

Cervical HPV Prevalence in Breast Cancer Patients on Tamoxifen Maintenance Therapy

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ABSTRACT

This study aimed to analyze cervical smear results and determine the prevalence of HPV in women using tamoxifen for breast cancer. This single-center retrospective study included patients using tamoxifen for breast cancer **who had undergone cervical smear sampling with HPV testing** at Ondokuz Mayıs University Faculty of Medicine Hospital between February 2015 and March 2022. Statistical analyses were performed using non-parametric statistical tests (Kruskal-Wallis and Dunn tests). Quantitative data were analyzed with SPSS.

Of 252 breast cancer patients **who underwent cervical smear sampling with HPV testing**, 199 met the inclusion criteria. Oncogenic HPV positivity was detected in 12 patients (6.03%). Normal cytology was found in 158 patients (79.4%), while abnormal results included ASC-US in 29 (14.6%), ASC-H in 7 (3.5%), LSIL in 3 (1.5%), and AGC-NOS in 2 (1.0%). Among 105 patients (52.8%) who had endometrial sampling, 60 (30.2%) had endometrial polyps. The mean endometrial thickness in those with polyps was 12.75 ± 6.37 mm. The most common comorbidity was thyroid disease, found in 28.8% of patients.

The prevalence of cervical HPV in women using tamoxifen for breast cancer was 6.03%. Endometrial polyps were the most common endometrial pathology among patients who underwent sampling. Although further studies are needed, women using tamoxifen may benefit from appropriate counseling regarding cervical and endometrial follow-up, as well as primary and secondary preventive strategies.

Keywords: cervical cancer, cervical smear, breast cancer, tamoxifen, HPV DNA

Introduction

The 2020 Global Cancer Statistics reports that, among 36 cancer types in 185 countries, breast and cervical cancers are the most commonly diagnosed in women: breast cancer in 159 countries, and cervical cancer in 23 of the remaining 26 (1). These two cancers are also leading causes of cancer-related death in 110 and 36 countries, respectively, and both are major cancers included in our national screening programs.

The most important etiologic factor in the development of cervical cancer is human papillomavirus (HPV) infection. HPV has been reported in 99.7% of cases of invasive cervical cancer (2). Approximately 84% of sexually active women are estimated to encounter HPV by 45 years of age (3). However, most HPV infections are transient. In a 2-year prospective study of HPV-infected women with ASC-US or LSIL, 91% of infections cleared within 24 months (4). In the same study, the probability that a newly detected infection would persist for another 6 months was

37%, whereas this rate increased to 65% for infections persisting for 18 months or longer. Precancerous lesions typically develop within 5-10 years in fewer than 10% of new infections, whereas invasive cancer develops over many years, or even decades, in a minority of women with precancer, with risk peaking at approximately 35-55 years of age (4,5). Because of this natural history, cervical cancer is considered a largely preventable malignancy through effective primary and secondary prevention strategies (1). Nevertheless, due to inequalities in access to HPV vaccination, inadequate cervical screening programs, and disparities in access to treatment services, cervical cancer remains the second leading cause of cancer-related death among women aged 20-39 years worldwide (6).

Breast cancer is the most common malignancy in women. Hormone receptor-positive tumors make up 75%-80% of cases (7). Tamoxifen is a nonsteroidal selective estrogen receptor modulator. It is used in adjuvant endocrine treatment of estrogen receptor- or progesterone receptor-positive breast cancer, especially in

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premenopausal and some postmenopausal patients (8). Tamoxifen acts as an antiestrogen in breast tissue, but may act as an agonist or antagonist in different genital tract tissues. Its effects on the endometrium are well studied. Tamoxifen is linked to endometrial polyps, hyperplasia, and malignancy in many studies. However, evidence on its effects in the cervix is limited, mainly focusing on benign squamous atypia or cytologic changes (9,10). While its endometrial effects are clear, its influence on cervical cytology and HPV prevalence is not.

The E6 and E7 oncoproteins of high-risk HPV types play a central role in the malignant transformation of cervical epithelial cells (11). In addition, long-term oral contraceptive use has previously been reported as a risk factor for cervical cancer (12,13). Experimental studies have demonstrated that continuous estrogenic stimulation promotes neoplastic progression in the cervical and vaginal epithelia of HPV16- and HPV18-E6/E7 transgenic models (11,14). Similarly, the growth-promoting effect of estrogen in cervical cancer cells has been reported to be associated with increased HPV E6/E7 expression (15). In one experimental study investigating the relationship between tamoxifen and cervical HPV, tamoxifen was shown to stimulate cell proliferation in cervical cancer cells, which may be associated with increased HPV16 mRNA and E7 protein levels (16). These findings suggest that tamoxifen's effects on cervical epithelium and HPV-related biological processes warrant clinical investigation.

Clinical studies on tamoxifen's cervical effects and HPV prevalence in users are limited. Population-level cervical screening data exist for our country, but little is known about women with breast cancer taking tamoxifen. Building on the work of Fotiou et al., who examined hysterectomy specimens from tamoxifen users, we evaluated women with breast cancer who had used tamoxifen for at least 5 months (17). Our main aims were to assess cervical smear results and HPV prevalence, and to describe endometrial findings and comorbidities. These findings may inform gynecologic follow-up and prevention strategies.

Materials and Methods

This retrospective single-center study included patients with breast cancer who were using tamoxifen and underwent HPV DNA testing during cervical screening at Ondokuz Mayıs

University Faculty of Medicine between February 2015 and March 2022. Ethical approval was obtained from the Ondokuz Mayıs University Clinical Research Ethics Committee (July 5, 2022; approval number OMU KAEK 2022/311). Patient data were retrieved retrospectively from archived records at the Department of Obstetrics and Gynecology.

We reviewed the archives and assessed 252 breast cancer cases. Of these, 199 met the inclusion criteria. Inclusion criteria were female sex, breast cancer diagnosis, no history of hysterectomy, use of tamoxifen for at least 6 months, and availability of HPV DNA testing at the time of smear screening. Exclusion criteria were tamoxifen use for 5 months or less and a history of hysterectomy.

Cervical cytology samples were obtained from the cervix using liquid-based thin-layer cytology (ThinPrep). Cytologic evaluation was performed according to the Bethesda system, and results were classified as normal, ASC-US, ASC-H, AGC-NOS, LSIL, and HSIL. HPV DNA genotyping was performed using real-time PCR with the Cobas 4800 HPV test on the Roche Cobas 4800 system. HPV DNA genotyping results were reported from the same cervical specimen. HPV types were grouped as HPV 16, HPV 18, and other high-risk types [31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68].

The following variables were recorded: age at breast cancer diagnosis, gravida, parity, comorbid diseases, stage of breast cancer, histologic type, hormone receptor status, receipt of chemotherapy and radiotherapy, duration of tamoxifen use, endometrial thickness, and histopathologic diagnosis if endometrial sampling had been performed. Endometrial thickness was evaluated based on measurements obtained by transvaginal or transabdominal ultrasonography. When sonographic findings warranted further assessment, endometrial sampling was performed using a pipelle biopsy or curettage.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. Quantitative data are presented as mean $\pm$ standard deviation and median (minimum-maximum), whereas categorical data are presented as number and percentage. The Kruskal-Wallis test was used to compare endometrial thickness according to endometrial sampling results, and multiple comparisons were performed using Dunn's test. A p-value of <0.05 was considered statistically significant.

Results

A total of 199 patients with breast cancer who had been using tamoxifen for at least 6 months and had undergone HPV DNA testing during cervical screening were included in the study. Of the 252 cases identified through archive review, 199 met the inclusion criteria. The mean age at breast cancer diagnosis was 46.8 ± 8.8 years, the median parity was 2 (0-8), and the median duration of tamoxifen use was 27 months (6–72) (Table 1).

When cervical cytology and HPV DNA results were evaluated, cytology was normal in 158 (79.4%) patients. Abnormal cytologic findings were ASC-US in 29 (14.6%) patients, ASC-H in 7 (3.5%), LSIL in 3 (1.5%), and AGC-NOS in 2 (1.0%). According to HPV DNA results, 12 (6.03%) patients were HPV positive and 187 (94.0%) were HPV negative. Regarding HPV type distribution among HPV-positive cases, other high-risk HPV types were detected in 9 (75.0%) patients, and HPV 16 in 3 (25.0%) patients, whereas HPV 18 was not detected (Table 2).

Regarding endometrial evaluation, endometrial sampling was performed in 105 of 199 patients (52.8%), whereas it was not performed in 94 of 199 patients (47.2%). Among the patients who underwent endometrial sampling, endometrial polyps were detected in 60 (57.1%) patients, other benign findings in 43 (41.0%) patients, and malignant findings in 2 (1.9%) patients. Overall, benign findings were identified in 103 (98.1%) patients, whereas malignant findings were detected in 2 (1.9%) patients. The benign group included endometrial polyps in 60 (57.1%) patients, benign endometrial findings in 38 (36.2%) patients, endocervical polyps in 3 (2.9%) patients, and non-atypical endometrial hyperplasia in 2 (1.9%) patients. The malignant group included polyp-associated mucinous carcinoma in 1 (0.95%) patient and low-grade endometrioid carcinoma in 1 (0.95%) patient (Table 3).

When ultrasonographic endometrial thickness measurements were evaluated, the mean endometrial thickness was 4.06 ± 1.97 mm in patients who did not undergo endometrial sampling, 12.75 ± 6.37 mm in patients with endometrial polyps, and 9.06 ± 3.88 mm in patients with benign histopathologic findings. Endometrial thickness differed significantly according to endometrial sampling results (Kruskal-Wallis $H = 78.12$, $p < 0.001$). Multiple comparisons showed that this difference was attributable to the non-sampled group compared

with the endometrial polyp and benign histopathology groups (Table 4).

When histologic subtypes of breast cancer were examined, the most common histologic type was invasive ductal carcinoma in 167 (83.9%) patients. This was followed by ductal carcinoma in situ in 13 (6.5%) patients, invasive lobular carcinoma in 12 (6.03%) patients, mucinous carcinoma in 4 (2.0%) patients, lobular carcinoma in situ in 2 (1.0%) patients, and mixed invasive carcinoma in 1 (0.5%) patient. In terms of stage distribution, the most common stage was stage 1A in 71 (35.7%) patients, followed by stage 2A in 56 (28.1%) patients, stage 2B in 26 (13.1%) patients, stage 3A in 28 (14.1%) patients, stage 3B in 4 (2.0%) patients, and stage 4 in 5 (2.5%) patients; stage information was unavailable in 9 (4.5%) patients. Regarding hormone receptor status, estrogen receptor positivity was present in 193 (98.5%) patients and progesterone receptor positivity in 173 (88.3%) patients. HER2 positivity was detected in 44 (23.0%) patients. Chemotherapy had been administered to 175 (87.9%) patients, and radiotherapy to 165 (82.9%) patients. Smoking was reported in 8 (4.0%) patients (Table 1).

Among the 170 patients with available comorbidity data (data were missing for 29 patients), 107 (62.9%, 107/170) had at least 1 comorbid disease. The most common comorbid disease group was thyroid disease, including hypothyroidism and hyperthyroidism, observed in 49 (28.8%, 49/170) patients, followed by hypertension in 38 (22.4%, 38/170) patients. Diabetes mellitus was present in 21 (12.4%, 21/170) patients, asthma in 9 (5.3%, 9/170) patients, migraine in 6 (3.5%, 6/170) patients, and arrhythmia in 4 (2.4%, 4/170) patients. Hyperlipidemia and chronic kidney disease were each observed in 2 (1.2%) patients, whereas varicose veins, HIV positivity, depressive disorder, ulcerative colitis, bronchiectasis, uveitis, Behcet disease, gastric cancer, fibromyalgia, panic attacks, and deep vein thrombosis were observed at lower frequencies (Table 1).

Discussion

In this retrospective single-center study, cervical smear results, HPV prevalence, endometrial findings, and comorbid diseases were evaluated in patients using tamoxifen for breast cancer. The main findings of the study were an HPV DNA positivity rate of 6.03%, normal cytology in 79.4% of patients, abnormal cytology in 20.7%,

Table 1: Baseline Demographic and Clinicopathologic Characteristics of the Study Population

Variable	Value, mean $\pm$ SD or median (min-max) or n (%)
Age at breast cancer diagnosis, years, mean $\pm$ SD	46.8 $\pm$ 8.8
Parity, median (min-max)	2 (0-8)
Duration of tamoxifen use, months, median (min-max)	27 (6-72)
Histologic subtype n(%)	
Invasive ductal carcinoma	167 (83.9%)
Ductal carcinoma in situ	13 (6.5%)
Invasive lobular carcinoma	12 (6.0%)
Mucinous carcinoma	4 (2.0%)
Lobular carcinoma in situ	2 (1.0%)
Mixed invasive carcinoma	1 (0.5%)
Stage n(%)	
1A	71 (35.7%)
2A	56 (28.1%)
2B	26 (13.1%)
3A	28 (14.1%)
3B	4 (2.0%)
4	5 (2.5%)
Unknown	9 (4.5%)
Hormone receptor status n(%)	
Estrogen receptor positive	193 (98.5%)
Progesterone receptor positive	173 (88.3%)
HER2 positive	44 (23.0%)
Chemotherapy	175 (87.9%)
Radiotherapy	165 (82.9%)
Comorbidities n(%)	
At least 1 comorbid disease (n=170***)	107/170 (62.9%)
Thyroid disease*	49/170 (28.8%)
Hypertension	38/170 (22.4%)
Diabetes mellitus	21/170 (12.4%)
Other comorbidities**	Reported at lower frequencies
n (%) Smoking	8 (4.0 %)

* Includes hypothyroidism and hyperthyroidism.

** Includes asthma, migraine, arrhythmia, hyperlipidemia, chronic kidney disease, varicose veins, HIV positivity, depressive disorder, ulcerative colitis, bronchiectasis, uveitis, Behcet disease, gastric cancer, fibromyalgia, panic attacks, and deep vein thrombosis. Multiple responses were possible.

***Comorbidity data were unavailable for 29 of 199 patients; percentages for comorbidities are calculated among the 170 patients with available data

endometrial polyps as the most common endometrial lesion, and thyroid diseases as the most frequent comorbidity. A distinguishing feature of our study is that, in addition to cervical cytologic findings, HPV results were also evaluated in patients receiving tamoxifen.

The primary finding of our study, HPV DNA positivity, is notable when compared with the large-scale study evaluating 4,099,230 women

screened within the HPV DNA-based cervical cancer screening program in Turkey. In that study, HPV DNA positivity was 4.39%, and cytology results were 69.2% normal, 16.6% inadequate sampling, and 14.2% abnormal ($\geq$ ASC-US). In our study, HPV DNA positivity was 6.03%, normal cytology was 79.4%, and abnormal cytology was 20.7%. A one-sample proportion test comparing the observed HPV positivity rate with the national

Table 2: Cervical Cytology and HPV DNA Results

Variable	n (%)
Cervical cytology	
Normal	158 (79.4%)
ASC-US	29 (14.6%)
ASC-H	7 (3.5%)
LSIL	3 (1.5%)
AGC-NOS	2 (1.0%)
HPV DNA result	
Positive	12 (6.0%)
Negative	187 (94.0%)
HPV genotype among HPV-positive patients (n=12)	
HPV 16	3 (25.0%)
HPV 18	0 (0.0%)
Other high-risk HPV types*	9 (75.0%)

*Other high-risk HPV types included HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Table 3: Endometrial Sampling and Histopathologic Findings

Variable	n (%)
Endometrial sampling performed	105 (52.8%)
No endometrial sampling	94 (47.2%)
Findings among patients who underwent endometrial sampling (n=105)	
Endometrial polyp	60 (57.1%)
Other benign findings*	43 (41.0%)
Malignant findings**	2 (1.9%)
Overall classification among sampled patients (n=105)	
Benign findings	103 (98.1%)
Malignant findings	2 (1.9%)

* Other benign findings included benign endometrial findings in 38 patients, endocervical polyps in 3 patients, and non-atypical endometrial hyperplasia in 2 patients.

** Malignant findings included polyp-associated mucinous carcinoma in 1 patient and low-grade endometrioid carcinoma in 1 patient

reference rate did not show a statistically significant difference ($z = 1.13$, $p = 0.26$; 95% CI: 2.72–9.34%); therefore, although the observed rate was numerically higher, this comparison should be interpreted with caution given differences in study design and population between the two cohorts. Most abnormal cytology results consisted of ASC-US (14.6%), followed by ASC-H (3.5%), LSIL (1.5%), and AGC-NOS (1.0%). Among HPV-positive patients, 75% had high-risk types other than HPV 16 and 18, and 25% had HPV 16; no HPV 18 positivity was detected. These findings suggest that HPV prevalence and cytologic distribution in women with breast cancer using tamoxifen may differ from those of the general screening population.

However, because of the retrospective design of our study, the lack of a control group, the absence of menopausal status data, and the reporting of high-risk HPV types other than HPV 16/18 collectively, this difference cannot be directly attributed to tamoxifen use.

Experimental data regarding the effect of tamoxifen on cervical biology suggest that this relationship merits further investigation. Tamoxifen has been reported to increase cell proliferation in cervical cancer cells, which may be associated with increased HPV16 mRNA and E7 protein levels. However, these data cannot be directly interpreted at the clinical level. Our findings suggest that HPV prevalence in patients

Table 4: Endometrial Thickness According to Endometrial Findings

Variable	Mean endometrial thickness, mm (mean $\pm$ SD)
No endometrial sampling	4.06 $\pm$ 1.97
Endometrial polyp	12.75 $\pm$ 6.37
Benign histopathologic findings	9.06 $\pm$ 3.88

* Endometrial thickness differed significantly according to endometrial sampling results (Kruskal-Wallis H = 78.12, n = 197, p<0.001; epsilon-squared (ϵ^2) = 0.39, indicating a large effect size). Patients with malignant endometrial histopathology (n = 2) were excluded from this analysis due to insufficient sample size for statistical comparison.

** Multiple comparisons showed that this difference was attributable to the non-sampled group compared with the endometrial polyp and benign histopathology groups

using tamoxifen should be investigated further in future studies.

The secondary findings of our study are also consistent with the literature. The effects of tamoxifen on the endometrium have been demonstrated in numerous previous studies, particularly regarding increased risks of endometrial polyps, hyperplasia, and carcinoma. In our study, endometrial sampling was performed in 105 (52.8%) of 199 patients. Among those who underwent endometrial sampling, endometrial polyps were detected in 60 (57.1%) patients, whereas other benign findings were observed in 43 (41.0%) patients and malignant findings in 2 (1.9%) patients. In addition, the mean endometrial thickness in patients with endometrial polyps was 12.8 $\pm$ 6.4 mm, which is consistent with previous reports. These results support the importance of endometrial evaluation in patients using tamoxifen.

It is also noteworthy that thyroid diseases were the most common comorbid condition accompanying breast cancer in our study. Previous studies have suggested a possible association between breast cancer and thyroid diseases. In our series as well, thyroid diseases were the most frequent comorbid condition, with a rate of 28.8%. This finding suggests that concomitant endocrine disorders should also be taken into consideration during the follow-up of patients with breast cancer.

This study has several limitations. Its single-center retrospective design limits the generalizability of the findings. The absence of a control group, lack of menopausal status data, and inability to perform detailed HPV genotyping are the main limitations. In addition, the relatively recent nationwide implementation of HPV DNA screening and the co-testing at our center may have also limited the number of eligible patients. Nevertheless, the strengths of the study include the use of real-world data, the presentation of co-test results in a clinical patient group receiving

tamoxifen, and the simultaneous evaluation of endometrial pathologies and comorbidities, as well as cervical findings.

In conclusion, HPV DNA positivity was detected in 6.03% of women with breast cancer using tamoxifen. Although this rate appears higher than the Turkish data from the general screening population, it cannot be directly attributed to tamoxifen use due to the current study design. Nevertheless, the findings support the importance of cervical and endometrial follow-up in patients using tamoxifen. To clarify this issue more definitively, prospective, multicenter studies with appropriate control groups and known baseline HPV status before initiation of therapy are needed.

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