INTRODUCTION

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death among women worldwide, accounting for 25% of total cancer cases ***(American Cancer Society, 2016).*** It ranks as the most prevalent cancer among women in the Middle East and Northern Africa ***(Ferlay et al., 2015).*** In Egypt, breast cancer is the most common type of cancer among females ***(Ibrahim et al., 2014).*** In Egypt, breast cancer represented 32% of all cancers among Egyptian females from 2008 -2011, which makes it the most frequent cancer among females ***(Ibrahim et al., 2014).***

In developed countries, around 65% of all breast cancer occurs in postmenopausal women, of which about 80% are hormone receptor-positive. In Egypt, 51% of breast cancers occur in postmenopausal women of whom 60% are hormone receptor-positive ***(Ferlay et al., 2015).***

The development of breast cancer is associated with numerous risk factors, including genetic, environmental and hormonal influences, yet 75% of women with this cancer have no readily identifiable risk factors ***(Jardines, 2015).***

Breast cancer is a heterogeneous disease in terms of histology, therapeutic response, patterns of distant metastasis, and patient outcomes ***(Prat and Perou, 2011).***

Management of breast cancer depends on the availability of clinical and pathological prognostic and predictive factors to guide the selection of treatment options ***(Rakha et al., 2010).***

Prognostic factors of breast cancer include clincopathological features such as tumor size, grade and the number of metastatic axillary lymph nodes ***(Hayes and Padnos, 2011).***

Predictive factors that identify the benefit from specific therapies include ER and PR expression, which identifies patients who will benefit from adjuvant endocrine therapy ***(Hammond et al., 2010)*** and overexpression of the HER2 protein which identifies patients who benefit from adjuvant HER2-directed therapy ***(Wolff et al., 2013).***

The Ki-67 index had a wide distribution of 1-99% in primary breast cancer, and the median was 20% in 3,652 cases. A higher Ki-67 index (≥20%) correlated significantly with young age, large tumors, positive lymph nodes, negative ER/PgR, p53 overexpression and positive HER2. A higher Ki-67 index correlated with a poorer prognosis and early recurrence (<2 years). On the other hand, a lower Ki-67 index correlated with a favorable prognosis and late recurrence (>10 years). Thus, proliferative activity determined by Ki-67 may reflect the aggressive behavior of breast cancer and predict the time of recurrence and the appropriate therapy ***(Nishimura et al., 2010).***

The anti-estrogen tamoxifen is the drug most often used for the long-term treatment of early breast cancer ***(Badia et al., 2007)***.

Tumor recurrence and mortality are significantly decreased by the use of 5 years of adjuvant tamoxifen both in the presence and absence of adjuvant chemotherapy. Adjuvant tamoxifen safely reduces 15-year risks of breast cancer recurrence and death. ER status was the only recorded factor importantly predictive of the proportional reductions. Hence, the absolute risk reductions produced by tamoxifen depend on the absolute breast cancer risks (after any chemotherapy) without tamoxifen ***(Breast, Trialists, & Group, 2011).***

Unfortunately, many patients present with primary resistance to endocrine therapy, despite high tumor levels of ER, and all patients with advanced disease eventually acquire resistance to therapy. The potential mechanisms for either intrinsic or acquired endocrine resistance are still poorly comprehended, but they clearly include ER-coregulatory proteins and cross-talk between the ER pathway and other GF and kinase networks. Identifying the factors and pathways responsible for this resistance, and defining ways to overcome it, are therefore important diagnostic and therapeutic challenges in current breast cancer research ***(Schiff et al., 2003).***

Aim of the Work

The aim of the study is to correlate the percentage of expression of Ki67 with the clinical outcomes of hormone-receptor positive for postmenopausal breast cancer patients who are receiving adjuvant tamoxifen in Department of clinical oncology and Nuclear Medicine, Ain Shams University hospitals, Cairo, Egypt from January 2010 to December 2015.

Chapter 1

EPIDEMIOLOGY AND ETIOLOGICAL FACTORS OF BREAST CANCER

Epidemiology:

According to a systematic analysis study for the global burden of cancer conducted in Global Burden of Disease Cancer Collaboration, breast cancer was the most common cancer overall, with an estimated 2.4 million incident cases in 2015. The vast majority occurred in women, with 2.4 million cases vs 44□000 cases in men ***(Review, 2017).***

It is considered the most frequent cancer among women with an estimated 1.7 million new cancer cases diagnosed in 2012. It represents 25% of all new cancer cases among women. Breast cancer occurs in more and less developed regions, with more cases in less developed (883,000 cases) than more developed ones (794,000) ***(Ferlay et al., 2015).***

Breast cancer ranks as the fifth cause of death from cancer worldwide. In less developed countries, it is the most frequent cause of cancer death (324,000 deaths, 14.3% of total). In more developed countries it is now the second cause of cancer death (198,000 deaths, 15.4%) after lung cancer ***(American Cancer Society, 2016).***

According to the American Cancer Society 2016, cancer facts and figures sheet, about 246,660 women in the United States will be diagnosed with Invasive breast cancer and about 61,000 with in situ breast cancer, with an estimate of about 40,450 deaths from breast cancer. But overall, the rate of breast cancer death has declined by 36% from 1989 to 2012 with avoidance of approximately 249,000 breast cancer deaths due to improvements in early detection and treatment ***(Siegel et al., 2016).***

In Europe, about 494,000 new cases of breast cancer were diagnosed in 2012 and about 143,000 died from breast cancer in the same year according to Globocan 2012 ***(Ferlay et al., 2015).***

In the Arab world, surgeons and oncologists dealing with breast cancer tend to believe that it presents at an earlier age with a more advanced stage at presentation ***(Najjar & Easson, 2010).*** According to ***Ibrahim et al, 2014;*** breast cancer proportion was 32% of all cancers among Egyptian females from 2008 -2011 which makes it the most common type of cancer among females deaths ***(Ibrahim et al., 2014).***

According to Globocan 2012, breast cancer is the most common cancer among Egyptian females with about 5127 new cases ***(Ferlay et al., 2015).***

According to the Clinical Oncology department, Ain Shams University Hospital Statistics; the incidence of breast cancer patients presented from January 2010 to December 2014 was 30% of total cancer patients. Except for 10 male patients all through the 5 years the rest were females. The age ranged from 20 years to 93 years with the majority of patients (69.6%) in the age group from 40 to 65 years, whereas 14.2% were younger than 40 and 9.4% were older than 65 ***(El-Hawi et al., 2015).***

Risk factors:

The development of breast cancer is associated with numerous risk factors, including genetic, environmental and hormonal influences, yet 75% of women with this cancer have no readily identifiable risk factors ***(Jardines, 2015).***

Risk factors for breast cancer include weight gain after age of 18 years, excess body weight (for postmenopausal women), using hormone replacement therapy (HRT), physical inactivity, alcohol consumption, long menstrual history, use of oral contraceptives, and nulliparity or older age at first birth. Breastfeeding decreases the risk of developing breast cancer ***(Chlebowski et al., 2013).***

Female gender is the leading risk factor for developing breast cancer as the risk for females is about 100 times greater than men ***(Siegel et al., 2013).***

Table (1): The risk of developing breast cancer increases with age. Estimated New Female Breast Cancer Cases and Deaths by Age, United States, 2013a.

Age	In situ cases	Invasive cases	Deaths
<40	1,900	10,980	1,020
<50	15,650	48,910	4,780
50-64	26,770	84,210	11,970
65+	22,220	99,220	22,870
All ages	**64,640**	**232,340**	**39,620**

(Desantis et al., 2014)

In US, the median age at time of breast cancer diagnosis among women was 61 (between 2009-2013) ***(Howlader et al., 2016).***

In Egypt, the age-specific incidence rates show a progressive increase after the age of 30 years, with a sharp peak at the age group of 60-64 years ***(Ibrahim et al., 2014).***

Women with a family history of breast cancer, especially in a first-degree relative are at increased risk of developing breast cancer; risk is higher with more than one affected first-degree relative ***(American Cancer Society, 2015).***

The overall relative risk of breast cancer in a woman with a positive family history in a first-degree relative is 1.7. Premenopausal onset of the disease in a first-degree relative increases the risk of breast cancer by 3 folds, whereas

postmenopausal diagnosis increases the relative risk by only 1.5 ***(Jardines, 2015).***

Hereditary forms of breast cancer constitute only 5% to 10% of breast cancer cases overall ***(Jardines, 2015).***

BRCA1 and BRCA2 are the most well-studied susceptibility genes. BRCA1 and BRCA2 mutations explain about 20% of the inherted breast cancer. Mutations in the other high-risk genes as TP53, PTEN and STK11 are found in <1% of breast cancer families and are usually associated with rare cancer syndromes (*Li–Fraumeni, Cowden* and *Peutz–Jeghers* syndromes, respectively) ***(Balmaña et al., 2011).***

Overweight and obesity have been associated with an increased overall risk of breast cancer. These associations are consistent for postmenopausal breast cancer; however, there is still controversy on their impact on the risk of premenopausal breast cancer ***(Amadou et al., 2013).***

Risk is 1.5 times higher in overweight women (BMI 25.0–29.9 kg/m²) and about 2 times higher in obese women (Body mass index (BMI) ≥ 30 kg/m²) than in lean women ***(La Vecchia et al., 2011).***

Breast cancer risk associated with excess body weight in postmenopausal women is likely due to high estrogen levels, as fat tissue is the main source of estrogen after menopause. This

association may also be explained by the higher levels of insulin among obese women ***(American Cancer Society, 2015).***

In contrast, studies have found that obesity protects against developing breast cancer in premenopausal women. A large meta-analysis found that among women aged 40 - 49, the risk for developing breast cancer was about 14% less in over-weight women and 26% less in obese women compared to women with normal weight ***(Nelson et al., 2012).*** The underlying mechanisms for this inverse relationship are not well understood, but the protective effect may be limited to estroger receptor (ER) positive breast cancers ***(Ritte et al., 2012).***

Although diabetes is not considered a breast cancer risk factor, a large pooled analysis from 17 prospective studies suggested that insulin growth factor-1 was associated with breast cancer risk in both premenopausal and postmenopausal women. However, these associations are assumed to be restricted to estrogen receptor ER+ tumors ***(Hormones, Cancer, & Group, 2010).***

The risk of developing breast cancer increases by about 5% for each year earlier menstruation begins and by 3% for each year later menopause begins ***(Hamajima et al., 2012).*** The increased risk may be due to longer exposure to reproductive hormones and has been more strongly linked to ER+ breast cancer ***(Anderson et al., 2014).***

A first full-term pregnancy before age of 30 is suggested to have a protective effect against breast cancer, whereas a late first full-term pregnancy or nulliparity is associated with a higher risk. It is also suggested that lactation may have a protective effect against developing breast cancer ***(Jardines, 2015).***

In a meta-analysis of 27 studies, breastfeeding resulted in approximately 11% lower risk of breast cancer. Furthermore, this protective effect increased to 28% when the period of breastfeeding was 12 months or longer ***(Anothaisintawee et al., 2013).***

External hormones that contain estrogen may increase the risk of breast cancer. A meta-analysis of 178 studies showed that ever users of oral contraceptives (OC) and hormone replacement therapy (HRT) had 10% and 23% higher risks of developing breast cancer, respectively, when compared with nonusers. The duration of exposure might also be a risk factor if the time of exposure was 10 or more years ***(Anothaisintawee et al., 2013).***

The use of combined HRT (estrogen plus progestin) was found to be associated with increased incidence of breast cancer, especially when its use is initiated shortly after menopause ***(Chlebowski et al., 2013).***

Higher risk for breast cancer was found to be associated with previous benign breast disease especially proliferative lesions with atypia ***(Tice et al., 2013).***

A personal history of ductal carcinoma in situ or invasive breast cancer increases the risk of developing an invasive breast cancer in the contra lateral breast. The incidence was found to be about 4% during an average follow-up of 7.5 years ***(Nichols et al., 2011).***

Higher density of breast tissue on mammograms is considered a strong risk factor. Women with high-density mammograms have six times higher risk than women with low density mammograms ***(Nazarali et al., 2014).***

Exposure to ionizing radiation is one of the most firmly established environmental causes of breast cancer. Ionizing radiation can increase the risk for breast cancer through a number of different mechanisms, including direct mutagenesis and genomic instability ***(Broeks et al., 2010).***

Scientific and clinical advances have brought dramatic improvements in the treatment and outcomes of Hodgkin's lymphoma (HL), with 10-year relative survival now exceeding 80%. However, the radiotherapy and chemotherapy regimens responsible for these improvements are themselves carcinogenic. Consequently, second malignancies are now the leading cause of death in long-term HL survivors. Among

female HL survivors, breast cancer is the most commonly diagnosed solid tumor. For women treated for HL before age 30 years, the risk of developing breast cancer is six times greater than in the general population, with an absolute excess risk of 20 to 40 occurrences per 10,000 annually. Most of this excess risk is attributed to irradiation of the axillae and mediastinum in HL, with relative risks varying by age at radiation, radiation dose, extent of radiation field, and receipt of chemotherapy ***(Broeks et al., 2010)***.

A recent study found that diagnostic radiation exposure before age of 30 years, increased risk of breast cancer in a dose-dependent manner among women with BRCA mutations ***(Pijpe et al., 2012).***

Breast cancer risk is 12% higher in current smokers, and 9% higher in former smokers, compared with never-smokers. The risk increases with amount, duration, and starting age of smoking ***(Gaudet et al., 2013).***

Pathology and Molecular Subtypes

Breast cancer is a heterogeneous disease in terms of histology, therapeutic response, patterns of distant metastasis, and patient outcomes ***(Prat et al., 2011).***

Expression of the estrogen receptor (ER), progesterone receptor (PgR), and HER2 receptors, along with clinic-pathologic features, as tumor grade, tumor size, nodal

involvement, histologic type, and surgical margins, are commonly used to determine treatment and to predict prognosis ***(Vallejos et al., 2010).***

Breast cancer is mainly categorized into in situ carcinoma and invasive breast carcinoma ***(Malhotra et al., 2010).*** Invasive carcinoma and carcinoma in situ were classified as ductal and lobular based on the site from which the tumor originated. Cancers originating from the ducts are known as ductal carcinomas, while those originating from the lobules are known as lobular carcinomas ***(Makki, 2015).***

In-situ carcinoma:

Ductal carcinoma insitu (DCIS) is a noninvasive potentially malignant intraductal proliferation of epithelial cells that is confined to the ducts ***(Makki, 2015).***

Lobular carcinoma in situ (LCIS) is generally not thought to be a precursor of invasive cancer. Instead, it is considered a marker for increased risk for developing invasive cancer. Features that determine aggressive behavior of LCIS include histological features as the degree of pleomorphism, bulk of disease, solid-duct involvement and the presence of comedo necrosis ***(American Cancer Society, 2015).***

LCIS is multicentric in about 70% of cases and bilateral in approximately 30%–40% of cases ***(Rosai, 2011).***

DCIS is characterized as having tendency to progress into invasive breast cancer. Grading of DCIS is based upon its nuclear features. Comedo-type necrosis is associated with high-grade DCIS ***(Sinn & Kreipe, 2013).***

DCIS are divided into subtypes: Comedo, solid, cribriform, papillary, and micropapillary. Some cases of DCIS have a single growth pattern, but the majority shows a mixed pattern ***(Robbins et al., 2010).***

Invasive breast carcinoma:

Most of the breast malignancies are adenocarcinomas, which constitute more than 95% of breast cancers ***(Robbins et al., 2010).***

Invasive ductal carcinoma (IDC) is the most common form of invasive breast cancer ***(Makki, 2015).*** It accounts for about 70-80% of invasive breast cancers ***(Nadia Howlader et al., 2014).***

In Egypt, similar results were found from different studies where IDC was the most common pathological subtype ***(Gado et al., 2017).***

Invasive lobular carcinoma of the breast comprises up to 15% of all cases. Typically, they are associated with a good prognosis, being low grade and estrogen receptor positive; however, the tumor can be highly metastatic ***(Reed et al., 2015).***