



The relationship of endometrial pathologies with endometrial thickness and inflammatory markers in breast cancers using tamoxifen

Esma Sarioglu¹ · Fisun Vural¹ · Ayşe Deniz Ertürk Coşkun¹

Received: 18 February 2022 / Accepted: 1 May 2022 / Published online: 1 June 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

Abstract

Purpose Some proliferative and neoplastic changes can be seen in the endometrium of breast cancers using tamoxifen adjuvant therapy (TMX-BC). Identifying risk groups is crucial, but methods and frequency of endometrial follow-up are still controversial. This study aimed to investigate the clinical, ultrasonographic, and inflammatory factors to differentiate pathological endometrium in TMX-BC.

Methods This study retrospectively analyzed endometrial biopsy results of TMX-BC (n 361). Normal endometrium (Group I, n 237) and pathological endometrium (Group II, n 124) were compared for clinical, ultrasonographic, and inflammatory features. Neutrophil and platelet to lymphocyte ratio (NLR; PLR), mean platelet volume (MPV), platelet distribution width (PDW), red blood cell distribution width (RDW), and lymphocyte–monocyte ratio (LMR) were the inflammatory markers.

Results The majority of TMX-BC with endometrial biopsy were asymptomatic (72.6%) and had normal endometrium (65.7%). Pathologic endometrium included endometrial polyp (31.9%), endometrial hyperplasia (1.7%), and endometrial cancer (0.8%). The duration of tamoxifen, cancer stage, vaginal bleeding, and menopause was similar in Group I and Group II ($p > 0.05$). Group II had increased endometrial thickness (11.22 ± 5.44 mm) compared to Group I (8.51 ± 3.43 mm). Group II had higher RDW and PDW than Group I ($p < 0.05$). Endometrial thickness ≥ 10 mm had significant diagnostic potential in postmenopausal women (AUC 0.676, p 0.000, CI 0.5–0.7), but not in premenopause.

Conclusion PDW and RDW may be promising markers for pathological endometrium differentiation, but these preliminary findings should be validated by clinical studies. Measurement of endometrial thickness in asymptomatic patients may predict high-risk women with pathological endometrium in postmenopausal women. Further studies are needed in premenopausal women and those using tamoxifen for more than 5 years.

Keywords Tamoxifen · Inflammation · Breast cancer · Endometrial thickness · Endometrial pathology · RDW · PDW

Introduction

The most common cancer in women worldwide is breast cancer. Tamoxifen, a groundbreaking drug in the oncology field, is being used as adjuvant therapy in estrogen receptor-positive breast cancer treatment for the last four decades [1, 2]. Since the use of tamoxifen decreases the recurrence and progression of the disease successfully, tamoxifen use was extended from 5 to 10 years after the ATLAS trial [3].

Tamoxifen, a selective estrogen receptor modulator, has competitive antagonism for estrogens in breast tissue, but it has an agonistic effect on the endometrium [2]. Despite tamoxifen preventing proliferation in breast tissue, it causes some proliferative changes in the endometrium [4]. For patients using tamoxifen, endometrial cancer prevalence is 1.26 per 1000 patient-years, approximately two times that of nonusers [5].

It is important to define risk groups with a high probability of developing endometrial pathology. Despite many years of experience, there is still no consensus on the frequency and methods of endometrial surveillance. Ultrasonographic evaluation of the endometrium is also controversial since tamoxifen-induced sub-endometrial hypertrophy can lead to challenges in the evaluation [6]. Although the relevance of inflammation and endometrial pathologies has

✉ Fisun Vural
fisunvural@yahoo.com.tr

¹ Obstetrics & Gynecology Department, University of Health Sciences, Hamidiye Medical Faculty, Haydarpaşa Numune Training and Research Hospital, Tıbbiye cad. No: 40, Üsküdar, 34668 Istanbul, Turkey

been investigated, this issue has not been investigated in tamoxifen users. This study aimed to investigate the clinical, ultrasonographic, and inflammatory factors to differentiate pathological endometrium in women with breast cancer using tamoxifen adjuvant therapy.

Materials and methods

Breast cancer patients using tamoxifen and undergoing endometrial biopsy between 2010 and 2020 in Gynecology and Obstetrics Clinic, Haydarpaşa Numune Training and Research Hospital, Istanbul, Turkey were investigated after ethical approval of the study (HNEAH-KAEK 2021/KK/14).

A total of 361 tamoxifen-using breast cancers (20 mg/day) with endometrial biopsy that met the study criteria were included. The patients were grouped as normal endometrium (Group I) and pathological endometrium (Group II) according to endometrial pathology results. Group I and Group II were compared for clinical presentation, ultrasonographic findings (endometrial thickness), and inflammatory markers (NLR, PLR, LMR, RDW, and PDW).

The data of this retrospective study were obtained from electronic database and patient files. Age, parity, duration of tamoxifen use, menopausal status, admission complaints, breast and endometrial pathology reports, breast surgery type, chemotherapy, radiotherapy history, medical history, comorbid conditions, transvaginal ultrasonography reports, and complete blood counts analysis were recorded. Patients' laboratory evaluation in other centers, previously known endometrial pathology, TMX use less than 3 months, metastatic breast cancer (Stage 4), active infection, rheumatological and hematological diseases, malignancies other than breast cancer, systemic diseases, and endocrine diseases were excluded from the study.

Patients were routinely evaluated by transvaginal ultrasound at 6-month intervals in our gynecology clinic. (Mindray, DC-7 MX29003997 China). Endometrium was evaluated in detail by ultrasonography, endometrial thickness was measured, and fluid collection or irregularities in the endometrium were reported. Endometrial biopsy was performed in cases of abnormal uterine bleeding or postmenopausal bleeding. In asymptomatic patients, we also obtained endometrial biopsy in cases of increased endometrial thickness, fluid collection, or irregularity in the endometrium.

We classified endometrial pathology reports as normal (secretory, proliferative, irregular endometrium, atrophic endometrium) and pathological results (endometrial polyp, endometrial hyperplasia, endometrial cancer).

All patients had complete blood count analysis by automatic analyzer at least 2 weeks before endometrial sampling. 2 ml of venous blood was taken into tubes with EDTA and studied with an automatic analyzer within 1 h at room

temperature (CELL-DYN 3700, Abbott Diagnostics, Abbott Park, IL). The complete blood count parameters, leukocyte, neutrophil, lymphocyte, monocytes and thrombocyte counts, hemoglobin, hematocrit, red cell distribution width (RDW), mean platelet volume (MPV), platelet distribution width (PDW), neutrophil and platelet to lymphocyte ratio (NLR and PLR), and lymphocyte–monocyte ratio (LMR) values, were evaluated.

The primary outcome measures were the clinical presentation, endometrial thickness, and nonspecific inflammatory markers in women with TMX-BC with and without pathologic endometrium.

The statistical analysis of data was evaluated by the SPSS Statistics 22 program. In addition to descriptive analysis, the comparison of quantitative data (Kruskal Wallis test), and qualitative data (Chi-square test and Fisher–Freeman–Halton exact test) was used appropriately. ANOVA test was used to compare the mean of more than two data and the LSD test for subgroup analysis. ROC analysis and AUC (area under the curve) values were calculated for endometrial thickness. The p value < 0.05 level was accepted for statistical significance.

Results

Table 1 shows the general characteristics of the patients. The mean age of the participants was 48.51 ± 7.54 years (range 30–80 years) and 56.5% of the patients were in the menopausal period (n 204). The average time of tamoxifen therapy duration was 24.74 ± 16.6 months (range 3–84 months). 27.4% (n 99) of the patients had vaginal bleeding at presentation, but 72.6% (n 262) of the patients were asymptomatic. The majority of the endometrial pathology results were normal (67.7%, n 237) and 34.3% of the women had pathologic endometrium.

The ratio of endometrial pathology was similar between TMX use ≥ 24 months (32.8%) and TMX use < 24 months (35.4%) in our cohort ($p > 0.05$). The ratio endometrial pathology in TMX use ≥ 5 years (31.2%) and TMX less than 5 years (34.4%) was also similar ($p > 0.05$).

Table 2 shows the pathology results. Accordingly, invasive breast carcinoma (n 281, 77.8%) was the most common pathology. Other common pathologies were ductal carcinoma in situ 8.6% (n 31) and invasive lobular carcinoma 6.9% (n 25). Most of the women had Stage I (33.8%, n 122) and Stage II breast cancer (49.9%, n 180). 66.5% of breast cancer underwent breast-conserving surgery (n 240). Endometrial biopsy results were normal endometrium in 237 women (65.7%), endometrial polyp in 115 women (31.9%), endometrial hyperplasia in 6 patients (1.7%), and endometrial cancer in 3 patients (0.8%). All endometrial cancers were endometrioid adeno cancer, grade 1–2, Stage 1.

Table 1 The findings for women with TMX-BC on endometrial biopsy

Characteristics	Min–Max	Mean ± SD
Age	30–80	48.51 ± 7.54
Parity	0–10	2.41 ± 1.55
Abortion	0–6	0.45 ± 0.83
D&C	0–17	0.54 ± 1.34
Tamoxifen duration (months)	1–84	24.74 ± 16.66
Endometrial thickness (mm)	2–39	9.44 ± 4.42
	<i>n</i>	(%)
Vaginal bleeding on admission	99	27.4
Asymptomatic on admission	262	72.6
Menopause	204	56.5
Premenopause	157	43.5
Endometrial pathology		
Normal endometrium	237	65.7
Pathologic endometrium	124	34.3

Table 2 Breast and endometrial pathologies

	<i>n</i>	Percentage (%)
Breast pathology		
Invasive ductal carcinoma	281	77.8
High-grade in situ ductal carcinoma	4	1.1
Invasive micropapillary carcinoma	6	1.7
In situ ductal carcinoma	27	7.5
Invasive lobüler carcinoma	25	6.9
Others	18	5
Breast cancer stage		
Stage 0	11	3
Stage I	122	33.8
Stage II	180	49.9
Stage III	48	13.3
Endometrial pathology		
Normal endometrium	237	65.7
Endometrial polyp	115	31.8
Simple hyperplasia without atypia	5	1.4
Complex hyperplasia without atypia	1	0.3
Endometrioid adenocancer	3	0.8

Table 3 The comparison of the clinical characteristics of normal (Group I) and pathological (Group II) endometrial biopsy results

	Group I (<i>n</i> 237) mean ± SD	Group II (<i>n</i> 124) mean ± SD	<i>p</i> value
Age	49.55 ± 8.02	46.53 ± 6.06	0.000
Gravidity	3.55 ± 2.68	3.14 ± 1.97	0.099
Parity	2.44 ± 1.63	2.34 ± 1.37	0.576
Symptoms on admission			
Vaginal bleeding	64 (26.8%)	35 (28.4%)	
Asymptomatic	174 (73.1%)	88 (71.5%)	0.353
Menopause	149 (73%)	55 (26.9%)	0.01
Tamoxifen duration(months)	24.75 ± 16.77	24.71 ± 16.50	0.982
Tamoxifen ≥ 24 months	102 (43%)	50 (40%)	
Tamoxifen < 24 months	135 (57%)	74 (60%)	0.203
Breast cancer stage			
Stage I	87/237 (36.7%)	46/124 (37%)	0.943
Stage II	93/237 (39.2%)	54/124 (43.5%)	0.428
Stage III	57/237 (24.1%)	24/124 (19.3%)	
Endometrial thickness (mm)	8.51 ± 3.43	11.22 ± 5.44	0.000

Table 3 shows the comparison of clinical findings of Group I and Group II. The mean age and the ratio of menopausal women in Group I were higher than in Group II ($p < 0.05$). The number of women with vaginal bleeding on admission and asymptomatic cases was similar between Group I and II ($p > 0.05$). The duration of tamoxifen treatment was identical in Group I (24.75 ± 16.77 months) and Group II (24.71 ± 16.50 months). The number of cases with tamoxifen use > 24 months was similar in Group I and II. We also compared the percentage of tamoxifen use less

than 60 months. Group I (n 226, 95.35%) and Group II (n 119, 95.9%) had similar results (p : 0.511), but only 16 women used tamoxifen above 60 months in our cohort. The comparison of Group I and II for the number of women in Stage I, II, and III were similar ($p > 0.05$). Group I had endometrial thickness (8.51 ± 3.43 mm) lower than Group II (11.22 ± 5.44 mm) (p 0.000).

Table 4 shows the comparison of normal pathology (n 237), endometrial polyp (n 115) and endometrial

Table 4 The comparison of the clinical findings between normal pathology, endometrial polyp and endometrial hyperplasia/cancer

	Normal Pathology (<i>n</i> 237)	Endometrial Polyp (<i>n</i> 115)	Endometrial Hyperplasia/cancer (<i>n</i> 9)	<i>p</i> value
Age	49.55 ± 8.02	46.25 ± 5.86	50.11 ± 7.72	0.000
Tamoxifen (months)	24.75 ± 16.77	23.96 ± 16.22	34.33 ± 18.00	0.199
Endometrial thickness (mm)	8.51 ± 3.43	11.24 ± 5.53	10.95 ± 4.36	0.000

Table 5 The comparison of complete blood count parameters in normal and pathological biopsy results

	Group I (<i>n</i> 237) <i>mean</i> ± <i>SD</i>	Group II (<i>n</i> 124) <i>mean</i> ± <i>SD</i>	<i>p</i> value
WBC (/mm ³)	6651.73 ± 1784.19	6301.61 ± 1647.25	0.070
Neutrophil (/mm ³)	4039 ± 1388.44	3833.95 ± 1258.56	0.168
Basophil (/mm ³)	40.21 ± 26.28	42.78 ± 26.08	0.377
Eosinophil (/mm ³)	122.27 ± 101.26	110.16 ± 114.69	0.304
Lymphocyte (/mm ³)	2029.32 ± 713.03	1948.22 ± 698.59	0.302
Monocyte (/mm ³)	414.21 ± 131.72	425.96 ± 425.21	0.696
Hemoglobin (g/dl)	12.53 ± 0.98	12.50 ± 0.93	0.816
Hematocrit (%)	38.02 ± 4.61	37.82 ± 2.64	0.659
MCV (fl)	87.85 ± 5.44	88.65 ± 7.48	0.244
RDW (%)	14.45 ± 2.31	14.96 ± 2.27	0.044
PLT (/mm ³) × 10 ⁵	237 ± 627	231 ± 566	0.357
MPV (fl)	8.79 ± 1.45	8.53 ± 1.45	0.110
PCT (ng/ml)	0.20 ± 0.05	0.19 ± 0.04	0.55
PDW (%)	16.69 ± 1.52	17.22 ± 1.16	0.001
NLR	2.22 ± 1.13	2.25 ± 1.50	0.836
PLR	129.23 ± 53.83	134.22 ± 69.52	0.451
LMR	5.36 ± 2.65	5.18 ± 2.10	0.496

hyperplasia/cancer (*n* 9). The mean age of women diagnosed with endometrial polyp was younger than those with normal endometrial pathology and endometrial hyperplasia/cancer (*p* 0.000). The endometrial thickness of normal pathology (8.51 ± 3.43 mm) was significantly lower than the endometrial thickness of endometrial polyp (11.24 ± 5.453 mm) and endometrial cancer (10.95 ± 4.46 mm) (*p* 0.000). Tamoxifen use duration was similar (*p* 0.199). Table 5 shows the comparison of Group I and II according to hematological parameters. The PDW (*p* 0.001) and RDW (*p* 0.044) values of Group II were higher than Group I. Comparison of other hematological parameters was similar (*p* > 0.05).

The correlation of endometrial thickness with the duration of tamoxifen and inflammatory markers (NLR, PLR, RDW, PDW, LMR, MPV) was insignificant (*p* > 0.05). The pathologic endometrium significantly correlated with the endometrial thickness (*r* 0.278 *p* 0.001). The ROC analysis of endometrial thickness for pathological endometrial biopsy results in postmenopausal patients had poor diagnostic

potential (AUC 0.676, *p* 0.000, CI 0.5–0.7). The endometrial thickness of 4 mm yielded 94.5% sensitivity and 11% specificity. The optimal cut-off was 10 mm with 55% sensitivity and 80% specificity. The ROC analysis of endometrial thickness for pathological endometrial biopsy results in premenopausal patients had failed diagnostic potential (AUC 0.514, *p* 0.781 CI 0.41–0.615).

Discussion

This study investigated ultrasonographic and inflammatory features in endometrial pathologies of women with breast cancer using tamoxifen adjuvant therapy. The majority of the women having pathological endometrium were asymptomatic. Patients with pathological endometrial results had an increased endometrial thickness, RDW, and PDW values. The measurement of endometrial thickness had the diagnostic potential for pathological endometrium in menopause.

36% of tamoxifen users have endometrial pathologies (hyperplasia, polyps, carcinomas, and sarcoma) (Polin et al. 2018) and the endometrial polyp is the most common pathology [7, 8]. The incidence of endometrial polyp in tamoxifen users ranges from 8 to 36%, but this ratio is less than 10% in nonusers [9]. The malignant transformation rate of TMX related polyps is 3–10.7%, while TMX unrelated ones have 0.48% malignant change [10, 11]. Similar to the literature, endometrial pathology was reported in 34.3% of our cohort. Endometrial polyps consisted of 31.9% of these pathologies.

Some studies have reported that endometrial polyps in tamoxifen are accompanied by vaginal bleeding [12, 13]. In the study, which included 821 patients using tamoxifen and undergoing an endometrial biopsy, patients presenting with vaginal bleeding comprised 29.8% of the entire population [14]. In another study involving postmenopausal patients using tamoxifen and undergoing an endometrial biopsy, 94.1% of patients were asymptomatic women [15]. Similarly, 27.4% of patients in our cohort had symptoms of vaginal bleeding.

Some studies have stated that endometrial changes develop depending on the tamoxifen dose and duration. Also, women receiving high-dose tamoxifen therapy are prone to more aggressive tumors than the standard dose [8, 12, 15–18]. Recently, the use of tamoxifen in breast cancer

has been increased from 5 to 10 years [3]. For this reason, it is important to identify groups at risk for the development of endometrial pathology. Fornander et al. (1989) reported an increase in endometrial pathology in those using tamoxifen for more than 2 years [12].

Franchi et al. (1999) reported the period of increased risk of endometrial pathology as 27 months and above [8]. In another study, the rate of detection of endometrial pathology was found to be 44% in the use of tamoxifen for less than 5 years, while this rate was found to be 58% in those with a treatment duration of more than 5 years [18]. A recent meta-analysis showed that endometrial malignancy risk increases in patients with 10-year therapy compared to 5-year therapy [17]. The ratio of endometrial pathology was similar between TMX use ≥ 24 months (32.8%) and TMX use < 24 months (35.4%) in our cohort ($p > 0.05$). The ratio of endometrial pathology in TMX use ≥ 5 years (31.2%) and TMX less than 5 years (34.4%) was also similar ($p > 0.05$). The reason why we did not find a significant difference in our study may be that the average duration of tamoxifen use was 24.74 ± 16.66 months. Few patients had been using tamoxifen for more than 5 years in our cohort. Our results confirmed another study [14] with a similar duration of tamoxifen use.

Although tamoxifen has been used in breast cancer for many years, there is still no consensus on which method and how often the endometrium should be checked. In addition, even the indications for endometrial biopsy are not standardized. In our cohort, all women with TMX-BC who underwent endometrial surveillance at 6-month intervals. All women underwent endometrial biopsy if they were symptomatic or had irregular endometrium, intrauterine fluid accumulation, or thickened endometrium.

Ultrasonographic evaluation of endometrial thickness, shape, and irregularity is the ultrasonographic parameter used in endometrium evaluation [19, 20]. Özsener et al. reported a significant relationship between endometrial thickness and tamoxifen duration [21]. In our cohort, the duration of tamoxifen use was not associated with endometrial pathology and endometrial thickness ($p > 0.05$). In our study, the endometrial thickness of normal pathology (8.51 ± 3.43 mm) was significantly lower than the endometrial thickness of endometrial polyp (11.24 ± 5.453 mm) and endometrial cancer (10.95 ± 4.46 mm) ($p 0.000$). These findings suggested that the measurement of endometrial thickness may be useful in endometrial surveillance as a distinctive condition. However, there are some concerns about the usability of endometrial thickness. Since tamoxifen triggers sub-endometrial glandular hypertrophy, it may cause an increase in endometrial thickness without any pathology [6]. The cutoff value of 10 mm is given in studies in the literature, and the predictive power is not very good [19, 22]. Our results showed failed diagnostic potential of endometrial

thickness measurements in premenopausal women. The postmenopausal women for cutoff 10 had 55% sensitivity and 80% specificity (AUC 0.676). In a study of premenopausal women using tamoxifen, Lee et al. showed that only abnormal vaginal bleeding was associated with hyperplasia and cancer [23]. In our study, there was no difference in the incidence of vaginal bleeding in the premenopausal group in patients with and without pathological endometrium.

The diagnostic and prognostic significance of inflammatory markers in endometrial cancers has been searched. However, this issue has not been sufficiently investigated in endometrial hyperplasia and polyps. To our knowledge, there is no study about the association of inflammatory markers with endometrial pathologies of tamoxifen users.

Some studies have shown increased local inflammation and decreased apoptosis in endometrial polyps in tamoxifen users [24]. The proliferative effects of tamoxifen through ER α and GPER1, protein pathways mTOR-signaling, stathmin, and DNA damage are the proposed mechanisms for the effects of tamoxifen on endometrial pathologies [25, 26]. The intrinsic and extrinsic pathways of inflammation are closely associated with cancers initiation and progress [27]. We hypothesized that tamoxifen may provide a pro-inflammatory milieu to promote pathological changes in the endometrium. RDW is used as an inflammation marker in cardiac, infections diseases, and some gastrointestinal cancers [28]. RDW defines the distribution of the size of red blood cells. PDW shows heterogeneity in the platelet volumes [29]. Increased PDW is related to poor prognosis in breast, colorectal, and laryngeal cancers [30–32]. There are few studies about PDW and endometrial pathologies with inconclusive results [33, 34]. Karateke et al. found increased PDW levels in endometrial cancers compared to normal [35]. However, other studies showed decreased PDW levels in endometrial cancers compared to normal pathology [33, 35]. In this study, we found increased PDW and RDW levels in women with TMX-BC on pathological endometrial findings. In our cohort, the stages were similar in women with normal and pathological endometrium results. However, it should be considered that many factors other than the stage may also affect the results of inflammation. It is difficult to interpret these findings in patients with underlying malignancies. The validity of these findings needs to be supported by studies in a large population.

The limitation of this study was its retrospective design and a small sample of tamoxifen users above 60 months. Because inflammation is affected by many comorbid conditions such as age, obesity, chronic diseases, and cancer caution should be exercised when interpreting inflammation-related results. When compared with the literature, the strengths of this study are that the number of cases is sufficient, results are from a single-center, endometrial thickness measurement, and pathological evaluation are performed by

the same clinics with standardized methods. In addition, the results of a clinic in which ultrasonography and endometrial biopsy were applied more liberally in tamoxifen follow-ups may provide a better prediction in terms of endometrial surveillance criteria.

In summary, most women with TMX-BC with pathological endometrium were asymptomatic. Endometrial thickness and inflammatory markers (RDW, PDW) were higher in women with pathological endometrial outcomes. PDW and RDW may be promising markers to differentiate pathological endometrium. The validity of these preliminary findings needs to be supported by further studies. This study suggests that an endometrial thickness > 10 mm in postmenopausal women may help identify the risk group. Studies are needed in premenopausal women and those using tamoxifen for more than 5 years.

Author contributions ES: contributed to study design; data management; formal data analysis; interpretation of data; drafting of the manuscript; read and approved the final version of the manuscript. FV: study design; concept; supervision of analyses; revision of the manuscript; read and approved the final version of the manuscript. ADEC: interpretation of data; critical revision of the manuscript for important intellectual content; read and approved the final version of the manuscript.

Funding No funding was received for this study.

Declarations

Conflict of interest There are no conflicts of interests that are directly or indirectly related to the research including the following: research grants from funding agencies; honoraria for speaking at symposia; financial support for attending symposia; financial support for educational programs; employment or consultation; support from a project sponsor; position on advisory board or board of directors or other type of management relationships; multiple affiliations; financial relationships, for example equity ownership or investment interest; intellectual property rights (e.g., patents, copyrights and royalties from such rights); holdings of spouse and/or children that may have financial interest in the work.

Ethics approval and consent to participate Informed consent was obtained from all individual participants included in the study. The ethical approval of the study was obtained from the ethics committee of Haydarpaşa Numune Training and Research Hospital(HNEAH-KAEK 2021/KK/14).

References

- Desantis C, Siegel R, Bandi P, Jemal A (2011) Breast cancer statistics. *CA Cancer J Clin* 61(6):408–418. <https://doi.org/10.3322/caac.20134>
- Park WC, Jordan VC (2002) Selective estrogen receptor modulators (SERMS) and their roles in breast cancer prevention. *Trends Mol Med* 8(2):82–88. [https://doi.org/10.1016/s1471-4914\(02\)02282-7](https://doi.org/10.1016/s1471-4914(02)02282-7)
- Davies C, Pan H, Godwin J et al (2013) Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 381(9869):805–816. [https://doi.org/10.1016/S0140-6736\(12\)61963-1](https://doi.org/10.1016/S0140-6736(12)61963-1)
- Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM (1994) Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the national surgical adjuvant breast and bowel project (NSABP)B-14. *J Natl Cancer Inst* 86(7):527–537. <https://doi.org/10.1093/jnci/86.7.527>
- Wickerham DL, Fisher B, Wolmark N, Bryant J, Costantino J, Bernstein L, Runowicz CD (2002) Association of tamoxifen and uterine sarcoma. *J Clin Oncol* 20(11):2758–2760. <https://doi.org/10.1200/JCO.2002.20.11.2758>
- Achiron R, Lipitz S, Sivan E, Goldenberg M, Horovitz A, Frenkel Y, Mashiah S (1995) Changes mimicking endometrial neoplasia in postmenopausal, tamoxifen-treated women with breast cancer: a transvaginal Doppler study. *Ultrasound Obstet Gynecol* 6(2):116–120. <https://doi.org/10.1046/j.1469-0705.1995.06020.116.x>
- Deligdisch L, Kalir T, Cohen CJ, de Latour M, Le Bouedec G, Penault-Llorca F (2000) Endometrial histopathology in 700 patients treated with tamoxifen for breast cancer. *Gynecol Oncol* 78(2):181–186. <https://doi.org/10.1006/gyno.2000.5859>
- Franchi M, Ghezzi F, Donadello N, Zanaboni F, Beretta P, Bolis P (1999) Endometrial thickness in tamoxifen-treated patients: an independent predictor of endometrial disease. *Obstet Gynecol* 93(6):1004–1008. [https://doi.org/10.1016/s0029-7844\(98\)00561-4](https://doi.org/10.1016/s0029-7844(98)00561-4)
- Cheng WF, Lin HH, Torng PL, Huang SC (1997) Comparison of endometrial changes among symptomatic tamoxifen-treated and nontreated premenopausal and postmenopausal breast cancer patients. *Gynecol Oncol* 66(2):233–237. <https://doi.org/10.1006/gyno.1997.4739>
- Cohen I, Azaria R, Shapira J, Yigael D, Tepper R (2002) Significance of secondary ultrasonographic endometrial thickening in postmenopausal tamoxifen-treated women. *Cancer* 94(12):3101–3106. <https://doi.org/10.1002/cncr.10587>
- Polin SA, Ascher AM (2008) The effect of tamoxifen on the genital tract. *Cancer Imaging* 8(1):135–145. <https://doi.org/10.1102/1470-7330.2008.0020>
- Fornander T, Cedermark B, Mattsson A, Skoog L, Theve T, Askergren J et al (1989) Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet* 333(8630):117–120. [https://doi.org/10.1016/s0140-6736\(89\)91141-0](https://doi.org/10.1016/s0140-6736(89)91141-0)
- Markovitch O, Tepper R, Aviram R, Fishman A, Shapira J, Cohen I (2004) The value of sonohysterography in the prediction of endometrial pathologies in asymptomatic postmenopausal breast cancer tamoxifen-treated patients. *Gynecol Oncol* 94(3):754–759. <https://doi.org/10.1016/j.ygyno.2004.06.033>
- Jeon J, Kim SE, Lee D-Y, Choi D (2020) Factors associated with endometrial pathology during tamoxifen therapy in women with breast cancer: A retrospective analysis of 821 biopsies. *Breast Cancer Res Treat* 179(1):125–130. <https://doi.org/10.1007/s10549-019-05448-w>
- Cohen I, Perel E, Flex D, Tepper R, Altaras MM, Cordoba M et al (1999) Endometrial pathology in postmenopausal tamoxifen treatment: comparison between gynaecologically symptomatic and asymptomatic breast cancer patients. *J Clin Pathol* 52(4):278–282. <https://doi.org/10.1136/jcp.52.4.278>
- Bernstein L, Deapen D, Cerhan JR, Schwartz SM, Liff J, McGann-Maloney E et al (1999) Tamoxifen therapy for breast cancer and endometrial cancer risk. *J Natl Cancer Inst* 91(19):1654–1662. <https://doi.org/10.1093/jnci/91.19.1654>
- Fleming CA, Heneghan HM, O'Brien D, McCartan DP, McDermott EW, Prichard RS (2018) Meta-analysis of the cumulative

- risk of endometrial malignancy and systematic review of endometrial surveillance in extended tamoxifen therapy. *Br J Surg* 105(9):1098–1106. <https://doi.org/10.1002/bjs.10899>
18. Hann LE, Giess CS, Bach AM, Tao Y, Baum HJ, Barakat RR (1997) Endometrial thickness in tamoxifen-treated patients: correlation with clinical and pathologic findings. *AJR Am J Roentgenol* 168(3):657–661. <https://doi.org/10.2214/ajr.168.3.9057510>
 19. Fung MFK, Reid A, Faught W, Le T, Chenier C, Verma S, Brydon E, Fung KFK (2003) Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. *Gynecol Oncol* 91(1):154–159. [https://doi.org/10.1016/s0090-8258\(03\)00441-4](https://doi.org/10.1016/s0090-8258(03)00441-4)
 20. Love CD, Muir BB, Scrimgeour JB, Leonard RC, Dillon P, Dixon JM (1999) Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. *J Clin Oncol* 17(7):2050–2054. <https://doi.org/10.1200/JCO.1999.17.7.2050>
 21. Ozşener S, Ozaran A, Itil I, Dikmen Y (1998) Endometrial pathology of 104 postmenopausal breast cancer patients treated with tamoxifen. *Eur J Gynaecol Oncol* 19(6):580–583
 22. Gerber B, Krause A, Müller H, Reimer T, Külz T, Makovitzky J, Kundt G, Friese K (2000) Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. *J Clin Oncol* 18(20):3464–3470. <https://doi.org/10.1200/JCO.2000.18.20.3464>
 23. Lee M, Piao J, Jeon MJ (2020) Risk factors associated with endometrial pathology in premenopausal breast cancer patients treated with tamoxifen. *Yonsei Med J* 61(4):317–322. <https://doi.org/10.3349/ymj.2020.61.4.317>
 24. McGurgan P, Taylor LJ, Duff SR, O'Donovan PJ (2006) Are endometrial polyps from pre-menopausal women similar to postmenopausal women? An immunohistochemical comparison of endometrial polyps from pre and post-menopausal women. *Maturitas* 54(3):277–284. <https://doi.org/10.1016/j.maturitas.2005.12.003>
 25. Nees LK, Heublein S, Steinmacher S, Juhasz-Böss I, Brucker S, Tempfer CB, Wallwiener M (2022) Endometrial hyperplasia as a risk factor of endometrial cancer. *Arch Gynecol Obstet*. <https://doi.org/10.1007/s00404-021-06380-5>
 26. Emons G, Mustea A, Tempfer C (2020) Tamoxifen and endometrial cancer: a janus-headed drug. *Cancers (Basel)* 12(9):2535. <https://doi.org/10.3390/cancers12092535>
 27. Ye Y, Wang X, Jeschke U, von Schönfeldt V (2020) COX-2-PGE₂-EPs in gynecological cancers. *Arch Gynecol Obstet* 301(6):1365–1375. <https://doi.org/10.1007/s00404-020-05559-6>
 28. Hu L, Li M, Ding Y, Pu L, Liu J, Xie J, Cabanero M, Li J, Xiang R, Xiong S (2017) Prognostic value of in cancers: a systematic review and meta-analysis. *Oncotarget* 8(9):16027–16035. <https://doi.org/10.18632/oncotarget.13784>
 29. Osselaer JC, Jamart J, Scheiff JM (1997) Platelet distribution width for differential diagnosis of thrombocytosis. *Clin Chem* 43(6):1072–1076
 30. Huang Y, Cui MM, Huang YX, Fu S, Zhang X, Guo H, Wang RT (2018) Preoperative platelet distribution width predicts breast cancer survival. *Cancer Biomark* 23(2):205–211. <https://doi.org/10.3233/CBM-181267>
 31. Cheng S, Han F, Wang Y, Xu Y, Qu T, Ju Y, Zhiming Lu (2017) The red distribution width and the platelet distribution width as prognostic predictors in gastric cancer. *BMC Gastroenterol* 17(1):163. <https://doi.org/10.1186/s12876-017-0685-7>
 32. Wen W, Wu P, Li J, Wang H, Sun J, Chen H (2018) Predictive values of the selected inflammatory index in elderly patients with papillary thyroid cancer. *J Transl Med* 16(1):261. <https://doi.org/10.1186/s12967-018-1636-y>
 33. Kurtoglu E, Kokcu A, Celik H, Sari S, Tosun M (2015) Platelet indices may be useful in discrimination of benign and malign endometrial lesions, and early and advanced stage endometrial cancer. *Asian Pac J Cancer Prev* 16(13):5397–5400. <https://doi.org/10.7314/apjcp.2015.16.13.5397>
 34. Song J, Lai X, Zhang Y, Zheng X, Su J (2019) Preoperative platelet morphology parameters as prognostic predictors for endometrial malignant carcinoma stage and progesterone receptor. *Medicine (Baltimore)* 98:e17818. <https://doi.org/10.1097/MD.00000000000017818>
 35. Karateke A, Kaplanoglu M, Baloglu A (2015) Relations of platelet indices with endometrial hyperplasia and endometrial cancer. *Asian Pac J Cancer Prev* 16(12):4905–4908. <https://doi.org/10.7314/apjcp.2015.16.12.4905>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.