RESEARCH COMMUNICATION

Effects of Tamoxifen on the Cervix and Uterus in Women with Breast Cancer: Experience with Iranian Patients and a Literature Review

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Abstract

Objective: Invasive breast cancer is the most common malignancy in women. Due to the declining mortality rate that is partly attributable to the use of screening mammography and effective adjuvant therapy, more women survive their breast cancers. The aim of this study was to evaluate the effects of tamoxifen on the genital tract with particular attention to the uterus and cervix. Methods: We investigated the relationship between tamoxifen and cervical or uterine cancer in Iran, reviewing all the studies performed by the Vali-Asr Gynecology Oncology Clinic in Tehran. In addition, the available data on Medline from 1980 until 2009 were reviewed. Results: A total of 182 articles showed associations with gynecologic malignancies. Although as many as 121 refered to links between the drug and endometrial abnormalities (polyps or cancers), 55 articles studied the relationship with changes of pap smears, four of which indicated isolated cervical metastasis followed tamoxifen use in patients with breast cancer. Conclusion: In spite of the significant relationship between tamoxifen and endometrial cancers, cervix is rarely involved in breast cancer patients. However, vaginal bleeding or abnormal vaginal discharge has been reported in all cases before the diagnosis was made. To rule out genital tract malignancy, it is necessary, therefore, to have an annual pelvic exam, pap smear and early endometrial with endocervical curettage for tamoxifen users following a breast cancer in those with abnormal uterine bleeding or persistent vaginal discharge.

Key Words: Tamoxifen - breast cancer - pap smear - cervical cancer - uterine cancer

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Introduction

Breast cancer is the most common malignancy in American women. It afflicts one in 8 women and that is to say every women may catch it at the probability of 12.6% during her life (Jemal et al.,2007).It is also the most common malignancy among Iranian women, so that the incidence is 18.2/100000 persons (Mousavi, 2007). Due to mammography and other screening techniques along with adjuvant therapies, more women can survive their breast cancers nowadays (Berry et al., 2003). It is necessary to be aware of cares to be taken during follow-up period of treatment. It is to be noted that the risk of endometrial cancer is increased by using tamoxifen after a breast cancer incidence (Berry et al.,2003; Jemal et al.,2007: Mousavi et al., 2008).

Tamoxifen, a nonestroid anti-estrogenic drug, is used in all stages of a breast cancer. As a prevention to a secondary breast cancer in high-risk patients,tamoxifen serves to increase their survival rate (Early Breast Cancer Trialists' Collaborative Group., 2005). Since it affects on estrogenic receptors, it can lead to some changes in genital organs (Gill et al.,1998; Abadi et al., 2000). As awareness of effective screening tests of cancer in breast cancer women and how tamoxifen affects cervical cytology or relates to with genital tract malignancies is very important.

The aim of this study is to evaluate pap smear changes due to using tamoxifen in Iranian breast cancer patients and to interpret different cervical abnormalities. The incidence of endometrial cancer, uterine sarcoma and cervical malignancies was studied in tamoxifen users following their breast cancer. The patients were all referred to the Gynecologic Oncology Clinic of Vali-Asr Hospital in Tehran, Iran.

Materials and Methods

As there was no recent review article about the association of tamoxifen with cervical/endometrial malignancies or cervical cytological changes in tamoxifen users, we searched and evaluated all medline articles between 1980 and 2008 by using tamoxifen, breast cancer, cervical cytology, cervical cancer, and uterine cancer as key words.

Therefore, all studies on breast cancer patients refered to Vali-Asr Gynecologic Oncology Clinic of Tehran, Iran from 1997 to 2009 were reviewed to verify the relationship of tamoxifen use with cervical/uterine malignancies.

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Table 1. Literature Review on Effects of Tamoxifen on the Cervix and Endometrium in Breast Cancer Patients

Effects	Method	Number	Reference
Increase of cervical hyperplasia, no abnormal Pap tests	Case control	94	Rayter 1994
Increase of atypical cell without cervical cancer	Clinical trial	52	Gill et al., 1998
Estrogenic effect on cervix, endometrial cancer in Pap test with abnormal endometrial cells			
	Case control	48	Abadi et al., 2000
3 abnormal Pap test, 1 cervical cancer and 2 cervisit	Observational	49	Beshtash et al., 2009
No increase of cervical, increase of endometrial cancer	Review	-------	Mortimer et al., 1999
Increase in small blue cells in Pap tests	Observational	48	Yang et al., 2001
Increase of atypical cells without cervical cancer	Review	-------	Senkus-Konefka, 2003
No antiestrogenic effect on cervix	Observational	42	Lesli et al., 2007

Results

Out of 842 reviewed articles, 182 papers showed a relationship between tamoxifen and gynecologic malignancies. Only 55 articles dealt with the effect of this drug on pap smear. Four articles reported isolated cervical metastases in tamoxifen user following a breast cancer (Livolsi,1995; Mousavi and Karimi Zarchi, 2007).Two articles studied cervical cancer in Iran in the word .They evaluated the breast cancer history and showed the role of HPV vaccine as a prevention of cervical cancer that is the most commonly observed gynecologic cancer in Iran(Behtash and Mehrdad, 2006; Behtash and Karimi Zarchi, 2007).

A study conducted on 52 breast cancer patients receiving 10 mg of tamoxifen (twice a day for at least 6 months) showed that tamoxifen increased the number of atypical cells in pap smear(61% of patients), while it happened in just 28% of non-users. It should be noted that 14 of cases received combined chemotherapy. None of the pap smears showed changes due to HPV and mild dysplasia. Also ASCUS (atypical squamous cell undetermined significant) was the most related atypical cells in pap smears.They came about mostly due to inflammatory and non malignant changes (Gill et al.,1998) (Table 1).

Another study carried out on 48 women with a positive history of breast cancer sought to investigate the value of pap smear in the diagnosis of the susceptible to endometrial cancer. The cases were devided into 3 groups:1-breast cancer cases using tamoxifen (n=20), 2-endometrial cancer cases without a history of tamoxifen use (n=32) and 3-Treated patient with tamoxifen without history of endometrial cancer (n=16). Studying 114 pap smears showed that, in patient developing endometrial cancer, the number of endometrial cells increased. Also, hystocytes were more frequently seen in this group rather than in the other 2 groups (Abadi et al., 2000).

Among the articles that were about relevance of tamoxifen use to cervical cancer in breast cancer patients, there was a case of isolated cervical metastasis in Iran (Mousavi and Karimi Zarchi, 2007). Only 28 metastatic cervical cancers have been reported with an origin of breast cancer until now. Only 4 of these cases were isolated and without any involvement of other organs (Livolsi et al.,1995; Mousavi and Karimi Zarchi, 2007).

Surprisingly, among more than 400 cervical cancer cases referring to Oncology Clinic of Vali-Asr Hospital in Tehran,Iran from 1997 to 2007, there was only 1 isolated metastatic cervical cancer following breast cancer in a tamoxifen user. Another study was done on patients referring to this clinic to evaluate uterine and cervical malignancies that occure along with breast cancer following tamoxifen use (Ghaemmaghami et al., 2008; Behtash et al., 2009). Among 330 registered uterine cancers, 5 cases noted positive history of breast cancer and tamoxifen use. The dosage and duration of tamoxifen use were 20 mg per day for 4-8years respectively. Some 4 to 5 of patients suffered from vaginal bleeding before diagnosis. The rest of patients had vaginal discharge resistant to treatment. There was a 2 to 11- years interval between the diagnosis of endometrial and the breast cancers. Except one case, the stages of other patients were Ia to Ic(primary stage). Pathology reported that 2 of the cases had sarcoma (Mixed malignant mullerian tumor), while the pathology of rest of patients was adenocarcinoma. The patients were followed up for 3-120 months. All the cases stayed alive except one. Free-disease survival rate of these cases was 6-120 months (Killackey et al.,1985).

Discussion

Tamoxifen, a nonstroid anti-estrogenic drug, was introduced as a preventive method of pregnancy in England (Fornander et al.,1989). FDA proved it as a treatment of metastatic breast cancer in postmenopausal patients in 1977.Nowadays it is used as an adjuvant therapy for breast cancer ,including its metastatic forms . It is also used as a preventive method for breast cancer in high-risk patients (Fornander et al.,1989: Rutqvist et al.,1995: Wickerhan, 2002).

Tamoxifen is a selective antagonist of estrogen receptor. So, it has an anti-estrogenic effect on the breast tissue, while estrogen keeps its effect on other tissues such as bone, endometrium, and cardiovascular system (Rutqvist et al.,1995). The estrogenic effect of tamoxifen on endometrium is reported to have worried some breast cancer patients about the likelihood of endometrial cancer (Curtis et al.,1996; Wickerhan, 2002).

For the first time in 1985, a case of association of tamoxifen and endometrial cancer was reported(Killackey MA et al.,1985). A large cohort study done by Curtis et al (1996) also showed that incidence of endometrial cancer could rise in breast cancer cases with or without history of tamoxifen use, but the relative risk (RR) was higher in tamoxifen users (2 vs. 1.2). However, Deligdisch et al (2000) showed that tamoxifen increases the probability

of progression in endometrial cancer .

The value of pap smear for breast cancer patients especially for tamoxifen users lies in an early diagnosis of endometrial abnormalies such as endometrial cancer or uterine sarcoma (Khatcheressian et al.,2006). The presence of endometrial or glandular cells can be indication of endometrial cancer in these patients (Khatcheressian et al.,2006: Emens LA et al.,2002).It is especially true about the cases suffering from vaginal bleeding or vaginal discharge resistant to treatment. So, all breast cancer cases using tamoxifen should undergo a vaginal sonography and a diagnostic curettage to rule out any endometrial cancer, if vaginal bleeding or resistant vaginal discharge occures (Emens et al., 2002; Khatcheressian et al., 2006).

There are many articles on the association of tamoxifen with endometrial polyps, uterine body cancer and uterine sarcoma (Magriples et al.,1993; Bissett et al., 1994; Fisher et al.,1994; Sismondi et al.,1994; Mignotte et al.,1998; Deligdisch et al., 2000; Wickerham et al., 2002; Behtash et al., 2009), but only a few studies have been performed on pathological effects of tamoxifen on female genital organs (Ferrazzi et al.,1977; Boccardo et al.,1981; Eells et al.,1990; Fornander et al.,1991; Athanassiadou et al.,1992; Wolf et al.,1992; Cohen et al.,1994; Sonnendecker et al.,1994).

There is some experimental evidences indicating that high doses of tamoxifen can induce a cervical tumor. It should be also noted that a low dose of tamoxifen may stimulate cell growth (Ferrazzi et al.,1977; Fornander et al.,1991).Some studies determined the presence of estrogenic receptors on the squamous and columnar cells of the cervix in premenopause and post-menopause women (Ferrazzi et al.,1977; Boccardo et al.,1981; Fornander et al.,1991; Athanassiadou et al.,1992; Wolf et al.,1992; Cohen et al.,1994; Sonnendecker et al.,1994). It is not known if these receptors are affected by menstrual cycle or agonist –antagonist estrogenic factors (Boccardo et al.,1981). Eells et al (1990) found out that in a few of menopausal women treated by tamoxifen, the metastasis of squamose cells was increased. Therefore, a review article was written by Fornanders et al (1991) to report the effect of tamoxifen on female genital system and that there was no difference in cervical cancer incidence between the tamoxifen user and the non-user group.

Gill et al (1998) reported that tamoxifen with or without chemotherapy led to the formation of atypical cells in the pap smear of 62% of cases half of whom were ASCUS and the restwere non-dysplastic. It should be noted that none of the smears progressed to a malignant or precancerous lesion during the follow-up. Mousavi and Karimi Zarchi (2007) reported some isolated metastatic cervical cancers in breast cancer patients, especially tamoxifen users . However, cervical involvement following a breast cancer was rare; only 28 cases of cervical involvement were reported 4 of which were isolated type.

In conclusion, when using tamoxifen following a breast cancer ,an anual pelvic examination and pap smear are needed as a part of gynecologic studies.It should be noted that tamoxifen does not have any significant effect on pap emear findings. If vaginal bleeding or discharge occurs, vaginal sonography as well as endocervial and endometrial curettage be helpful to rule out endometrial/ cervical cancer in patients with breast cancer followed by tamoxifen.

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