Hong Kong J Gynaecol Obstet Midwifery 2022;22(2):107-13 | https://doi.org/10.12809/hkjgom.22.2.02

Risk factors for endometrial pathology in women with breast cancer and tamoxifen treatment

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Objectives: To identify risk factors for development of endometrial pathology in both premenopausal and postmenopausal women who received tamoxifen treatment for breast cancer.
Methods: Medical records of women who had breast cancer and tamoxifen treatment and received endometrial sampling at Queen Elizabeth Hospital between 1 January 2017 and 31 December 2020 were retrospectively reviewed. Histology of the endometrial tissue was classified as normal, endometrial polyp, endometrial hyperplasia (with or without atypia), and endometrial cancer. Women with normal endometrium were compared with women with endometrial cancer/hyperplasia or women with endometrial polyp. Risk factors of endometrial pathology were identified through univariate and multivariate analyses.
Results: 249 women (mean age, 50.8 years) were included. Of 249 endometrial samplings, 169 (67.9%) showed normal endometrium, 71 (28.5%) showed endometrial polyp, 5 (2.0%) showed endometrial hyperplasia, and 4 (1.6%) showed endometrial cancer. In univariate analysis, endometrial cancer/hyperplasia was associated with lower parity, longer duration of menopause, longer duration of breast cancer diagnosis, longer duration of tamoxifen treatment, completion of tamoxifen therapy, longer duration of tamoxifen cessation, endometrial thickness of ≥5 mm, and endometrial thickness of ≥9 mm, whereas endometrial polyp was associated with older age, postmenopausal status, abnormal endometrium on ultrasound, endometrial thickness of ≥5 mm, and endometrial thickness of ≥9 mm. In multivariate analysis, risk factors for endometrial cancer/hyperplasia were nulliparity (odds ratio [OR]=8.7, p=0.035), duration of breast cancer diagnosis >10 years (OR=11.6, p=0.019), and endometrial thickness ≥9 mm (OR=11.9, p=0.031), whereas the risk factor for endometrial polyp was endometrial thickness ≥9 mm (OR=5.3, p<0.001).
Conclusion: In women who had breast cancer and tamoxifen treatment, nulliparity, a history of breast cancer >10 years earlier, and endometrium thickness of ≥9 mm are independent risk factors for endometrial cancer/hyperplasia. Early hysteroscopic assessment should be arranged for these patients, especially when they presented with abnormal uterine bleeding.

Keywords: Breast neoplasms; Endometrial hyperplasia; Endometrial neoplasms; Tamoxifen

Introduction

Tamoxifen is the most-prescribed adjuvant treatment for oestrogen-receptor-positive breast cancer, as it reduces the risk of contralateral breast cancer and prevents tumour recurrence. Compared with the traditional 5-year regimen, the 10-year extended regimen has higher efficacy in improving both disease-free and overall survival[1,2]. However, breast cancer survivors are at risk of developing tamoxifen-induced endometrial malignancy. Being a selective oestrogen receptor modulator, tamoxifen has modest oestrogenic activity on the endometrium. Uterine pathologies including polyps, hyperplasia, and endometrial cancer are found in 30% to 40% of tamoxifen-treated women[3-7]. Changes develop in a dose- and time-dependent manner and last several years beyond drug cessation[7]. Therefore, tamoxifen-treated women remain at an increased risk of endometrial proliferation, even after completion of the treatment. The International Agency for Research on Cancer[8] labels tamoxifen as a carcinogen owing to the causal relationship between the drug and endometrial cancer, with the relative risk two to three times higher than that of an age-matched population[9,10].

According to the American College of Obstetricians and Gynaecologists[11], there are potential benefits in identifying postmenopausal women who have endometrial polyps before tamoxifen initiation[12,13]. However, for low-risk tamoxifen users, routine endometrial surveillance is not cost-effective and thus not recommended. Nevertheless, endometrial pathologies can arise, especially in those who received the 10-year extended regimen for high-risk breast cancer[14]. Therefore, it is important to identify other clinical predictors for endometrial pathologies so that an optimal surveillance plan can be formulated. Lower parity, increased

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endometrial thickness, and the presence of abnormal vaginal bleeding have been reported to be associated with the development of endometrial hyperplasia and cancer[4,6,15-17]. However, multivariate analysis was not performed in these studies, and only one study focused on premenopausal women treated with tamoxifen. This study aims to identify risk factors for development of endometrial pathology in both premenopausal and postmenopausal women who received tamoxifen treatment for breast cancer.

Materials and Methods

This study was approved by the Kowloon Central/ Kowloon East Cluster Research Ethics Committee (reference: KC/KE-21-0218/ER-1). Medical records of women who had breast cancer and tamoxifen treatment and received endometrial sampling (including endometrial aspirate and uterine curetting) at Queen Elizabeth Hospital between 1 January 2017 and 31 December 2020 were retrospectively reviewed through the Clinical Data Analysis and Reporting System. Women were excluded if they had tamoxifen treatment for <3 months, unclear treatment duration, incomplete clinical data, inadequate sampling for histological diagnosis, or metastatic cancer to the uterus. Repeat sampling was performed in those with inadequate sampling, and the final endometrial sample was used for analysis.

As there was no pretreatment screening or regular gynaecological surveillance for endometrial pathology for these women, ultrasound scanning (preferably transvaginal) and endometrial sampling were offered only to those with symptoms (abnormal vaginal bleeding and/ or endometrium). Endometrial thickness was measured on the sagittal plane of the uterus, from the anterior basalis to the posterior basalis of the endometrial surfaces. An abnormal endometrium was defined as one with an endometrial thickness >4 mm in postmenopausal users, or ultrasound features suggestive of endometrial lesions such as polyps or tumours. Endometrial sampling was obtained through Pipelle aspiration or uterine curettage. Hysteroscopic evaluation was offered to women who could not tolerate bedside endometrial aspiration, had suspicious endometrial lesions on ultrasound scan, or had persistent vaginal bleeding. Women with normal endometrium and subsided symptoms were discharged and advised to seek early medical attention if symptoms recur.

Demographic data collected were age, parity, body weight and height, menopausal status (menopause is defined as amenorrhea for at least 12 months, combined with the postmenopausal range of serum oestradiol levels in women on tamoxifen[18]), medical history, and family history of cancer. Breast cancer data collected were cancer duration, treatment modality, tamoxifen treatment duration and status, and duration of tamoxifen cessation (if applicable). Clinical data collected were the presence of abnormal vaginal bleeding and endometrial thickness. Histology of the endometrial tissue was classified as normal, endometrial polyp, endometrial hyperplasia (with or without atypia), and endometrial cancer.

Statistical analysis was performed using SPSS (Windows version 26; IBM Corp, Armonk [NY], US). Women with normal endometrium were compared with women with endometrial cancer/hyperplasia or women with endometrial polyp using the Mann-Whitney *U* test for continuous variables and the Chi-square test or Fisher exact test for categorical data. Multivariate analysis was performed to identify risk factors for endometrial cancer/ hyperplasia and endometrial polyp. A p value of <0.05 was considered statistically significant.

Results

Of 268 women recruited, 19 were excluded who had <3 months of tamoxifen treatment (n=9), incomplete clinical data (n=1), insufficient endometrial tissue for histological diagnosis (n=3), or metastatic cancer to the uterus (n=6). The remaining 249 were included for analysis (Table 1). None of the 249 women (mean age, 50.8 years) had received a pre-tamoxifen assessment for uterine pathology before drug initiation. 140 (56.2%) were menopausal, with 43.6% of them having chemotherapy-induced amenorrhea. The mean duration of breast cancer diagnosis was 4.7 years; 205 (81.4%) had stage I or II cancer. 67.9% and 75.1% received chemotherapy and radiotherapy, respectively. The mean duration of tamoxifen use was 41.0 months; 181 (72.7%) were on active tamoxifen treatment at the time of endometrial biopsy. The mean endometrial thickness was 8.3 mm. 77.5% had abnormal vaginal bleeding, and 38.6% had abnormal endometrium on ultrasound scan.

Indications for endometrial sampling included abnormal vaginal bleeding (n=151, 60.6%), abnormal endometrium on ultrasound scans (n=54, 21.7%), both (n=42, 16.9%), and other reasons (n=2, 0.8%). Two patients received an endometrial biopsy owing to non-specific fluorodeoxyglucose uptakes in the endometrium on positron emission tomography–computed tomography (n=1) or the presence of atypical glandular cells, not otherwise specified, on a routine cervical smear test (n=1).

Table 1. Clinical characteristics of 249 women who had breast cancer and received tamoxifen

Variable	Value*
Age at biopsy, y	50.8±8.4
No. of parity	1.1±1.0
Body mass index, kg/m^2	24.2±4.1
Menopause	140 (56.2)
Chemotherapy-induced amenorrhea	61 (43.6)
Age at menopause, y	49.1±4.1
Duration of menopause, y	6.2 ±6.3
Diabetes mellitus	19 (7.6)
Smoking	6 (2.4)
History of breast/ gynaecological cancers in 1st degree relatives	37 (14.9)
Stage of breast cancer	
I	111 (43.6)
II	94 (37.8)
III	37 (14.9)
IV	7 (2.8)
Duration of breast cancer diagnosis, y	4.7±3.8
Duration of tamoxifen treatment, months	41.0±27.0
Actively on tamoxifen treatment	181 (72.7)
Completed tamoxifen treatment	68 (27.3)
Duration since cessation, months	38.0±43.5
History of chemotherapy	169 (67.9)
History of radiotherapy	187 (75.1)
Endometrial thickness, mm	8.3±6.3
Abnormal vaginal bleeding	193 (77.5)
Abnormal endometrium on ultrasound	96 (38.6)

* Data are presented as mean ± standard deviation or No. (%) of participants

Of 249 endometrial samplings, 169 (67.9%) showed normal endometrium, 71 (28.5%) showed endometrial polyp, 5 (2.0%) showed endometrial hyperplasia, and 4 (1.6%) showed endometrial cancer. The four patients with endometrial cancer did not have any pre-existing endometrial pathology; all presented with postmenopausal bleeding and thickened endometrium (mean, 15 mm). Two of them had stage I endometrioid adenocarcinoma after 5 years of tamoxifen therapy. One had stage IIIC high-grade adenocarcinoma with mixed endometrioid, serous, and clear cell components. She received extended tamoxifen adjuvant therapy and developed postmenopausal bleeding at the 9th year of drug use. The remaining one had stage I malignant mixed mesodermal tumour of the uterus after 5 years of tamoxifen treatment. She underwent cancer surgery and adjuvant radiotherapy. However, she had pulmonary and pleural metastasis (uterine origin) 2 years later and died 2 more years later. All five women with endometrial hyperplasia had abnormal vaginal bleeding (postmenopausal bleeding or menorrhagia) and thickened endometrium (9-24 mm). Three had complex hyperplasia without atypia, one had simple hyperplasia without atypia, and one had hyperplasia with focal atypia. Histological examinations confirmed that all cases of hyperplasia without atypia were developed from endometrial polyps.

Compared with women with normal endometrium, women with endometrial cancer/hyperplasia were associated with lower parity (0.4 vs 1.1, p=0.026), longer duration of menopause (10.4 vs 5.5 years, p=0.016), longer duration of breast cancer diagnosis (9.9 vs 4.3 years, p=0.002), longer duration of tamoxifen treatment (58.0 vs 38.5 months, p=0.017), completion of tamoxifen therapy (66.7% vs 23.7%, p=0.010), longer duration of tamoxifen cessation (89.9 vs 31.8 months, p=0.021), endometrial thickness of ≥5 mm (100% vs 59.2%, p=0.013), and endometrial thickness of ≥9 mm (88.9% vs 27.2%, p<0.001) [Table 2]. Compared with women with normal endometrium, women with endometrial polyp were associated with older age (52.7 vs 49.9 years, p=0.027), postmenopausal status (67.6% vs 51.5%, p=0.022), abnormal endometrium on ultrasound (56.3% vs 31.4%, p<0.001), endometrial thickness of ≥5 mm (81.7% vs 59.2%, p=0.001), and endometrial thickness of ≥9 mm (64.8% vs 27.2%, p<0.001) [Table 2].

In multivariate analysis, risk factors for endometrial cancer/hyperplasia were nulliparity (odds ratio [OR]=8.7, p=0.035), duration of breast cancer diagnosis >10 years (OR=11.6, p=0.019), and endometrial thickness ≥9 mm (OR=11.9, p=0.031), whereas the risk factor for endometrial polyp was endometrial thickness ≥9 mm (OR=5.3, p<0.001) [Table 3].

Discussion

In the present study, nulliparity was associated with 8.7-fold higher risk of developing endometrial pathology in tamoxifen users. It is believed that the elevated progesterone level during pregnancy protects against endometrial cancer through inhibition of the oestrogen-driven endometrial cell proliferation. The postpartum involution of the uterus also helps in shedding the premalignant lesions[19]. As tamoxifen activates the oestrogenic receptors and stimulates endometrial proliferation, nulliparous users are more susceptible to developing pathologies such as cancer and hyperplasia.

Table 2. Women with normal endometrium versus women with endometrial cancer/hyperplasia versus women with endometrial polyp

Variable	Normal endometrium (n=169)*	Endometrial cancer/ hyperplasia (n=9)*	P value	Endometrial polyp (n=71)*	P value
Age at biopsy, y	49.9±8.1	52.9±10.6	0.511	52.7±8.6	**0.027**
No. of parity	1.1±0.9	0.4±0.9	**0.026**	1.2±1.3	0.721
Body mass index, kg/m^2	24.1±4.0	23.8±7.0	0.198	24.4±3.8	0.687
Menopause	87 (51.5)	5 (55.6)	1.000	48 (67.6)	**0.022**
Chemotherapy-induced amenorrhea	34 (39.1)	2 (40)	1.000	25 (52.1)	0.145
Age at menopause, y	49.1±4.2	50±3.7	0.539	49.0±4.1	0.761
Duration of menopause, y	5.5±5.5	10.4±4.7	**0.016**	7.2±7.5	0.115
Diabetes mellitus	12 (7.1)	1 (11.1)	0.503	6 (8.5)	0.925
Smoking	3 (1.8)	0 (0)	1.000	3 (4.2)	0.365
History of breast/ gynaecological cancers in 1st degree relatives	21 (12.4)	3 (33.3)	0.105	13 (18.3)	0.233
Duration of breast cancer diagnosis, y	4.3±3.4	9.9±5.2	**0.002**	5.2±3.9	0.073
Duration of tamoxifen treatment, months	38.5±25.9	58.0±23.9	**0.017**	44.7±28.9	0.109
Actively on tamoxifen treatment	129 (76.3)	3 (33.3)	**0.010**	49 (69.0)	0.237
Completed tamoxifen treatment	40 (23.7)	6 (66.7)	**0.010**	22 (31.0)	0.237
Duration since tamoxifen cessation, months	31.8±38.9	89.9±45.8	**0.021**	35.4±43.4	0.926
History of chemotherapy	110 (65.1)	7 (77.8)	0.720	52 (73.2)	0.219
History of radiotherapy	123 (72.8)	8 (88.9)	0.448	56 (78.9)	0.322
Endometrial thickness ≥ 5mm	100 (59.2)	9 (100)	**0.013**	58 (81.7)	**0.001**
Endometrial thickness ≥ 9mm	46 (27.2)	8 (88.9)	**<0.001**	46 (64.8)	**<0.001**
Abnormal vaginal bleeding	134 (79.3)	9 (100)	0.208	50 (70.4)	0.138
Abnormal endometrium on ultrasound	53 (31.4)	3 (33.3)	1.000	40 (56.3)	**<0.001**

* Data are presented as mean ± standard deviation or No. (%) of participants

Table 3. Risk factors for endometrial cancer/hyperplasia and endometrial polyp in women with breast cancer treated with tamoxifen

	Odds ratio (95% confidence interval)	P value
Endometrial cancer/ hyperplasia		
Nulliparous	8.687 (1.162-64.950)	**0.035**
Duration of menopause	1.242 (0.748-2.062)	0.403
Duration of breast cancer diagnosis ≥10 years	11.594 (1.502-89.473)	**0.019**
Duration of tamoxifen	0.999 (0.963-1.036)	0.953
Completed tamoxifen treatment	2.483 (0.317-19.419)	0.386
Duration since tamoxifen cessation, months	0.991 (0.760-1.294)	0.950
Endometrial thickness ≥9 mm	11.935 (1.257-113.293)	**0.031**
Endometrial polyp		
Age >50 years	1.815 (0.901-3.658)	0.905
Menopaused	1.413 (0.704-2.839)	0.331
Abnormal endometrium on ultrasound	1.017 (0.530-1.949)	0.960
Endometrial thickness ≥9 mm	5.313 (2.605-10.839)	**< 0.001**

In the present study, tamoxifen users who had a history of breast cancer >10 years earlier had an 11.6-fold increased risk of endometrial pathology. Breast cancer survivors are at a higher risk of developing uterine malignancy, compared with the general population[4,20-22], because breast cancer and endometrial cancer share similar risk-factor profiles such as obesity and older age[4]. Endometrial neoplastic changes are more likely to occur in those with a longer history of breast cancer.

Tamoxifen induces cystic changes and subepithelial stromal hypertrophy[23-25]. After a year of tamoxifen treatment, ≥80% of women have an endometrial thickness ≥5 mm[26,27]. In the present study, an endometrial thickness of ≥9 mm was a risk factor of both endometrial cancer/hyperplasia and endometrial polyp in tamoxifen-treated women. This finding is consistent with that in previous studies[4,28,29]. Early hysteroscopic assessment should be arranged for these women.

According to the Early Breast Cancer Trialists Collaborative Group[30], the incidence of endometrial cancer quadrupled after 5 years of tamoxifen treatment. However, in the present study, a longer duration of tamoxifen treatment was not associated with endometrial cancer/hyperplasia in the multivariate analysis. Further study is warranted to clarify the association between tamoxifen duration and pathological endometrial lesions.

Although the endometrial thickness reduces significantly after discontinuation of tamoxifen treatment[31], we cannot conclude that this change represents a reversal of abnormal endometrial stimulation. Women with breast cancer should be aware of escalating endometrial proliferation over time even after discontinuation of tamoxifen, because the effect of tamoxifen can last several years beyond drug cessation[7,9].

Tamoxifen-related polyps have a higher rate of cancerous change at 3.0% to 10.7%[3,5-7,25,32]. However, only about 50.0% of patients with endometrial polyps are symptomatic before malignant transformation[7,33]. The present study showed that older age and menopausal status were associated with the development of endometrial polyp, but the association was not significant in the multivariate analysis. Larger scale studies are needed to identify the independent risk factors of polyp formation to aid early detection and treatment.

International guidelines are of the consensus that regular surveillance for low-risk tamoxifen users is not recommended[11,34], as their overall cancer prevalence is low, and universal screening substantially increases healthcare costs. However, endometrial cancer in women treated with tamoxifen tends to be less favourable subtypes with poorer prognosis[6,7,9,35,36]. In the present study, 50% of patients had more aggressive tumour cell types (high-grade adenocarcinoma and malignant mixed mesodermal tumour). The presence of postmenopausal bleeding was the primary trigger for these women to seek gynaecological opinion[10]. Therefore, it is important to identify the risk factors for endometrial pathology in tamoxifen users so that early endometrial screening can be provided to improve the overall cancer prognosis. Large-scale multicentre randomised trials can be conducted to assess the cost-effectiveness of selected screening.

There are several limitations to the present study. Patient selection may be biased, as patients presented to our clinic were symptomatic with abnormal vaginal bleeding or abnormal endometrium, and the decisions on performing endometrial sampling vary among medical practitioners. In addition, the sample size is small and of a single centre. However, the prevalence of endometrial cancer over the 4-year study period (1.6%) is similar to the 1.9 per 1000 women per year reported by the Early Breast Cancer Trialists' Collaborative Group[37]. Large-scale multicentre randomised controlled trials are needed to address the potential small number variations effect.

Conclusion

In women who had breast cancer and tamoxifen treatment, nulliparity, a history of breast cancer >10 years earlier, and endometrium thickness of ≥9 mm are independent risk factors for endometrial cancer/hyperplasia. Early hysteroscopic assessment should be arranged for these patients, especially when they presented with abnormal uterine bleeding.

Contributor

The author designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. The author had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

The author has disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any

funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Kowloon Central/ Kowloon East Cluster Research Ethics Committee (reference: KC/KE-21-0218/ER-1). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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