)	Endometrial Pathology
Case1	53	19.14	2	2	Yes	Unknown	Unknown	No	No	84	Yes	1.5	Endometrioid adenocarcinoma
Case2	53	27.53	4	2	No	Invasivecarcinoma(NST)	II	Yes	Yes	72	Yes	1.9	Endometrioid adenocarcinoma
Case3	37	25.07	3	0	No	Invasivecarcinoma(NST)	III	No	No	60	No	2.3	Endometrioid adenocarcinoma
Case4	42	19.11	5	2	No	Invasivecarcinoma(NST)	I	No	No	36	Yes	1.2	Endometrioid adenocarcinoma
Case5	55	22.86	3	3	Yes	In-situcarcinoma	0	No	No	36	No	3.7	Endometrioid adenocarcinoma
Case6	53	27.74	4	2	No	Invasivecarcinoma(NST)	II	Yes	Yes	72	Yes	2	Endometrioid adenocarcinoma
Case7	51	20.98	1	1	No	Invasivecarcinoma(NST)	I	No	No	48	No	1.5	Endometrioid adenocarcinoma
Case8	51	21.16	1	1	Yes	Invasivecarcinoma(NST)	I	No	No	48	No	1.5	Endometrioid adenocarcinoma

Abbreviations: BMI, body mass index; G, gravidity; P, parity; NST, no special type.

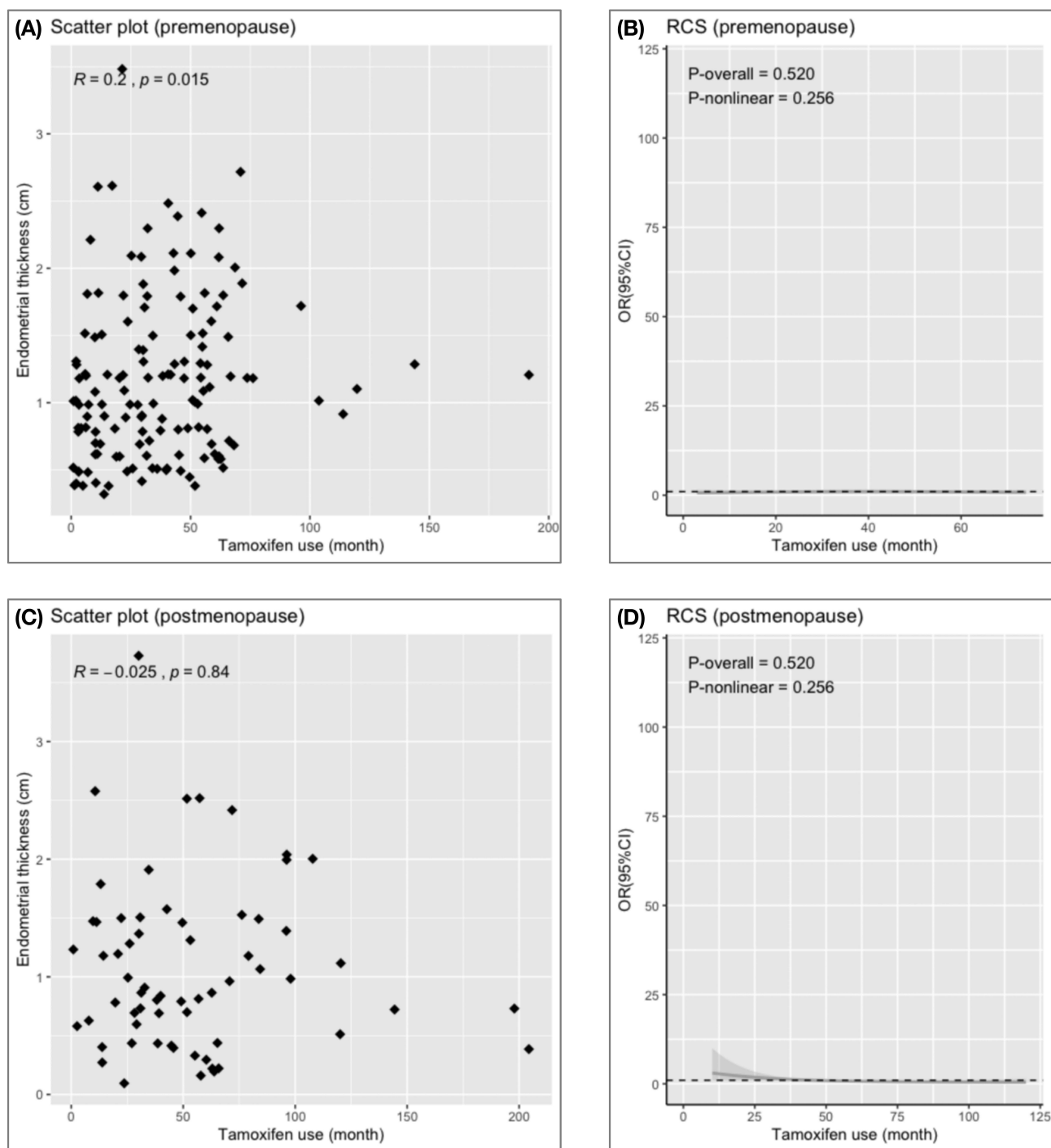


Figure 1 Scatter plot for visualisation of the relationship between endometrial thickness and duration of tamoxifen use, and RCS analysis for correlation between duration of tamoxifen use and OR of endometrial pathologies. **(A and B)** For premenopausal patients; **(C and D)** For postmenopausal patients.

Abbreviations: RCS, restricted cubic spline; OR, odds ratio.

There are considerable heterogeneities in the variables included across studies on this topic, and some results from previous research are comparable to our findings, which is noteworthy. First, we observed that the most common endometrial pathology in both pre- and postmenopausal patients was endometrial polyps (87/205, 42.44%). Malignant changes were relatively rare in this population, consistent with previous studies.^{16,17} Second, other researchers have reported that patients on tamoxifen therapy tend to have a significantly thicker endometrium,¹⁸ and this phenomenon may

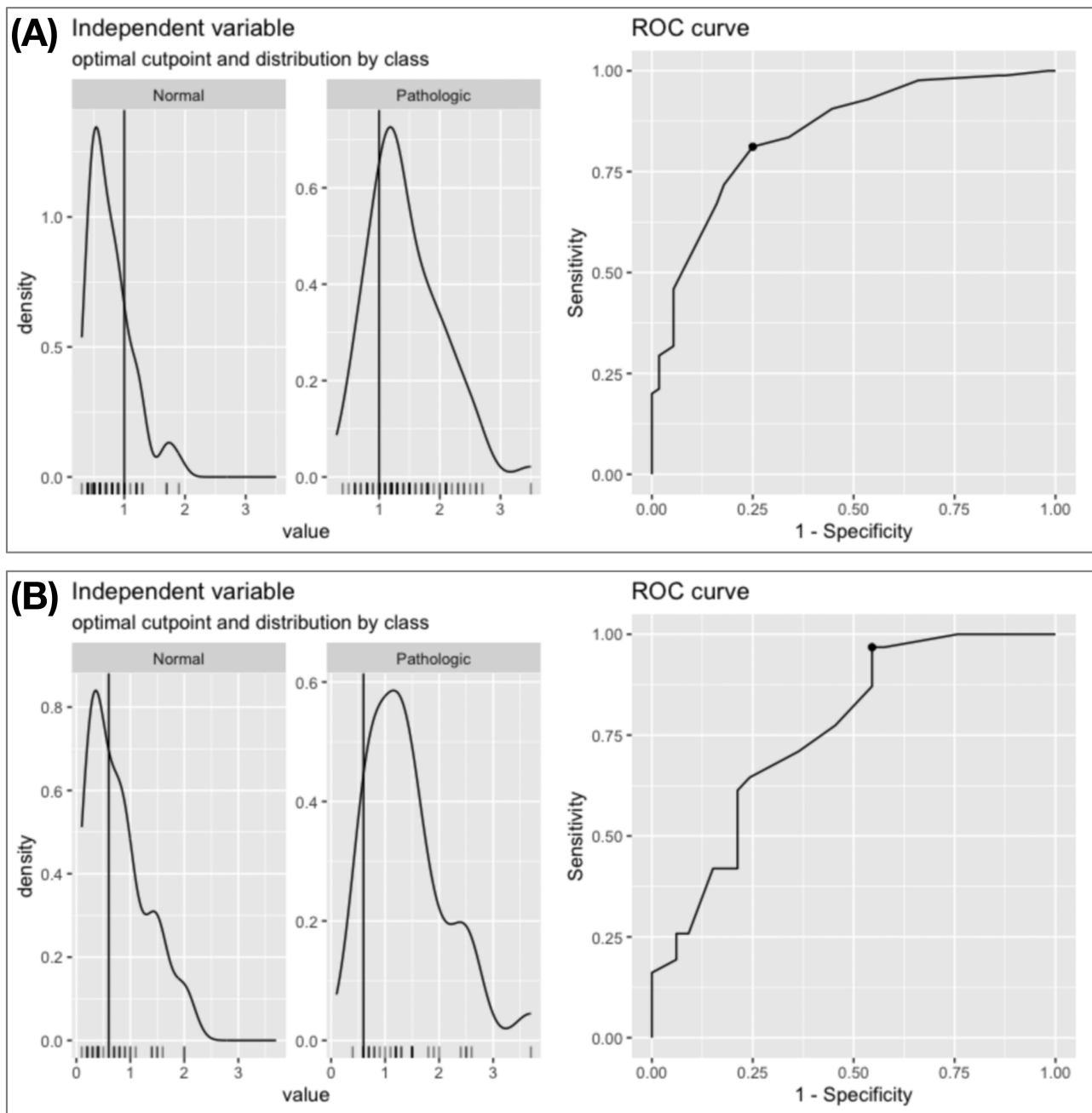


Figure 2 ROC curve analysis for the optimal cut-off value of the endometrial thickness for predicting the risk of endometrial pathologies. **(A)** For premenopausal patients; **(B)** For postmenopausal patients.

Abbreviation: ROC, Receiver operating characteristic.

be reversible following the cessation of tamoxifen.¹⁹ However, in the current study, neither the thickened endometrium nor the increased risk of endometrial pathologies were significantly correlated with the longer duration of tamoxifen therapy. This may reflect several study-specific factors: Our cohort contained relatively few long-duration users, limiting the power to detect duration-dependent effects; and the inherent variability in ultrasound measurements may have obscured subtle progressive changes. Additionally, endometrial thickness alone showed poor correlation with tamoxifen duration, suggesting clinical decisions should incorporate multiple risk factors. Third, a critical topic in clinical practice is establishing cutoff values for endometrial thickness to facilitate timely applications of hysteroscopy and histological examinations in the follow-up of breast cancer patients during SERM therapy. Fung's study,²⁰ which set an endometrial

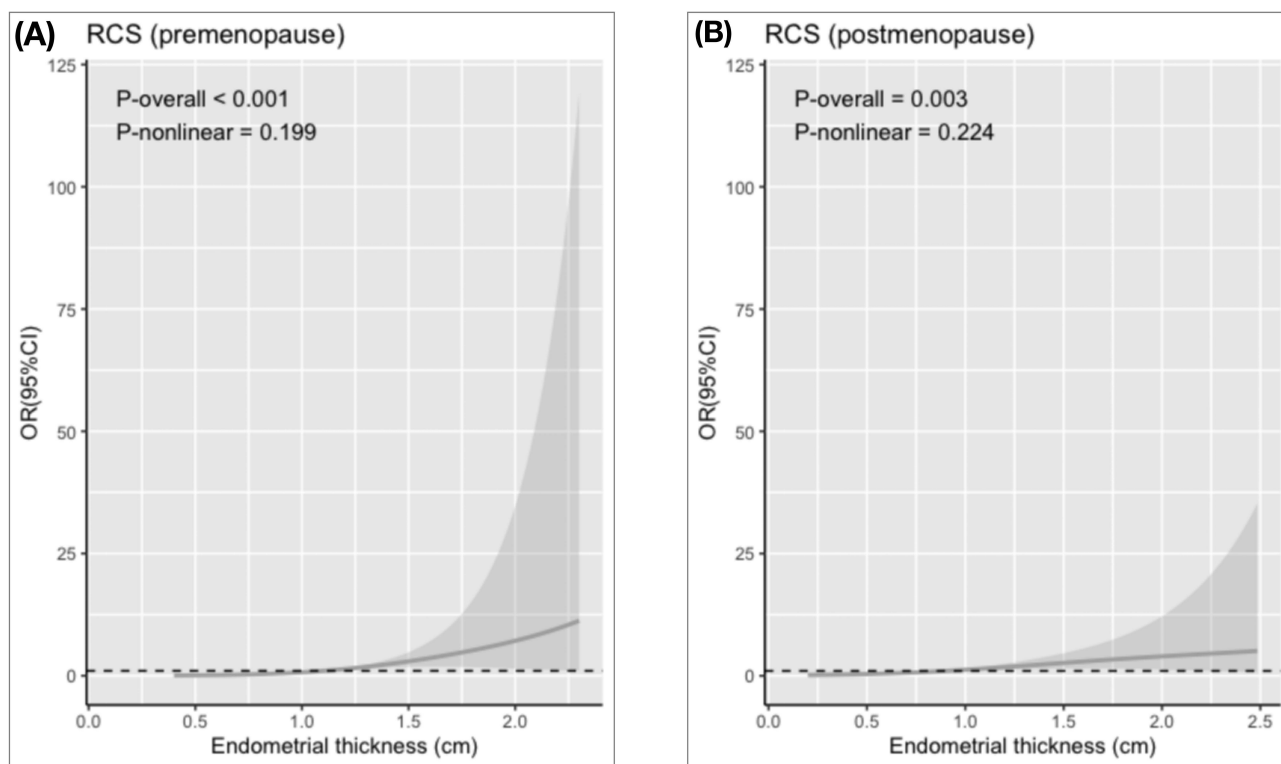


Figure 3 RCS analysis for correlation between endometrial thickness and OR of endometrial pathologies. **(A)** For premenopausal patients; **(B)** For postmenopausal patients.

Abbreviations: RCS, restricted cubic spline; OR, odds ratio.

thickness cutoff of more than 9 mm, showed that only thickness greater than 9 mm was associated with significant uterine abnormalities. Another study reported that using a 5 mm cutoff threshold for endometrial thickness resulted in 100% sensitivity, but only 15% specificity, while a 10 mm cutoff resulted in 84% sensitivity and 69% specificity in detecting endometrial atypia.²¹ However, these studies included patients of all ages. The effectiveness of endometrial thickness in diagnosing endometrial pathologies during tamoxifen therapy in pre- and postmenopausal breast cancer patients has not been investigated separately. In comparison to these reports, we noted the influence of menopausal status on endometrial thickness and determined two cutoff values (0.55 cm for postmenopausal patients and 0.95 cm for premenopausal patients) based on our analysis. Additionally, two studies reported that endometrial hyperplasia was less likely to occur in premenopausal patients during SERM therapy when endometrial thickness was less than 15 mm,²² and that endometrial thickness of 10 mm or greater had significant diagnostic potential in postmenopausal women but not in premenopausal women, with an area under the curve (AUC) of 0.676 ($p < 0.000$, CI 0.5–0.7).²³ The thresholds from these studies were higher than our results and may be less likely to be clinically recommended due to increased anxiety regarding endometrial diseases in breast cancer patients, especially among postmenopausal patients. Furthermore, although the studies vary in methodology, including the study populations and analysis of variables, a thicker endometrium is generally demonstrated to be associated with a higher likelihood of endometrial or intracavitary pathology.²⁴ This association was also confirmed by the RCS analysis in our current study.

The limitations of this study require careful consideration. Notably, the lack of a population not undergoing tamoxifen therapy limits our ability to draw definitive conclusions regarding the causal relationships between tamoxifen treatment and changes in endometrial thickness. Additionally, the relatively small sample size from a single hospital may restrict the generalizability of our findings to broader populations of breast cancer patients. Furthermore, the retrospective design of this study introduces inherent risks of bias. For instance, missing data were unavoidable and had to be classified as “unknown” due to the unavailability of reports for this retrospective analysis. These limitations underscore the need for further research to validate our findings and to explore the underlying mechanisms of tamoxifen’s effects on endometrial

health. We also acknowledge that our retrospective design did not allow for a longitudinal assessment of screening intervals. Future prospective studies should evaluate the optimal frequency (eg, quarterly vs annual) in breast cancer patients, particularly in high-risk subgroups.

Conclusion

Our study identifies a significant correlation between increased endometrial thickness and the risk of endometrial pathologies. We recommend annual transvaginal ultrasound monitoring, and early intervention should be prompted by endometrial thickening with measurements above the threshold (0.95 cm for premenopausal patients and 0.55 cm for postmenopausal patients). Our research establishes critical thresholds for endometrial thickness in breast cancer patients undergoing tamoxifen therapy, providing valuable insights that may enhance clinical practice and improve patient outcomes.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author, Jian An, upon reasonable request.

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Disclosure

The authors declare no conflicts of interest in this work.

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