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Endometrial pathologies in clinical follow-up of patients with hormone receptor-positive/negative breast cancer

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Ethics Committee Approval
The study was approved by Non-Interventional Health Research Ethics Committee of Dokuz Eylul University (Date: May 6, 2021, approval number 2021/14-45 and protocol number 6167-GOA).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Breast cancer is the leading cause of cancer-related fatalities in women. Tamoxifen, a selective estrogen receptor modulator (SERM), is frequently employed for chemoprevention in hormone receptor (HR)-positive breast cancer patients due to its anti-estrogenic impact on breast tissue. Nevertheless, tamoxifen exhibits agonistic effects on the endometrium, particularly in postmenopausal women. This study aims to assess gynecological issues and endometrial pathologies that emerge during the treatment and follow-up phases of women diagnosed with HR-positive/negative breast cancer.

Methods: This cohort study involved a data review from 857 breast cancer patients diagnosed over a decade at a tertiary center. Histopathological endometrial findings were evaluated for 166 patients who underwent gynecological consultations before breast cancer treatment with normal examination results and underwent invasive assessments due to gynecological symptoms that arose during treatment and follow-up. The study encompassed cases culminating in total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO).

Results: The study analyzed 166 cases meeting the inclusion criteria. The mean age at breast cancer diagnosis was 48 years with a standard deviation of 8.4 years, and the average follow-up duration was 4.1 (3.8) years. The predominant histopathological type was invasive ductal carcinoma (75.3%). Of the cases, 68.6% occurred during premenopausal and 31.4% during postmenopause. HR positivity was identified in 136 cases (81.9%), while 30 (18.1%) exhibited negative HR status. Among HR-positive cases, 113 (83.0%) received tamoxifen treatment, while 23 (17.0%) were treated with letrozole. Common clinical findings during and after treatment encompassed increased endometrial thickness (ET) and abnormal uterine bleeding (AUB). Histopathological evaluation of invasive procedures prompted by increased ET indicated the following frequent endometrial findings: proliferative endometrium (33.1%), endometrial polyp (20.5%), and endometrial hyperplasia (EH) without atypia (9%). The histopathological outcomes of invasive procedures prompted by AUB included atrophic endometrium (11.4%), proliferative endometrium (3.6%), and endometrial cancer (1.8%). Among the endometrial malignancies, three occurred in the premenopausal phase and four in the postmenopausal phase. Notably, three of the seven endometrial malignancies were observed in the tamoxifen hormone therapy group, all HR-positive. Four cases were from the non-tamoxifen hormone therapy group with negative HR status.

Conclusion: Globally, breast cancer ranks as the most prevalent malignancy in women. Tamoxifen, a frequently utilized adjuvant therapy post breast cancer surgery, can exert diverse effects on gynecological organs, encompassing benign pathologies like increased ET and malignant pathologies like uterine neoplasia. There is a rising suspicion that etiopathogenetic factors contributing to breast cancer progression might also precipitate uterine cancer, irrespective of tamoxifen use. Vigilant patient monitoring is paramount for detecting uterine neoplasia and other gynecological pathologies.

Keywords: breast cancer, endometrial pathologies, tamoxifen

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Introduction

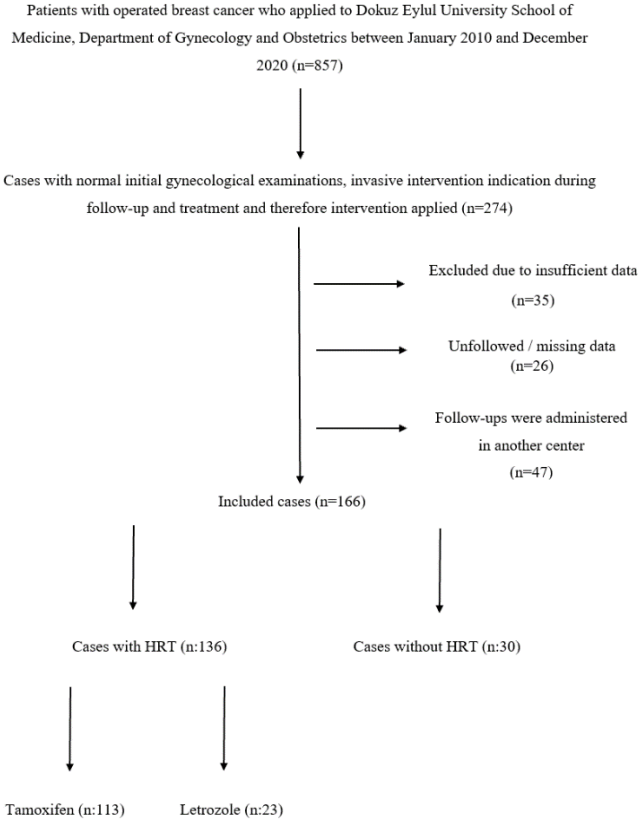
Breast cancer holds the unfortunate distinction of being the most prevalent cancer among women globally, and it maintains its grim position as a leading cause of cancer-related fatalities in this demographic. Despite its prevalence, advancements in early diagnostic capabilities, coupled with a multidisciplinary treatment approach encompassing surgery, radiotherapy, collaboration with medical oncologists, and diligent post-treatment monitoring, have collectively contributed to reducing breast cancer mortality rates [1,2]. Originally conceived as a contraceptive measure, tamoxifen emerged as a selective estrogen receptor modulator (SERM) and was initially employed as an oral contraceptive. However, its significance has evolved considerably, finding its niche in preventing and managing hormone-dependent breast cancer. Its anti-estrogenic properties have proven valuable in offering chemoprevention for women at elevated risk of cancer, particularly those afflicted with estrogen receptor (ER) positive breast cancer. Renowned for its low toxicity and widespread availability, tamoxifen has become one of the most commonly prescribed anticancer medications globally [3,4].

Tamoxifen hormone therapy introduces a spectrum of effects encompassing the development of endometrial polyps, hyperplasia, atypia, and even uterine malignancies [4]. These consequences are notably more prevalent among postmenopausal women. Research has illuminated a concerning trend—underlying endometrial pathology coupled with prolonged tamoxifen treatment exceeding 2 years escalates the risk of uterine malignancy, particularly aggressive histopathological variants such as type 2 endometrial cancer and sarcoma, by a factor of 2 to 7 [4,5]. With this backdrop, the primary objective of this study is to scrutinize the trajectory of endometrial pathologies emerging during and post breast cancer treatment in a cohort of patients who presented no initial evidence of uterine pathology during their initial gynecological examination, regardless of their adherence to adjuvant tamoxifen therapy.

Materials and methods

The study was conducted at a tertiary center from January 2010 to December 2020. Cases were assessed through the utilization of the diagnosis code 'ICD-C50'. Non-Interventional Health Research Ethics Committee of Dokuz Eylul University clearance was secured (Date: May 6, 2021, approval number 2021/14-45 and protocol number 6167-GOA). All patients provided informed consent both prior to treatment and examination. The study entailed the analysis of 857 cases over 10 years. Of these, 166 breast cancer cases were identified that aligned with the stipulated inclusion and exclusion criteria, warranting their inclusion in the evaluation. The assessment encompassed a spectrum of data, including demographic attributes of breast cancer patients, tumor histology, hormone receptor (HR) positivity, administration of adjuvant hormone therapy, mean duration of follow-up, the emergence of gynecological complications during follow-up, and the endometrial pathologies ascertained via preoperative and postoperative invasive procedures. Procedures such as probe curettage, fractionated curettage, and hysteroscopy constituted the 'preoperative' endometrial biopsy interventions, while the term 'postoperative' was associated with the final pathology post total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO). The patient cohort was bifurcated into two distinct groups: those subjected to hormonal therapy and those who were not. HR positivity was established upon detecting at least one of three receptors – estrogen, progesterone, or human epidermal growth factor receptor 2. Within the hormonal therapy subgroup, patients were further categorized into two subdivisions: those utilizing tamoxifen and those employing aromatase inhibitors (Figure 1).

Figure 1: Flowchart for defining and recording the study criteria.



Determination of menopausal status was guided by serum follicle-stimulating hormone (FSH) and estradiol (E2) levels, circumventing factors such as age and duration of amenorrhea [6]. Cases with serum FSH levels surpassing 75 mIU/ml were deemed postmenopausal, while those exhibiting serum FSH levels below 25 mIU/ml were classified as premenopausal. E2 levels came into play for cases with serum FSH levels ranging between 25 and 75 mIU/ml; E2 levels below 20 pg/ml pointed to postmenopausal status, while levels exceeding 20 pg/ml indicated perimenopausal status. The study's purview included patients devoid of any gynecological pathology at the outset of breast cancer treatment, individuals undergoing invasive interventions (probe, fractionated curettage, hysteroscopy) due to gynecological symptoms during treatment, and subsequently receiving hysterectomy and salpingo-oophorectomy. Exclusions comprised patients who had undergone hysterectomy prior to breast cancer diagnosis, those undergoing hormonal therapy or intrauterine device medication for premalignant endometrial conditions, individuals with a history of gynecological or colon cancer, and those with concurrent or preceding malignancies, whether synchronous or asynchronous. Cases lacking pertinent patient information, subjects continuing care at another facility, and patients treated

outside the study's parameters were also omitted from the analysis.

Statistical analysis

The statistical analysis was executed using IBM SPSS Statistics 24 software. Continuous variables were presented in the form of mean (standard deviation) or median (minimum-maximum) values, while categorical variables were expressed as n (%). The data's adherence to normality was assessed using the Kolmogorov-Smirnov test. Comparative statistical analysis was conducted between outcomes of breast cancer patients who underwent surgery following the detection of uterine pathologies during their follow-up and the relevant dependent and independent variables. The Mann-Whitney U test was employed to evaluate non-parametric independent data, while the categorical data analysis utilized the Chi-square and Fisher precision tests. A significance level of $P<0.05$ was deemed statistically meaningful.

Results

The demographic characteristics of the 166 patients included in the study are presented in Table 1. The participants' mean age was 48 (8.4) years, with a gravida of 2 (1.7) and parity of 2 (1.0). The median follow-up period for breast cancer was 4.1 (3.8) years. The predominant histopathological types of breast cancer were invasive ductal carcinoma (75.3%) and invasive lobular cancer (16.3%). Under the category 'other,' which accounted for 8.4%, histopathological types included ductal/lobular, mucinous, and medullary. HR positivity was observed in 136 (81.9%) cases, while HR negativity was observed in 30 (18.1%) cases. Of the HR-positive cases, 113 (83.0%) received tamoxifen, and 23 (17.0%) received letrozole treatment. Among the cases, 114 (68.6%) were in the premenopausal period, and 52 (31.4%) were in the postmenopausal period. Specifically, 91 (66.9%) of the HR-positive cases were premenopausal, and 45 (33.1%) were postmenopausal. In contrast, 23 (76.6%) of the HR-negative cases were premenopausal, while 7 (23.4%) were postmenopausal (Table 1).

Table 1: Demographic characteristics of all cases

Parameter	Value
Age, years, mean (SD)	48 (8.4) (min-max: 31-81)
Menopausal status of the cases (pre/postmenopause)	114 (68.6%) / 52 (31.4%)
Menopausal status of HR-positive cases (pre/postmenopause)	91 (66.9%) / 45 (33.1%)
Menopausal status of HR-negative cases (pre/postmenopause)	23 (76.6%) / 7 (23.4%)
Gravida, mean (SD)	2 (1.7) (min-max: 0-12)
Parity, mean (SD)	2 (1) (min-max: 0-6)
Follow-up period, years, mean (SD)	4.1 (3.8) (min-max: 0-22)
The histopathological type of breast cancer	
Invasive ductal carcinoma	125 (75.3%)
Invasive lobular carcinoma	27 (16.3%)
Other	14 (8.4%)
HR status	
*Positive	136 (81.9%)
Tamoxifene	113 (83.0%)
Letrozole	23 (17.0%)
*Negative	30 (18.1%)
Invasive procedure indications	
Endometrial thickness increases	114 (68.7%)
Abnormal uterine bleeding	28 (16.9%)
Genetic	13 (7.8%)
Other	11 (6.6%)

SD: standard deviation, HR: Hormone receptor

The most frequently reported gynecological symptoms during and after breast cancer treatment included vaginal dryness, dyspareunia, and vaginal bleeding. Notably, the most common finding was increased endometrial thickness (ET). Invasive interventions were primarily indicated for increased ET and abnormal uterine bleeding (AUB), accounting for 68.7% and 16.9%, respectively (refer to Table 1). Genetic mutation analysis revealed BRCA 1-2, STK-11, and PALB-2 mutations in 11 out of 13 cases in the genetic mutation group. Additionally, 11 cases fell under the 'other' category, while 6 exhibited benign adnexal masses. Furthermore, myoma uteri, previously undetected, was identified in five cases (Table 1).

Diagnostic invasive procedures were performed on cases with the indications above before surgery. Subsequently, all cases underwent a postoperative TAH+BSO (total abdominal hysterectomy and bilateral salpingo-oophorectomy) procedure. In instances of malignancy, supplementary treatments were administered based on the malignancy type and the frozen pathology examination results obtained during the operation. The preoperative and postoperative endometrial histopathology findings are detailed in Table 2. Notably, the final pathology report revealed hyperplasia with atypia among five cases initially diagnosed with benign pathologies from endometrial sampling. Similarly, all cases initially diagnosed with endometrial cancer from endometrial sampling were confirmed as endometrial cancer in the final pathology results (Table 2). A comparison of postoperative final pathology results concerning preoperative endometrial biopsy indications is provided in Table 3. Proliferative endometrium emerged as the most frequent histopathological outcome among cases operated on due to increased ET (33.1%).

Table 2: Preoperative and postoperative endometrial histopathological results of all cases

Endometrial histopathology	Preoperative (n=166)	Postoperative (n=166)
Proliferative endometrium	71 (42.8%)	69 (41.6%)
Endometrial polyp	40 (24.1%)	37 (22.3%)
Atrophic endometrium	26 (15.7%)	26 (15.7%)
Hyperplasia without atypia	19 (11.4%)	19 (11.4%)
Hyperplasia with atypia	3 (1.8%)	8 (4.8%)
Malignancy	7 (4.2%)	7 (4.2%)

Table 3: Final pathology results according to preoperative endometrial biopsy indications

	Postoperative histopathological results (n=166)					
Indications	Proliferative endometrium	Endometrial polyp	Endometrial atrophy	Hyperplasia without atypia	Hyperplasia with atypia	Endometrial malignancy
Endometrial thickness increasing	55 (33.1%)	34 (20.5%)	0 (0.0%)	15 (9%)	7 (4.2%)	3 (1.8%)
Abnormal uterine bleeding	6 (3.6%)	0 (0.0%)	19 (11.4%)	0 (0.0%)	0 (0.0%)	3 (1.8%)
Genetic mutations	4 (2.4%)	1 (0.6%)	4 (2.4%)	3 (1.8%)	0 (0.0%)	1 (0.6%)
Other	4 (2.4%)	2 (1.2%)	3 (1.8%)	1 (0.6%)	1 (0.6%)	0 (0.0%)

Conversely, endometrial atrophy constituted the prevailing histopathological outcome (11.4%) in patients operated on for AUB. The correlation between preoperative ultrasonically measured ET values and postoperative histopathological results for all cases is outlined in Table 4. Notably, proliferative endometrium was elevated in cases with 5-10 mm ET measurements, while endometrial polyps were significantly more frequent in cases with ET >15 mm ($P<0.001$). Conversely, ET <5 mm cases exhibited significantly higher instances of endometrial atrophy ($P<0.001$). Within the four cases with ET measurements below 5 mm, 1 displayed endometrioid adenocarcinoma, while the remaining three exhibited serous carcinoma histology. Cases with ET measurements between 10-15 mm showed significantly higher instances of endometrial hyperplasia (EH) with or without atypia compared to other groups ($P<0.001$, $P<0.001$, respectively).

Notably, there were no noteworthy differences between ET measurement groups in terms of endometrial malignancy.

Table 4: Distribution of endometrial thickness values measured by ultrasound in all cases according to final histopathological diagnoses

	<5 mm n=36	5-10 mm n=73	10-15 mm n=31	>15 mm n=26	*P*-value
Proliferative endometrium	6 (16.6%)	55 (75.3%)	7 (22%)	1 (3.8%)	<0.001*
Endometrial polyp	0 (0.0%)	8 (10.9%)	9 (29%)	20 (76.9%)	<0.001*
Endometrial atrophy	26 (72.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.001*
Hyperplasia without atypia	0 (0.0%)	7 (9.5%)	9 (29%)	3 (11.5%)	<0.001*
Hyperplasia with atypia	0 (0.0%)	1 (1.3%)	6 (19.3%)	1 (3.8%)	<0.001*
Endometrial malignancy	4 (11.1%)	2 (2.7%)	0 (0.0%)	1 (3.8%)	0.1

Table 5 presents a comparison of histopathological findings based on menopausal status. Among the cases, 114 were premenopausal (68.6%), while 52 were postmenopausal (31.4%). The diagnosis of proliferative endometrium was notably higher in the premenopausal group than the postmenopausal group (P<0.001, respectively; 35.5% vs. 6%). Conversely, the diagnosis of endometrial atrophy was significantly more prevalent in the postmenopausal group (P<0.001, respectively; 6% vs. 9.6%). Comparable results were observed between the groups regarding other final histopathological findings. Notably, among endometrial cancer cases, 4 were identified in the postmenopausal period, while 3 were identified in the premenopausal period.

Table 5: Comparison of histopathological findings according to menopausal status

	Premenopause n=114 (68.6%)	Postmenopause n=52 (31.4%)	*P*-value
Proliferative endometrium	59 (35.5%)	10 (6%)	<0.001*
Endometrial polyp	23 (13.9%)	14 (8.4%)	0.331
Endometrial atrophy	10 (6%)	16 (9.6%)	0.001*
Hyperplasia without atypia	15 (9%)	4 (2.4%)	0.327
Hyperplasia with atypia	4 (2.4%)	4 (2.4%)	0.207
Endometrial malignancy	3 (1.8%)	4 (2.4%)	0.193

Discussion

This study presents findings on endometrial pathologies observed during the clinical monitoring of breast cancer patients with positive and negative HR statuses. Notably, our study highlights the significant increase in ET due to hormonal therapy and the heightened occurrence of endometrial pathologies associated with this increase in ET. Interestingly, our results diverge from existing literature, revealing a higher incidence of endometrial malignancies among patients who did not undergo hormone therapy.

Breast cancer exhibits diverse biological behaviors and treatment responses, thus constituting a heterogeneous spectrum of pathologies. Roughly half of all cases are linked to risk factors, including reproductive elements and proliferative breast disorders, with another 10% attributed to familial history and genetic influences [1,2]. Furthermore, environmental factors, encompassing demographic and lifestyle considerations, play a role in breast cancer risk [1–3].

Around 20% of breast cancer cases in the United States are diagnosed within the 45-54 age bracket [7]. Correspondingly, our study indicates an average age of diagnosis at 48 (8.4) years. The prevailing literature reflects that 75% of breast cancer cases exhibit HR positivity, thus making the HR-positive type the predominant form of breast cancer [1]. Our findings mirror these previous studies, with 81.9% of cases displaying HR-positive breast cancer.

Research indicates that HR-negative breast cancer predominantly occurs during the premenopausal phase, with prevalence rates ranging between 15–20% [8]. Our study aligns with this trend, as HR-negative breast cancer constituted 18.1% of all cases, consistent with existing literature.

Tamoxifen, a commonly employed adjuvant therapy for breast cancer patients, functions as a competitive inhibitor of estrogen receptors, binding to estrogen receptors within the breast to hinder tumor proliferation. This agent yields diverse impacts across different tissues. Despite its anti-estrogenic role in breast tissue, it can manifest as an estrogen agonist within distinct regions of the female reproductive system [3,4]. In premenopausal women, the antagonistic effect of tamoxifen on the endometrium is due to its interaction with endogenous estradiol, which surpasses its agonistic influence. Conversely, the postmenopausal endometrium experiences lower endogenous estrogen levels, prompting tamoxifen to assume an agonistic role [3–5].

Reports indicate that as many as 67% of women undergoing tamoxifen treatment for breast cancer may encounter endometrial pathologies [9,10]. Uterine gynecological issues manifest incidentally during pelvic imaging or present symptomatically, such as abnormal uterine bleeding. A frequently observed pelvic imaging finding is an escalation in ET. Likewise, within our study, the most prevalent outcome during monitoring breast cancer patients receiving hormone therapy was an augmentation in ET, evident in 68.7% of cases. Following this, cases featuring AUB were recorded in 28 instances (16.9%). In extant literature, AUB surfaces in approximately 50% of premenopausal cases and 25% of postmenopausal cases [10–13]. Notably, the preponderance of cases within our study was situated in the premenopausal period, and the routine gynecological surveillance of breast cancer patients is more frequent within our country due to medical practices. This might account for the comparatively reduced occurrence of cases with AUB compared to the literature.

Within our study, the histopathological outcomes of most cases that underwent invasive evaluation due to heightened ET predominantly indicated benign conditions, with proliferative endometrium (33.1%) and endometrial polyps (20.5%) being the primary findings.

While the prevalence of endometrial polyps within the general population fluctuates between 0-10%, patients undergoing tamoxifen treatment face an elevated risk, with incidence rates ranging from 6-42% [9–12]. Although endometrial polyps are benign, the likelihood of malignant transformation among endometrial polyps in the broader population is approximately 2% during the premenopausal phase and 5% during the postmenopausal phase. This risk escalates to 11% among women employing tamoxifen [14,15]. In alignment with existing literature, our study reveals a comparable risk of endometrial polyps among patients receiving hormone therapy, with a prevalence of 21.1%, thereby holding statistical significance.

Research has revealed an increased risk of EH in postmenopausal women using tamoxifen, whereas no elevated risk has been established for premenopausal patients. The NSABP P-2 study highlighted an annual rate of atypical EH at 0.77 per 1000 women among postmenopausal patients receiving tamoxifen, alongside a rate of 3.63 per 1000 women for simple hyperplasia [11,16]. An additional retrospective study depicted a

risk of approximately 12% for simple hyperplasia, 3% for complex hyperplasia, and approximately 2% for endometrial cancer among postmenopausal breast cancer patients subjected to four years of tamoxifen treatment [10]. However, our study's outcomes deviate from the literature. Among the 27 instances of EH, 19 encompassed simple hyperplasia without atypia, and eight exhibited hyperplasia with atypia. Of these cases, 19 occurred during the premenopausal period, while 8 manifested during the postmenopausal period. Intriguingly, 50% of the hyperplasia with atypia cases were identified in the premenopausal phase. A noteworthy 88.8% (24/27) of hyperplasia cases were under hormone therapy. Although progesterone and levonorgestrel intrauterine devices can serve as treatment options for EH, HR-positive breast cancer patients without fertility expectations should prioritize hysterectomy as their treatment choice [17,18].

Determining the menopausal status is crucial in assessing tamoxifen's impact, as neoplastic transformations typically manifest more prominently during the postmenopausal phase. Following a five-year course of tamoxifen treatment, the incidence of endometrial cancer stands at 0.3% among postmenopausal patients and 0.1% among premenopausal patients [14,19,20]. Interestingly, the American College of Obstetricians and Gynecologists (ACOG) affirms that the risk of uterine cancer does not rise in premenopausal women undergoing tamoxifen therapy and suggests that routine gynecological monitoring suffices for these patients [20]. In this context, our findings diverge from existing literature. Among the seven malignancies identified in our study, four occurred during the postmenopausal period, while 3 emerged during the premenopausal phase. Consequently, we advocate for a case-specific evaluation that considers individual dynamics. We further recommend meticulous assessment for all patients, irrespective of their menopausal status.

The risk of endometrial cancer attributed to tamoxifen is well-established and correlates with the duration of tamoxifen usage. Numerous studies indicate that postmenopausal patients using tamoxifen experience an endometrial cancer incidence that is 2-3 times higher than that of the general population [4,5,10,13,14]. Nonetheless, certain studies also highlight an elevated occurrence of HR-positive/negative endometrial cancer among breast cancer patients compared to the general population, irrespective of drug utilization [21,22]. This hints at a potential etiological similarity between various breast cancer subtypes and the onset of endometrial cancer [23]. Our study demonstrates a notable disparity in endometrial malignancy cases within the group that did not undergo hormone therapy. Consequently, we posit that gynecological assessments should form an integral component of the routine monitoring of breast cancer patients, regardless of the positive or negative HR status.

Extended tamoxifen usage has been linked to an elevated susceptibility to uterine sarcoma, and this risk may persist for a certain duration even after discontinuing tamoxifen therapy [24–26]. In alignment with this concern, ACOG advises that patients undergoing tamoxifen treatment be educated about and assessed for the risk of uterine sarcoma, alongside other potential risks [20]. It's worth noting that our study group did not yield any instances of uterine sarcoma.

Our study has several strengths, including utilizing a homogenous cohort within a single tertiary care center. Notably, the study employed stringent exclusion criteria, ensuring the robustness of the data. The extended follow-up period spanning a decade further contributes to the study's credibility. Worth mentioning is the fact that the absence of patient information was among the exclusion criteria, bolstering the quality of our findings. A limited number of patients was the major limitation of this study.

Conclusion

In summary, breast cancer is the most prevalent malignancy among women worldwide. Recent years have witnessed a decline in breast cancer mortality due to advancements in diagnostic and therapeutic approaches, transforming the ailment into a manageable chronic condition. Alongside tumor attributes, factors such as menopausal status, reproductive history, and current health status wield notable influence over the treatment trajectory. The research underscores the augmented susceptibility to uterine pathologies – such as endometrial polyps, endometrial carcinoma, EH, uterine sarcoma, and carcinosarcoma – in patients employing tamoxifen for breast cancer therapy. Consequently, vigilant surveillance and assessment of women receiving tamoxifen treatment for potential gynecological pathologies are important. Furthermore, it's imperative to recognize that etiopathogenetic factors implicated in breast cancer development might similarly contribute to endometrial cancer development, irrespective of hormonal therapies employed, thereby heightening the risk of endometrial cancer in such patients. Future investigations with larger sample sizes possess the potential to furnish insights into the impact of tamoxifen in breast cancer cases and the optimal frequency for follow-up care.

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