



# Pap Smear Results of Women with Breast Cancer Using Tamoxifen Therapy

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## Abstract

**Objective:** Our aim was to investigate the effect of tamoxifen on cervical smear of patients with breast cancer at our clinic.

**Methods:** The data of patients with breast cancer who had received tamoxifen were analyzed between 2006 and 2014, retrospectively. Pap smear results, age, gravidity, parity, smoking status, age of first birth, and detailed gynecologic and obstetric history of patients were noted. Patients who had not received at least one-year tamoxifen therapy and patients without cervicovaginal smear controls or those who left or had received interrupted tamoxifen treatment were excluded. The pap smear results of the tamoxifen and control groups were analyzed.

**Results:** A total of 246 patients (123 in the tamoxifen group and 123 in the control group) were included in this study. None of the patients had cervical squamous intraepithelial lesions and atypical glandular lesions. Atypical squamous cells were significantly higher in the tamoxifen group than in the control group ( $p=0.03$ ).

**Conclusion:** The use of tamoxifen may be associated with benign squamous atypia in cervical smears. Therefore, pelvic examination and pap smear test are recommended for breast cancer patients annually.

**Keywords:** Tamoxifen, cervical smear, atypia

## Introduction

Breast cancer is the most common type of cancer in the world (1). Similarly in Turkey, the frequency of breast cancer is 16.7 %, and it is the most prevalent cancer in women aged 45–49 years (2). For all stages of breast cancer, the first-line endocrine therapy is tamoxifen for premenopausal women (3).

Tamoxifen, a nonsteroidal partial agonist of estrogen, is well tolerated and has minimal side effects. It behaves as an antiestrogen in breast tissues, but it has proliferative effects on the endometrium (4, 5). Therefore, the endometrium of patients with breast cancer should be screened annually to rule out endometrial malignancy (6). In addition, pap smear tests are valuable for tamoxifen users for the early detection of endometrial abnormalities such as endometrial cancer or uterine sarcoma (7). Moreover, some studies have found that tamoxifen, which effects on estrogenic receptors, can lead to changes in the cervicovaginal epithelium (8, 9). Concerning the proliferative effects, Fornander et al. (10) performed.

Our aim was to investigate the effect of tamoxifen on cervicovaginal smears, particularly on the squamous epithelium) in patients with breast cancer at our clinic.

## Methods

A retrospective study was performed at our Obstetrics and Gynecology and Medical Oncology Clinic of Kayseri Training and Research Hospital of Medicine, a tertiary referral center in Turkey. The data of patients with breast cancer were analyzed between 2006 and 2014. Approval from the local ethics committee was obtained.

Medical records of patients with breast cancer who had received tamoxifen were examined. Data of this retrospective study were retrieved from patient files and hospital records. Pap smear results, age, gravidity, parity, smoking status (defined as smoking >10 cigarettes a day for at least 1 year without a quit attempt), age of first birth, and detailed gynecologic and obstetric history of patients were noted. Patients who had not receiving at least one-year tamoxifen therapy and those without smear controls or those who had left or had received interrupted tamoxifen treatment were excluded. In addition, patients whose medical records could not be obtained were excluded. From a total of 178 patients, only 123 patients were included in our study. A set of 123 healthy patients were included in the control group.

In our department, the control smear results of patients with breast cancer before tamoxifen therapy were obtained and pap smear control tests were performed annually. None of the patients had a prior history of cervical squamous intraepithelial lesions. The pap smear results of the tamoxifen and control groups were analyzed. The presence of inflammation in pap smear results were recorded.

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The results were described according to the Bethesda System (11). In the Bethesda system reports, there are classifications. The categories are negative for intraepithelial lesion or malignancy, epithelial cell abnormalities and other malignant neoplasms. Cytologic epithelial abnormalities of squamous cells are defined as atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells that cannot exclude a high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), and high-grade squamous intraepithelial lesion (HSIL), and those that cannot be suggestive of squamous cell cancer. Glandular cell abnormalities are defined as atypical glandular cells not otherwise specified (AGC-NOS), atypical glandular cells, suspicious for adenocarcinoma in situ or cancer (AGC-neoplastic), and adenocarcinoma in situ (AIS).

### Statistics analysis

The collected data were analyzed using Statistical Package for Social Sciences software version 18.0 (SPSS Inc.; Chicago, IL, USA). Quantitative variables were expressed as mean value±standard deviation for parametric variables and median and minimum–maximum levels for nonparametric variables. Continuous variables were analyzed for normal distribution using Kolmogorov–Smirnov test. Student's t-test and Mann–Whitney U test were used to compare the continuous variables. A two-tailed p value of <0.05 was considered statistically significant.

### Results

A total of 246 patients were included in this study. The properties and characteristics of patients of the tamoxifen group are presented in Table 1. The mean age of the patients in the tamoxifen group was 52 years. Of them, 29 were smokers. The mean age of first pregnancy was 20 years and the mean duration of tamoxifen use was 48 months. Forty of the 123 patients had chronic diseases and 16 had undergone gynecologic operations (15, total abdominal hysterectomy and bilateral oophorectomy and 1, abdominal hysterectomy).

The distribution of the pap smear results of both the groups are presented in Table 2. None of the patients had cervical squamous intraepithelial lesions and atypical glandular lesions and 9 had atypical squamous cells (7 ASC-US, 2 ASC-H) in the tamoxifen group. Atypical squamous cells were significantly higher in patients in the tamoxifen group compared to those in control group ( $p=0.03$ ). Patients who had atypical cells underwent cervical biopsy after colposcopic examination, and none of them had a preneoplastic lesion.

Pap smear results of 53 patients in the control group and 36 patients in the tamoxifen group indicated inflammation. The presence of inflammation was significantly higher in the control group than the tamoxifen group ( $p=0.024$ ).

### Discussion

The major finding of the present study is that cervical atypical cells are associated with tamoxifen therapy in women with breast cancer. Tamoxifen, widely used drug for the treatment of all stages of breast cancer, is a partial agonist of estrogen. Moreover, it is well tolerated and has minimal side effects.

Some studies have reported that tamoxifen has estrogenic effects in experimental models and human endometrial specimens (12, 13). Because tamoxifen is a partial agonist of estrogen, it behaves as an antiestrogen in breast tissues (5) and has proliferative effects on the endometrium. In contrast to the studies on the endometrium, there have been few studies concerning the effects of tamoxifen on other tissues of the female genital tract, especially the cervix and vagina. It was demonstrated that there are estrogen receptors in cervical squa-

**Table 1. Some Demographic and clinical characteristics of the tamoxifen group (n=123)**

Number of patients	Tamoxifen group n=123	Control group n=123	p
Age (Mean±SD)	52±9	50±8	0.2
Gravidity (Median, 25–75 percentiles)	3 (2–4)	3 (2–4)	0.2
Parity (Median, 25–75 percentiles)	3 (2–4)	3 (2–4)	0.7
Smoking status (n, %)	26 (21)	20 (21)	0.3
History of gynecologic surgery (n, %)	16 (13)	10 (8)	0.2
First pregnancy age (Mean±SD)	21±4	20±4	0.2
Tamoxifen use (Median, 25–75 percentiles)	48 (36–68)		

SD: standart deviation

**Table 2. Pap smear results of groups**

Smear results	Tamoxifen group n=123	Control group n=123	p
Atypical squamous cells (ASC-US, ASC-H)	9	2	0.03

ASC-US: atypical squamous cells of undetermined significance; ASC-H: atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion

mous and columnar cells in pre- and postmenopausal women (14). It was shown that the number of these receptors did not change during the menstrual cycle and it was thought that these receptors did not appear to function by an affinitive agent (14, 15). On the other hand, it is possible that these estrogen receptors may play a role in the tamoxifen effects on cervicovaginal tissues.

Similarly to our study, Gill et al. (8) concluded in 1998 that the use of tamoxifen may be associated with benign squamous atypia in cervical smears and that atypia is not associated with intraepithelial lesions. They evaluated cervical smears of 52 women with breast cancer receiving tamoxifen therapy and they also evaluated cervical smears of 21 women with breast cancer who did not receive tamoxifen. Thirty-two of the patients had more frequent atypical cells compared with women (6 of 21) who had no hormonal therapy (tamoxifen). These data suggest that atypical cells were found in 61% of the cases; half of them were ASC-US and the rest were non-dysplastic. None of the smears progressed to a malignant or precancerous lesion during follow-up. In addition, they reported that tamoxifen therapy was not associated with an increase in the presence of blood or inflammation. Also, in another former study, Eells et al. (16) (1990) found an increase in squamous maturation in serial cervical smears in a few postmenopausal women treated with tamoxifen. Moreover, Fornander et al. (10) reported that there was no difference in occurrence of cervical cancers in group of breast cancer patients treated with tamoxifen when compared with controls. In contrast, Mousavi and Karimi Zarchi reported some isolated metastatic cervical cancers in patients with breast cancer, especially in tamoxifen users (17). In our study, none of the patients had cervical squamous intraepithelial lesions or had cervical tumors in the following years. In our tamoxifen group, 9 of the 123 (7.3%) patients had atypical squamous cells (7 ASC-US, 2 ASC-H). Only 2 of 123 healthy control patients had atypical squamous cells. Atypical squamous cells were significantly higher in the tamoxifen group than in the control group. It can be thought that tamoxifen may affect estrogenic receptors on cervicovaginal tissues. The presence of estrogen receptors in cervical squamous and columnar cells in pre- and postmenopausal women was showed by Hwang et al. (14). On the other hand, tamoxifen

could potentially affect the immune function of tumor infiltrating lymphocytes by creating an immunosuppressive microenvironment (18). It is thought that these immunosuppressive effects in the tumor microenvironment may contribute to the development of antiestrogen resistance in breast cancer. Also, it may affect the pap smear results causing atypical squamous cells. In addition, there are no proper studies concerning the correlation of the human papilloma virus and tamoxifen effects. Similar studies in larger groups investigating the presence of human papilloma virus in tamoxifen-treated patients with breast cancer should be planned.

In addition, 53 patients in the control group and 36 patients in the tamoxifen group had inflammation, according to the pap smear results. The presence of inflammation was significantly higher in the control group ( $p=0.024$ ). Thus, it can be summarized that the estrogenic effects of tamoxifen on cervicovaginal cells may lower the presence of inflammation; this can also be because of the immunosuppressive effect of tamoxifen.

As mentioned above, cervical atypical cells are associated with tamoxifen therapy in women with breast cancer. The main purpose of this study was to determine whether tamoxifen had any effect on cervical smears. Although the pap smear tests are very valuable for patients with breast cancer receiving tamoxifen for the early detection of endometrial abnormalities such as endometrial cancer or uterine sarcoma, it may also be promising for the detection of early cervical epithelial lesions. In fact, we had planned to compare the pap smear results of patients with breast cancer who received tamoxifen and those who did not receive tamoxifen; however, we could not find any patients who had not received tamoxifen at our department. In addition, there were no human papilloma virus records in patients with breast cancer who were tamoxifen user in our archive. Therefore, we suggest that similar studies in larger groups using new methods should be planned.

## Conclusion

In conclusion, tamoxifen use may be associated with benign squamous atypia in cervical smears. Therefore, patients with breast cancer should undertake pelvic examinations and pap smear tests annually.

**Ethics Committee Approval:** Ethics committee approval was received for this study.

**Informed Consent:** Written informed consent was not received due to the retrospective nature of this study.

**Peer-review:** Externally peer-reviewed.

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