

Evaluation of the Effect of Tamoxifen Therapy on the  
Endometrium in Premenopausal Breast Cancer

Patients

*Thesis*

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**تقييم تأثير العلاج بعقار التاموكسيفين على  
بطانة الرحم في السيدات المصابات بسرطان  
الثدى قبل مرحلة سن انقطاع الطمث**

بحث  
مقدم توطئة للحصول على درجة الماجستير  
فى أمراض النساء و التوليد

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## *Introduction*

Tamoxifen citrate is a selective estrogen receptor modulator that is widely used for the treatment of breast cancer (**Osborne, 1998**). Recently, it has been found to prevent breast cancer in high-risk woman (**Fisher et al., 1998**).

Although it acts as an antiestrogen in breast tissue, it has an estrogenic effect in the postmenopausal endometrium and myometrium.

Long-term tamoxifen therapy is reported to be associated with an increased number of uterine lesions, including endometrial polyps, leiomyomas, endometrial hyperplasia, endometrial carcinoma, and adenomyosis (**Cohen et al., 1995 and Berliere et al., 1998**). However, the beneficial effects of tamoxifen in women with breast cancer outweigh the potential endometrial adverse effects of the drug.

National Surgical Adjuvant Breast and Bowel Project (NSABP) (**Fisher et al., 1994**). Performed a randomized trial of tamoxifen versus placebo in women with ER-positive breast cancer confined to the breast with

## *Introduction*

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negative axillary nodes. Results from this trial of 4,063 patients revealed a 7.5-fold increase in the risk of developing endometrial cancer in the tamoxifen-treated group. The average annual hazard rate for endometrial cancer was 0.2 per 1,000 women in the placebo group and 1.6 per 1,000 women in the randomized tamoxifen-treated group.

In a case-control study using surveillance, epidemiology, and end-results data (*Bernstein et al., 1999*). Confirmed a four-fold increased risk of endometrial cancer in breast cancer patients with more than 5 years of tamoxifen use compared with nonusers. This effect was most pronounced, however, in those with known risk factors for endometrial cancer, including higher body mass index and prior use of estrogen replacement therapy.

The proliferation index in benign endometrial epithelium is higher in tamoxifen users than in non-users, and this might play a role in the reported higher incidence of endometrial cancer in postmenopausal tamoxifen users (*Mourits et al., 2002*).

Tamoxifen treatment is associated with an increased incidence of proliferative and neoplastic endometrial changes. No obvious correlation was found between the length of tamoxifen exposure time and occurrence of endometrial pathologies. It is mandatory to undertake twice per year gynecological evaluations for patients treated with tamoxifen to promptly identify and correctly manage endometrial changes (*Colacurci et al., 2000*).

Several techniques such as tritiated thymidine autoradiography, bromodeoxyuridine incorporation, Ki-67 immunohistochemistry, and crypt cell production rate, were used for the evaluation of cell proliferation. Ki-67 immunohistochemistry is one of the most widely available methods for measuring cell proliferation and is also a valuable prognostic indicator in several types of neoplasm. Although Ki-67 immunohistochemistry developed first needed frozen sections, recently developed Ki-67 immunohistochemistry in formalin-fixed and paraffin-embedded tissues can be used as a reliable marker of the cell proliferation activity in both normal and neoplastic epithelium (*Ikuko Akedo et al., 2001*).

## *Aim of the Work*

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### *Aim of the Work*

The aim of this study is to evaluate the effect of tamoxifen therapy on the endometrium in premenopausal women with cancer breast.

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## List of Abbreviations

|              |   |                                                         |
|--------------|---|---------------------------------------------------------|
| <b>CT</b>    | : | Computed Tomography                                     |
| <b>E</b>     | : | Eosine                                                  |
| <b>E2</b>    | : | Estradiol                                               |
| <b>EIC</b>   | : | Endometrial intraepithelial carcinoma                   |
| <b>ER+</b>   | : | Estrogen receptor-positive                              |
| <b>ESC</b>   | : | Eosinophilic syncytial change                           |
| <b>FCM</b>   | : | Flow cytometry                                          |
| <b>FSH</b>   | : | Follicular stimulating hormone                          |
| <b>HBD</b>   | : | Hormone-binding domain                                  |
| <b>HR+</b>   | : | Hormone –receptor-positive                              |
| <b>Hx</b>    | : | Haematoxylin                                            |
| <b>IUP</b>   | : | Intra-uterine Pregnancy                                 |
| <b>LH</b>    | : | Leutinizing hormone                                     |
| <b>MR</b>    | : | Magnetic resonance                                      |
| <b>NSABP</b> | : | The National Surgical Adjuvant Breast and Bowel Project |

|                                |   |                                        |
|--------------------------------|---|----------------------------------------|
| <b>PCNA</b>                    | : | Proliferating cell nuclear antigen     |
| <b>PgR+</b>                    | : | progesterone-receptor-positive         |
| <b>SERMs</b>                   | : | Selective estrogen receptor modulators |
| <b>TAM</b>                     | : | Tamoxifen                              |
| <b>TGF<math>\beta</math>-1</b> |   | transforming growth factor $\beta$ -1  |
| <b>TVU</b>                     | : | Transvaginal Ultrasonography           |
| <b>US</b>                      | : | Ultra-Sound                            |

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**Table (4): Patients characteristics**

|                                               | Group(2) :Control Group |        |       |       |
|-----------------------------------------------|-------------------------|--------|-------|-------|
|                                               | Mean                    | ±SD    | Range |       |
| <b>Age (years)</b>                            | 36.92                   | ±3.65  | 35.00 | 44.00 |
| <b>Parity</b>                                 | 3.20                    | ±1.47  | 0.00  | 6.00  |
| <b>Weight (kg)</b>                            | 75.04                   | ±10.38 | 58    | 90    |
| <b>Duration of Tamoxifen therapy (months)</b> | 12.00                   | ±4.96  | 6.00  | 25.00 |

The mean age of patients' age, parity and weight were 36.92, 3.20and 75.04 respectively.