CORRELATION BETWEEN BODY MASS INDEX AND HORMONAL TREATMENT IN BREAST CANCER PATIENT

Thesis

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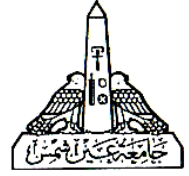Faculty of Medicine - Ain Shams University

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بِسْمِ اللهِ الرَّحْمَنِ الرَّحِيمِ

قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا

إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

صَدَقَ اللهُ الْعَظِيمُ

Acknowledgement

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INTRODUCTION

Breast cancer is one of the most serious diseases, not only because of its high incidence but also because it leads to high death rate in women in the western industrial countries. Breast cancer in women is a major public health problem throughout the world. It is the most common cancer among women both in developed and developing countries. *(Pazdur et al , 2008).*

Approximately more than 700.000 breast cancer patients are diagnosed in the whole world annually and it remains the leading cause of death among women aged 40 to 50 years *(Arslan et al , 2000).*

Median age at diagnosis in Egypt is one decade younger than in countries of Europe and North America and most patients are premenopausal. Tumors are relatively advanced at presentation *(NCI registry data).*

Developed countries experienced a rapid rise in incidence rates starting in the 1980s that continued through the 1990s, largely as a result of the widespread adoption of screening mammography.

While incidence rates have historically been higher in developed compared to developing countries, rates have also increased among populations in developing countries. *(Christopher, 2010).*

Breast cancer is the commonest malignancy among egyptian females, accounting for about 33% of female cancer cases in egyptian National Cancer Institute (NCI) *(El-Bolkainy et al , 2005).*

The incidence of breast cancer has increased steadily in the United States over the past few decades, but breast cancer mortality appears to be declining, suggesting a benefit from early detection and more effective treatment. The etiology of the vast majority of breast cancer cases is unknown. However, numerous risk factors for the disease have been established *(Ragaz et al , 1997).*

These risk factors include: female gender; increasing patient age; family history of breast cancer at a young age; early menarche; late menopause; older age at first live childbirth; prolonged hormone replacement therapy; previous exposure to therapeutic chest wall irradiation; benign proliferative breast disease; and genetic mutations such as the *BRCA1/2* genes.

Proliferative abnormalities of the breast are limited to the lobular and Ductal epithelium. In both the lobular and Ductal epithelium, a spectrum of proliferative abnormalities may be seen, including hyperplasia, atypical hyperplasia, in situ carcinoma, and invasive carcinoma. Approximately 85% to 90% of invasive carcinomas are ductal in origin *(Arthur and Vicini , 2005)*.

The invasive Ductal carcinomas include unusual variants of breast cancer, such as colloid or mucinous, adenoid cystic and tubular carcinomas, which have especially favorable natural histories *(Burstein et al , 2004)*.

The treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy (RT), or both, and the treatment of systemic disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy or combinations of these. The

need for and selection of various local or systemic therapies are based on a number of prognostic and predictive factors. These factors include tumor histology, clinical and pathologic characteristics of the primary tumor, axillary node status, tumor hormone receptor content, tumor HER2 status, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status*(Vicini et al , 2007)*.

Before discovery of the ER, all breast cancers were considered potentially sensitive to endocrine therapy. Gradually, clinical trials and laboratory research established that only cancers containing ER (ER-positive cancers) respond to endocrine treatments, either additive or ablative. In 1985, a second important growth factor receptor was discovered, the HER-2 or erb-B2/neu protein. This protein is the product of the erb-B2 gene and is amplified in about 20% of human breast cancers. The human epidermal growth factor receptor 2 (HER-2/neu) gene, a member of the epidermal growth factor receptor (EGFR) family, was discovered independently in four different laboratories, and therefore it has alternative names like, HER-2 neu or c-erbB-2 *(Millikan et al , 2008).*

Seventy-five percent of all breast cancer occur in postmenopausal women, of which about **80%** are hormone receptors positive *(Anderson et al , 2002).*

Adjuvant endocrine therapy with tamoxifen 5 years significantly prolongs disease free and overall survival in post menopausal women with hormone receptors positive, early stage breast cancer *(Michael et al , 2009).*

Tamoxifen citrate is a selective estrogen receptor modulator that is used for the treatment of breast cancer. Although it acts as an antiestrogen in breast tissue, it has an estrogenic effect in the postmenopausal endometrium and moymetrium *(Osborne, 1998).*

Third-generation aromatase inhibitors have been widely used in postmenopausal women for the adjuvant treatment of hormone receptor–positive breast cancer. As aromatase inhibitors work by inhibiting the conversion of androgens to estrogens in adipose tissue.   Data from clinical trials comparing third generation aromatase enzyme inhibitors (AEI) with tamoxifen have confirmed that aromatase inhibitors (AI) offer significant efficacy and tolerability advantages over tamoxifen during treatment phase and so they are recommended as adjuvant treatment for postmenopausal women with hormone receptors positive early breast cancer *(Forbes et al , 2008 & Jakesz et al , 2008).*

So, as hormonal receptors becomes one of the risk factors that must be considered when treating breast cancer as well as pre or post menopausal state, obesity was for a long time as the hidden enemy that must be taken as in eye of consideration.

The relationship between obesity and breast cancer is a complex one. Obesity is associated with breast cancer risk in qualitatively different ways before and after menopause with decreased risk in premenopausal women and increased risk in postmenopausal women. whereas similar associations of obesity with prognosis are seen in pre- and postmenopausal women (obese women in both groups experience poorer outcomes). This

complexity likely reflects, at least in part, the variable relationships between obesity and estrogen (a major contributor to the growth of hormone receptor–positive breast cancer) before and after menopause *(Binnaz Demirkan et al , 2007).*

Body mass index (BMI), is a heuristic measure of body weight based on a person's weight and height. Though it does not actually measure the percentage of body fat, it is used to estimate a healthy body weight based on a person's height, assuming an average body composition. Due to its ease of measurement and calculation, it is the most widely used diagnostic tool to identify weight problems within a population *(Eknoyan & Garabed , 2008)*

Dependance on BMI to assess how much an individual's body weight departs from what is normal or desirable for a person of his or her height. The weight excess or deficiency may, in part, be accounted for by body fat (adipose tissue) although other factors such as muscularity also affect BMI significantly. The **WHO** regard a **BMI of less than 18.5** as underweight and may indicate malnutrition, an eating disorder, or other health problems, while a **BMI greater than 25** is considered overweight and **above 30** is considered obese. These ranges of BMI values are valid only as statistical categories when applied to adults, and do not predict health.*(Adapted from WHO, 1995, WHO, 2000 and WHO 2004).*

Body mass index is defined as the individual's body weight divided by the square of his or her height *(Eknoyan & Garabed, 2008).*

The formulae universally used in medicine produce a unit of measure of kg/m2. BMI can also be determined using a BMI chart, which displays BMI as a function of weight (horizontal axis) and height (vertical axis) using contour lines for different values of BMI or colors for different BMI categories *(**Adapted from WHO, 1995, WHO, 2000 and WHO 2004).***

AIM OF THE WORK

This thesis aimed to compare the effectiveness (disease free survival DFS & over all survival OS) , safety and tolerability in the adjuvant therapy Tamoxifen & Anastrozole in postmenopausal, operable, non-metastatic & hormonal receptors positive breast cancer patients, in relation to their Body Mass Index value (BMI).

REVIEW OF LITERATURE

BREAST CANCER EPIDEMIOLOGY & ETIOLOGY

Breast cancer is the most common malignancy in women, accounting for 32% of all female cancers. Breast cancer also is responsible for 15% of cancer deaths in women, making it the number-two cause of cancer death. An estimated 212,930 new breast cancer cases will be diagnosed in the United States in the year 2005, and 40,410 women will die of this cancer *(Lori gardines, et al, 2010).*

Epidemiology:

Gender, Breast cancer is uncommon in men; the female-to-male ratio is approximately 100:1. It accounts for < 1% of all cancer cases in men. The incidence of breast cancer in men has remained relatively stable over the past decades, except in Africa, where for unclear reasons, the incidence is rising. *BRCA* mutations are associated with an increased risk for breast cancer in men *(Lori gardines, et al,2010).*

Age, The risk of developing breast cancer increases with age. The disease is uncommon in women younger than 40 years of age; only about 0.8% of breast cancers occur in women < 30 years old and approximately 6.5% develop in women between 30 and 40 years old.

Race, Caucasian women have a higher overall rate of breast cancer than African- American women; however, this difference is not apparent until age 50 and is marked only after menopause.