SHORT COMMUNICATION

CONTENTS

Analysis of histopathological results of the endometrium in breast cancer patients treated with tamoxifen. Preliminary report

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ABSTRACT

Aim: The study aimed to compare histopathological outcomes of the endometrium in breast cancer patients treated with tamoxifen. The analysis included asymptomatic women referred for abnormal ultrasound findings and symptomatic women with abnormal uterine bleeding.

Materials and Methods: The study included 86 patients hospitalized between 2013 and 2024 at the Medical University of Warsaw. Group I (n=42) comprised patients with abnormal ultrasonographic findings, while Group II (n=44) included women with abnormal uterine bleeding. All patients underwent hysteroscopy with subsequent histopathological tissue analysis.

Results: The most frequent histopathological diagnosis in both groups was the presence of endometrial polyps (Group I: 50.0%; Group II: 36.36%). Endometrial cancer was diagnosed in 7.14% of Group I and 9.09% of Group II patients, indicating a comparable prevalence of serious pathology. Statistically significant differences ($p < 0.05$) were noted between the groups only for non-atypical hyperplasia and proliferative endometrium.

Conclusions: The findings confirm that endometrial polyps are the most frequent pathology associated with tamoxifen use in this cohort. This preliminary report underscores the critical need for further targeted research focusing on population-specific factors and menopausal status to develop clear, personalized clinical guidelines for screening and surveillance, particularly for premenopausal women, independent of symptomatic presentation.

KEY WORDS: breast cancer, endometrial hyperplasia, endometrial carcinoma, endometrial polyps, tamoxifen therapy

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INTRODUCTION

Breast cancer is one of the most common malignancies in women and is a heterogeneous, phenotypically diverse disease composed of several biologic subtypes that have distinct behavior and response to therapy [1]. A significant proportion (75%) of cases are characterized by positive estrogen receptor (ER) and progesterone receptor (PR) status [2].

One of the most frequently used substance in a patient with positive ER is tamoxifen (TAM), a nonsteroidal selective estrogen modulator (SERM) with mixed antagonist and agonist properties [3]. Tamoxifen was approved by the Food and Drug Administration in 1977 for the treatment of women with advanced breast cancer and several years later for adjuvant treatment of primary breast cancer [3]. It is antiestrogenic in breast cancer and by mechanism of binding to estrogen receptors it blocks tumour proliferation. For premenopausal women at diagnosis, the NCCN Guidelines for Breast Cancer suggest tamoxifen for 5 years, with or without ovarian suppression, or an AI for 5 years combined with ovarian suppression or ablation (category 1). Women who remain premenopausal can consider tamoxifen for another 5 years (10 total) or no further endocrine therapy. Those who become postmenopausal can consider 5 more years of tamoxifen or switch to an AI for 5 years [4]. The use of TAM as adjuvant hormonal therapy is effective in reducing recurrences and extending survival in premonopausal and some postmenopausal patients with breast cancer. It is also used in chemoprevention in selected patients at increased risk for breast cancer.

Despite tamoxifen's effectiveness in inhibiting estrogen receptors in breast tissue, it also exhibits agonistic effects on the endometrium, leading to adverse proliferative changes. Although premenopausal women with breast cancer are usually treated with tamoxifen as first-line adjuvant hormone therapy, it remains unclear whether the use of tamoxifen in premenopausal women is associated with an increased risk of

several uterine diseases [5]. Over the past decades tamoxifen was correlated with the risk of endometrial carcinoma with an increased risk in postmenopausal women [6, 7]. However, the most common type of pathology are endometrial polyps also in postmenopausal women [8, 9]. Other types of uterine pathology (endometrial hyperplasia and carcinoma) may also occur and the risk depends on many factors such as previously mentioned menopausal status or aim of use (whether the tamoxifen is used for chemoprevention or treatment of breast cancer). Currently, there are no clear guidelines regarding routine screening for gynaecologic diseases in premenopausal women taking tamoxifen, which remains a subject of ongoing debate.

AIM

The study aimed to compare the histopathological results of the endometrium in breast cancer patients who underwent adjuvant tamoxifen therapy among two groups: asymptomatic women, those referred for an ultrasound procedure due to abnormal endometrial imaging, and patients with abnormal uterine bleeding (e.g., postmenopausal bleeding or heavy, irregular menstrual bleeding).

MATERIALS AND METHODS

The population consists of 86 patients hospitalized at the Department and Clinic of Obstetrics, Gynecological Diseases, and Oncological Gynecology at the Medical University of Warsaw between 2013 and 2024. The study included patients with a history of breast cancer who were receiving adjuvant tamoxifen therapy and underwent hysteroscopy, during which histopathological examination was performed and adequate tissue samples were obtained for analysis. The study population was divided into two subgroups: Group I comprised 42 (48.84%) patients whose histopathological verification was prompted by abnormal endometrial findings on follow-up ultrasonography, while Group II included 44 (51.16%) women with abnormal uterine bleeding. Abnormal bleeding was defined as postmenopausal bleeding or heavy, irregular menstrual bleeding. The average age of patients in Group I was 58 years, whereas in Group II, it was 54 years. The mean BMI was 27.85 for bleeding patients and 26.13 for non-bleeding patients. A detailed analysis of histopathological differences in the two subgroups was performed, followed by further data interpretation.

RESULTS

In groups I and II, the most common histopathological diagnoses were endometrial polyps, occurring in 21 (50.0%) women in group I and 16 (36.36%) in group II. Endometrial polyps hyperplasia was found in 8 (19.05%) in group I and 7 (15.91%) in group II. Endometrial cancer was diagnosed in 3 women (7.14%) in group I and 4 (9.09%) in group II. Atypical hyperplasia was observed in 2 patients (4.76%) in group I and 1 (2.27%) in group II. Non-atypical hyperplasia was identified in 1 patient (2.38%) in group I and 3 (6.82%) in group II. Other histopathological diagnoses, such as atrophic endometrium, submucosal fibroids, and proliferative endometrium, were respectively present in group I as 4 (9.52%), 1 (2.38%), and 1 (2.38%), while in group II, they were 1 (2.27%), 1 (2.27%), and 10 (22.73%). Significant differences were found only for non-atypical hyperplasia and proliferative endometrium ($p < 0.05$), while other changes were not statistically significant (Fig. 1-2).

DISCUSSION

Patients treated with tamoxifen may develop uterine pathology, often presenting as asymptomatic or with abnormal uterine bleeding (AUB). Studies show that AUB occurs in over 50% of premenopausal patients and up to 25% of postmenopausal patients on tamoxifen [10, 11]. In our study, AUB was present in 60.0 % of premenopausal patients and 45.5% of postmenopausal patients, corroborating these findings.

Tamoxifen use significantly increases the risk of uterine pathology, including endometrial polyps, hyperplasia, and carcinoma, with reported risks of uterine pathology reaching up to 67% within four years of use [12–14]. In our cohort, endometrial pathology was diagnosed in 83.33 % of patients in group I and 70.45 % in group II, slightly exceeding reported data, possibly due to rigorous diagnostic protocols in our institution.

The most common uterine pathology associated with tamoxifen use is endometrial polyps, reported in approximately 21.1 per 1,000 patients annually in the NSABP P-2 trial [11]. Similarly, our study found endometrial polyps in 50.0 % of group I and 36.36% of group II patients. This aligns with findings from other studies, such as Ryu et al., where tamoxifen users exhibited higher rates of polyps than non-users [15]. However, our slightly higher rates may reflect differences in cohort characteristics or regional variations in care practices.

Endometrial carcinoma (EC) is a well-recognized risk associated with tamoxifen, particularly in postmenopausal patients. The NSABP P-2 trial reported an average annual EC incidence of 2.3 per 1,000 patients [11], and studies like Taponeco et al. observed a 7.8% EC rate among patients with postmenopausal bleeding [14]. In our study, EC was diagnosed in 7.14% of group I and 9.09% of group II patients, indicating a comparable

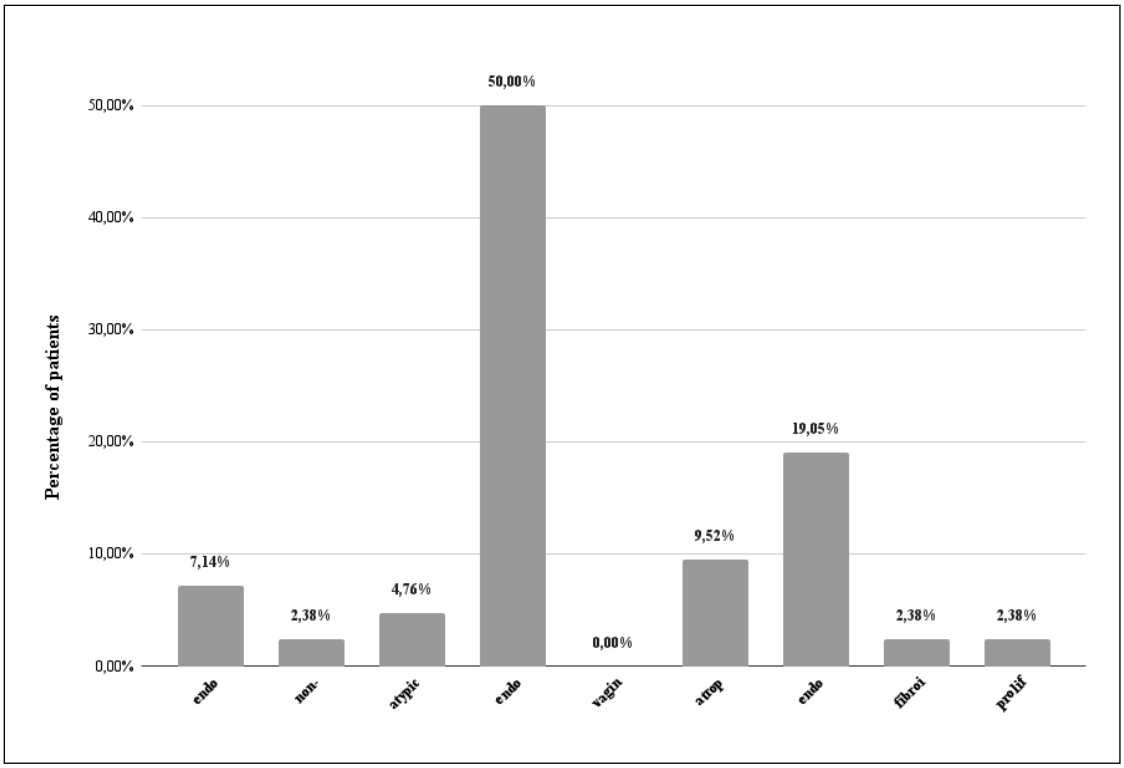

Fig. 1. Histopathological alternations in Group I
Source: compiled by the authors of this study

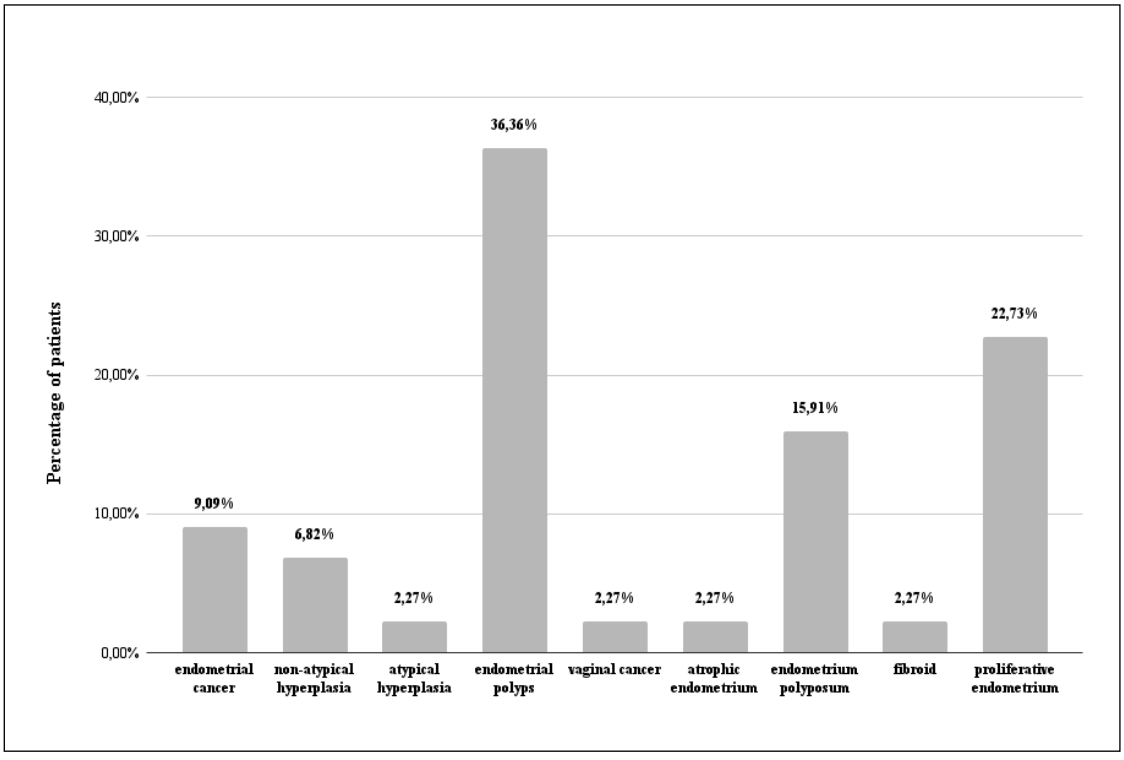

Fig. 2. Histopathological alternations in Group II
Source: compiled by the authors of this study

prevalence. Interestingly, no EC cases were identified in premenopausal patients with AUB in our cohort, consistent with findings by Taponeco et al. [14].

Non-atypical and atypical hyperplasia are other notable pathologies. Cohen et al. reported a time-dependent increase in hyperplasia rates in tamoxifen users [13]. In our cohort, non-atypical hyperplasia was identified in 2.38% of group I and 6.82% of group II patients, while atypical hyperplasia was found in 4.76% of group I and 2.27% of group II patients. These results are within expected ranges but highlight a slight increase in non-atypical hyperplasia in group II, potentially due to longer tamoxifen exposure.

Some cases in our study presented diagnostic challenges.

Given the high prevalence of tamoxifen-associated uterine pathologies, further studies are needed to

refine diagnostic criteria and management strategies. Future research should focus on stratifying risk factors and evaluating alternative therapies to mitigate these adverse effects while maintaining tamoxifen's efficacy.

In the latest NCCN Clinical Practice Guidelines in Oncology for Uterine Neoplasms (Version 1.2025), tamoxifen use is highlighted as a risk factor for uterine neoplasms, alongside increased estrogen levels due to obesity, diabetes, and high-fat diet; early age at menarche; nulliparity; late age at menopause; Lynch syndrome; and ages between 55 and 64 years . These guidelines recommend hormonal therapy predominantly for lower-grade endometrioid histologies, especially in patients with small tumor volume or indolent growth [16].

Tamoxifen is also listed among other recommended regimens for hormonal therapy in recurrent or metastatic endometrial carcinoma. It is used alone or in combination with megestrol acetate as an alternating regimen [17].

CONCLUSIONS

While this study confirms endometrial polyps as the most frequent pathology in tamoxifen-treated patients, it critically highlights the need for targeted research focusing on population-specific factors (especially within the Polish population), menopausal status, and the role of BMI. Developing clear, personalized clinical guidelines for screening and surveillance, particularly for premenopausal women, is essential to optimize the early detection of serious pathologies, independent of symptomatic presentation.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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