# The effects of tamoxifen therapy on the endometrium

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**Summary**

From January 1992 to December 1998, 219 women (aged between 30 and 81 yrs; average 55 years) affected by breast cancer were treated. These women in addition to the usual adjuvant therapy, were treated with TAM 20 mg/day, for a period between 24 and 72 months (average 40). In this group there were 84 postmenopausal and 31 premenopausal women. In 8 fertile patients ovarian activity was suppressed with GnRh analogue therapy and one patient underwent attinic castration. Before performing TAM therapy, a hysteroscopic exam was done and patients were followed-up with an annual check-up. None had any endometrial side-effects after the first check-up. After two years, 31 women (26.9%) complained of endometrial alterations (hyperplasia, polyps and endometrial cancer).

One women only after 6 years of follow-up, had metrorrhagia; an endometrial adenocarcinoma was found.

We would like to point out the necessity of monitoring these patients with an annual check-up (transvaginal sonography and/or hysteroscopy).

*Key words:* Tamoxifen-Endometrial cancer; Breast cancer; Female genital tract; Hyperplasia.

## Introduction

Tamoxifen (TAM) is a non-steroid antiestrogen usually utilized in patients with breast cancer. This synthetic antiestrogen is largely utilized as an adjuvant therapy at a dose of 20 mg/day in women with positive estrogen receptors; it is actually giving interesting results with a 40% increase of survival rate at 5 years without particular side-effects [1]. Many studies have shown that the development of controlateral breast cancer has decreased in patients assuming tamoxifen [2].

Clinical studies have been started to establish whether TAM is useful in the prevention of breast cancer in women with increased risk factors. The National Cancer Institute (NCI) reports a 49% reduction in invasive and a 50% in *in situ* cancers [3]. The rate between risk and benefits is more advantageous when TAM is used for not more than 5 years.

TAM has limited estrogen effects as well: it reduces LDL concentrations preventing risk of cardiovascular disease, reduces bone demineralization risk preventing osteoporosis, and induces fibromyoma volume increase; however, it stimulates the endometrium causing polyps, hyperplasia and cancer [2, 4].

Further risks connected with the use of TAM are thromboembolic phenomena, cataracts, retinic haemorrhage, hepatotoxicity inducing steatosis and in rare cases cirrhosis [5].

Probably, TAM has a carcinogenetic effect on the liver, the intestine and the endometrium [4]. For liver and intestinal tumors a certain association with TAM has not been proved, while for endometrial cancer the risk increases from 2 to 7.5 times [6, 7, 8].

Risk percentage, however, cannot be easily quantified, because both breast and endometrial cancer have a common genetic background and some common risk factors [9].

Endometrium-stimulating effects force a follow-up of the uterine cavity with transvaginal sonography, hysteroscopy and biopsy.

Echography permits the evaluation of endometrial thickness and structure with a reference cut-off of 5 mm. This parameter may change in patients treated with TAM, due to increased thickness of the endometrial stroma. These cases provides a high number of false positives. Therefore, in all cases of thick endometrium, although it may be a false positive, hysteroscopy and biopsy are necessary [9-11].

Hysteroscopy is the most accurate method for diagnosing endometrium disease because it provides a direct vision of the endometrium, allows different endometrial lesions to be distinguished, reveals focal hyperplasia areas and permits aimed bioptsies.

## Methods and Materials

From January 1992 to December 1998, at the 2nd Institute of Obstetrics and Gynaecology, University of Catania, 219 women ranging in age from 30 to 81 yrs. (average 55 years) affected with breast cancer were treated: 114 patients underwent mastectomy, 94 quadrantectomy, 8 tumorectomy, 3 tru-cut (table 1). Histotypes were divided as shown in table 2.

Estrogen and progesterone receptor research was carried out on the removed tumors, with a 65% positive outcome. The patients underwent adjuvant TAM therapy administered at a dose of 20 mg/day. All women had hysteroscopy except in case of previous hysterectomy.

Subjects with a history of thromboembolic disease, hysterectomy or endometrial disease at hysteroscopy were excluded. Furthermore, all patients with a duration of TAM therapy < 2 years were excluded.

Applying these criteria, of the 219 women only 115 participated in the study and 38 of these patients underwent antiblastic chemotherapy as well.

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Table 1.

| Surgical operation | No. | (%) |
|---|---|---|
| Mastectomy | 114 | 52.05 |
| Quadrantectomy | 94 | 42.92 |
| Tumorectomy | 8 | 3.65 |
| Tru-cut | 3 | 1.36 |
| Total | 219 | 100 |

Table 2.

| Histotypes | No. | (%) |
|---|---|---|
| *IDC | 150 | 68.49 |
| ILC | 22 | 10.04 |
| Medullary | 13 | 5.93 |
| Adenocarcinoma | 9 | 4.10 |
| **ISDC | 8 | 4 |
| Inflammatory | 5 | 2.28 |
| Others | 12 | 5.47 |
| Total | 219 | 100 |

*IDC = Infiltrating ductal carcinoma.
ILC = Infiltrating lobular carcinoma.
**ISD = In situ ductal carcinoma.

Table 3.

| Polyps | Hyperplasias low-risk | Hyperplasias high-risk | Endometrial cancer | Total |
|---|---|---|---|---|
| 10 (8.69%) | 15 (13.04%) | 5 (4.34%) | 1 (0.86%) | 31 (26.95%) |

Table 4.

| Polyps | Hyperplasias simple | Hyperplasias polypoid microcystic | Complex hyperplasia | Endometrial cancer | Total |
|---|---|---|---|---|---|
| 10 (8.69%) | 11 (9.56%) | 4 (3.47%) | 5 (4.34%) | 1 (0.86%) | 31 (26.9%) |

Mean duration of treatment was approximately 40 months (range: 24-72 months).

In this group there were 84 postmenopausal and 31 premenopausal women. In 8 fertile patients ovarian activity was suppressed with GnRh-analogue therapy and one patient underwent attinic castration.

After hysteroscopy at the beginning of treatment, all women were followed-up with annual hysteroscopy and, if necessary, biopsy to evaluate endometrial alterations induced by TAM.

Although hysteroscopy is a more invasive method, we preferred it as an alternative to transvaginal sonography for its higher sensitivity and specificity.

## Results

No endometrial pathology was found in the 115 patients checked during the two following annual hysteroscopies.

After two years endometrial disease was diagnosed in 31 patients mean (age 57): 28 postmenopausal and 3 premenopausal women. Two were treated with GnRh analogues and one underwent bilateral salpingo-oophorectomy.

In the remaining 84 patients (73.04%) no relevant endometrial disease was observed during TAM therapy.

In 15 cases hysteroscopy showed "low risk" hyperplasia in 5 cases "high risk", in 10 patients a polyp and in one case an endometrial cancer (table 3).

Histologic findings were: 11 simple hyperplasias, 4 polypoid and microcystic hyperplasias, 5 complex hyperplasias, 10 endometrial polyps, one endometrial adenocarcinoma (table 4).

The patient affected with adenocarcinoma assumed TAM for 6 years but presented for follow-up only in the first year. After 6 years the woman showed a moderate metrorrhagia and biopsy displayed the adenocarcinoma.

## Conclusion

In 26.9% of the examined women, a correlation between endometrial disease and the use of TAM was found but all observed diseases, excluding the case of adenocarcinoma, were not severely life threatening. In these events interruption of TAM therapy is sufficient. If hormone therapy is necessary, prophylactic intervention with endometrial ablation or hysterectomy may be performed.

The reduced incidence (4.34%) of complex hyperplasia (lesions probably evolving into cancer) may be due to selection criteria of the patients and to a strict follow-up during the treatment, in order to permit early diagnosis and therapy.

Regular follow-up of TAM-treated patients is necessary because this treatment is associated with endometrial lesions and because there is a higher incidence of endometrial cancer in breast cancer patients [9].

In our opinion, for these women annual hysteroscopy is the most accurate method as it is more reliable and allows, if necessary, an immediate biopsy to be performed.

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