INTRODUCTION

Breast cancer is the most common malignancy in women, accounting for 27% of all female cancers; it accounts for < 1% of all cancer cases in men. Breast cancer also is responsible for 15% of cancer deaths in women, making it the number-two cause of cancer death. An estimated 226,870 new breast cancer cases were diagnosed in women and 2,190 new cases were diagnosed in men in the United States in 2012, and 39,510 women and 410 men died of this cancer. As of 2012, there were approximately 2.9 million breast cancer survivors in the United States. Metastatic disease is found at presentation in 5% to 10% of patients with breast cancer. The most common sites of distant metastasis are the lungs, liver, lymph nodes, and bone ***(Lori Jardines et al., 2013).***

In Egypt data reported by Gharbiah population based cancer registry (2001) indicated that breast cancer ranked first among females (37.5%), with an age standardized rate of 49.6/100000. On the other hand carcinoma of the male breast was only .5%. Prostate cancer represents 3.7% of all cancer cases among men, while lung cancer represents 7% of all cancer cases among men and 2.4% among women ***(Ibrahim et al., 2002).***

Due to the limited prognostic and predictive power of the existing classifications, at the beginning of the new century, new approaches have been considered to unveil the molecular

basis for heterogeneity of breast cancer. Molecular subtyping is a way of classifying breast cancer tumors into one of four genetically-distinct categories, or subtypes: Luminal A, Luminal B, Basal (a subset of triple negative), and HER2-enriched subtype. Each subtype responds differently to different kinds of treatments, and some subtypes indicate a higher risk of disease recurrence ***(Blows et al., 2010).***

The underlying purpose of staging is to describe the extent or severity of an individual's cancer, and to bring together cancers that have similar prognosis and treatment. Staging of breast cancer is one aspect of breast cancer classification that assists in making appropriate treatment choices, when considered along with other classification aspects such as (ER, PR, HER2/neu) status, menopausal status, and the person's general health ***(Edge et al., 2010).***

Treatment for systemic disease is palliative in intent. Goals of treatment include improving quality of life and prolongation of life. Treatment of metastatic breast cancer will usually involve hormone therapy and/or chemotherapy with or without targeted agents. Radiation therapy and/or surgery may be indicated for patients with limited symptomatic metastases.

Various monotherapy and combination regimens have been evaluated as candidate therapies for MBC patients who experience disease progression after treatment with anthracyclines and taxanes (A/T). At present, capecitabine,

ixabepilone, and eribulin are the only cytotoxics approved by the (FDA) as single agents in the third-line setting and beyond. In terms of combination therapy for human epidermal growth factor receptor-2 (HER2)-negative MBC, the FDA, based on Phase III clinical trials demonstrating benefits in progression-free survival (PFS), time to progression (TTP), objective response rates (ORR), and in some cases OS, approved the following regimens: capecitabine plus docetaxel, capecitabine plus ixabepilone, and gemcitabine plus paclitaxel. The superiority of combination chemotherapy over single-agent sequential therapy is debatable. Therefore, sequential monotherapy tends to be favored in order to minimize toxicity and maximize patients' quality of life ***(Cortazar et al., 2008).***

Two thirds of women with diagnosed breast cancer have disease that is estrogen receptor/progesterone receptor-positive (ER/PR^+) ***(Rakha et al., 2007).*** These tumors are highly responsive to anti-estrogen therapeutic strategies. However, despite widespread use of hormonal adjuvant therapy, a quarter of women with ER^+ disease will relapse ***(Tischkowitz et al., 2007).*** In this situation, a determination regarding further hormonal therapy versus chemotherapy as the next step must be made. Patients whose disease is viscerally relatively 'low'-volume, bone/soft tissue-predominant, and asymptomatic are reasonable candidates for upfront endocrine therapy.

There is currently no preferred standard chemotherapy for previously treated patients with TNBC, as previous randomised studies in the metastatic setting have not addressed the predictive values of the molecular subtypes of breast cancers. Treatment is therefore selected (as for other subtypes) from a number of current recommended agents that are approved in the general breast cancer population. Conventional treatments for relapsed patients are limited, particularly, because standard chemotherapeutic regimens containing anthracyclines and taxanes have usually already been given in the adjuvant and neoadjuvant settings. Anthracyclines and taxanes have been suggested as rechallenge regimens in patients with 6–12 months of disease-free survival following completion of adjuvant chemotherapy and recurrence ***(Palmieri et al., 2010).***

AIM OF THE WORK

This is a retrospective study to assess the clinico-epidemiological features of metastatic breast cancer in cases with her2neu receptor negative with either ER, PR positive and negative status and systemic treatment outcome as regard toxicity, response rate, progression free survival and overall survival in metastatic breast cancer patients represented between 2008 to 2012 at department of clinical oncology and nuclear medicine, Ain Shams University.

EPIDEMIOLOGY

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Also in Egypt breast cancer constitutes 33% of all females' cancers at NCI and 50% in private series. The median age is 46 years ***(El-Bolkainy et al., 2005).***

Table 1 depicts the proportions and rates of the most frequent cancer sites by gender. In females, breast and liver cancer occupied the top ranks accounting for around 45% of all cancers, while figure 5 shows age specific incidence of breast cancer in females in Egypt ***(Amal et al., 2014).***

Table (1): The most frequent cancers in Egypt estimated using the results of the National Population-Based Registry Program of Egypt 200-2011.

	Site	%	Crude rate	ASR
Males	Liver	33.63	39.5	61.8
	Bladder	10.71	12.6	21.1
	Lung*	5.69	6.7	10.4
	Non-Hodgkin lymphoma	5.48	6.4	8.8
	Brain**	5.48	6.4	8.8
	Prostate	4.27	5.0	9.3
Females	Breast	32.04	35.8	48.8
	Liver	13.54	15.1	24.4
	Brain**	5.18	5.8	8.0
	Ovary	4.12	4.6	6.3
	Non-Hodgkin lymphoma	3.80	4.2	6.1
	Thyroid	3.28	3.7	4.3
Both Sexes	Liver	23.81	27.5	43.6
	Breast	15.41	17.8	24.3
	Bladder	6.94	8.0	13.5
	Brain**	5.29	6.1	8.5
	Non-Hodgkin lymphoma	4.64	5.4	7.5
	Lung*	4.22	4.9	7.5

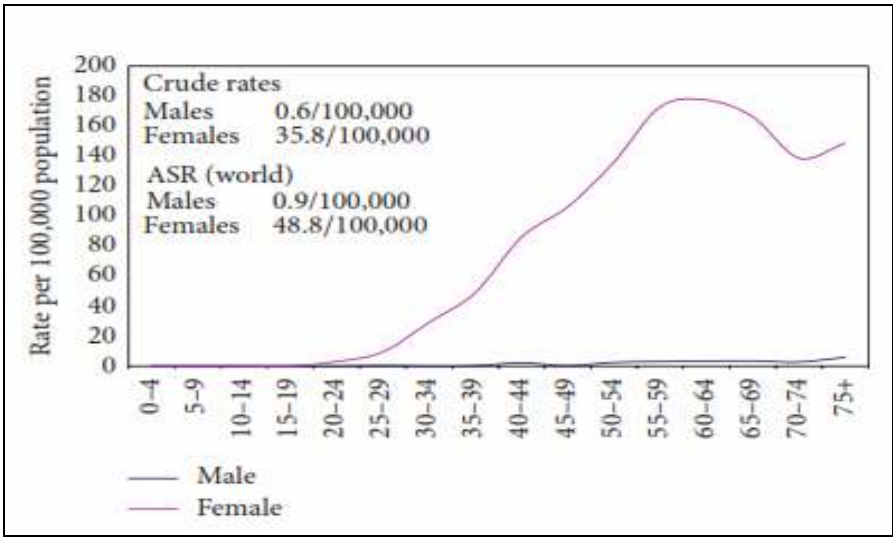

Figure (1): Calculated age specific incidence rates for breast cancer in Egypt 2008-2011.

Estimated Number of Incident Cancer Cases 2013–2050. During the period 2013–2050, population of Egypt is expected to increase to approximately 160% the 2013 population size. This would lead to a progressive increase in number of incident cases from 114,985 in 2013 to 331,169 in 2050, approximately 290% of 2013 incidence (Figure 2). This increase reflected both population growth and demographic change mainly due to ageing of population ***(Amal et al., 2014).***

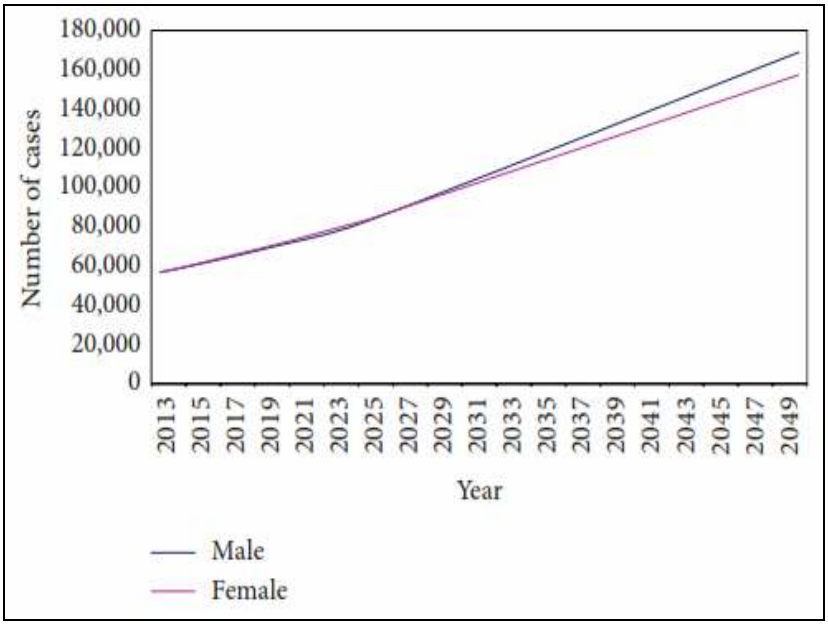

Figure (2): Estimated number of cases in Egypt (2013-2050).

RISK FACTORS

Increasing age: The risk of breast cancer increases with older age and peaks in the sixth decade, Epidemiology, and End Results (SEER) database, the incidence of breast cancer by age range was ***(Jemal et al., 2010):***

- 20 to 34 years of age – 2 percent
- 35 to 44 years – 10 percent
- 45 to 54 years – 23 percent
- 55 to 64 years – 24 percent
- 65 to 74 years – 20 percent
- 75 to 84 years – 16 percent
- Age 85 and older – 6 percent

Female gender: Breast cancer occurs 100 times more frequently in women than in men ***(Jemal et al., 2010).***

Race: The highest rate of breast cancer occurs among white women in us, although breast cancer remains the most common cancer among women of every major ethnicity ***(Kohler et al., 2011).***

Postmenopausal women: A higher body mass index and/or weight gain have been consistently associated with a higher risk of breast cancer among postmenopausal women ***(Ahnj et al., 2007)***. As examples:

- In a 2000 analysis of seven cohort studies, women with a BMI >33 kg/m ^{2} had a higher breast cancer risk compared with those with a BMI <21 kg/m ^{2} (relative risk [RR] 1.27, 95% CI 1.03-1.55) ***(van Den Breut et al., 2007).***

- In the Nurses' Health Study, women who gained 10 kg or more since menopause had a higher risk of breast cancer compared with women who maintained their weight (400 versus 339 per 100,000 person-years; RR 1.18, 95% VI 1.03-1.35) ***(Eliassen, 2006).***

This may be explained by higher estrogen levels resulting from the peripheral conversion of estrogen precursors (from adipose tissue) to estrogen ***(Key et al., 2006).*** In addition, hyperinsulinemia may also explain the obesity-breast cancer relationship because a high BMI is associated with higher insulin levels ***(Ganter et al., 2009).***

Premenopausal women: on the other hand, an increased BMI is associated with a lower risk of breast cancer in premenopausal women In the 2000 pooled analysis discussed above, premenopausal women with a BMI ≥31 kg/m ^{2} were 46 percent less likely to develop breast cancer than those with a BMI <21 kg/m ^{2} ***(Nelson et al., 2012) .***

Estrogen exposure: High endogenous estrogen levels increase the risk of breast cancer in both postmenopausal and premenopausal women. In postmenopausal women, the

correlation between an increased risk for breast cancer and increasing hormone levels (eg, estradiol, estrone) has been established ***(Farhat et al., 2011).***

Other hormonal factors:

Androgens: Data suggest that androgens exert dual effects on breast tumorigenesis, with a proliferative effect mediated by the ER, and an antiproliferative effect mediated by the androgen receptor ***(Brettes et al., 2008).*** Elevated androgen levels have been associated with an increased risk of postmenopausal and premenopausal breast cancer ***(Missmer et al., 2008; Dorgan et al., 2010),*** although this has not been consistently demonstrated ***(Thomas et al., 2000).***

Insulin pathway and related hormones: Despite diabetes is not considered a breast cancer risk factor a large pooled analysis drawing from 17 prospective studies suggested that insulin growth factor-1 was associated with breast cancer risk in both premenopausal and postmenopausal women ***(The Lancet, 2010).***

In addition, the Women's Health Initiative reported that higher endogenous insulin levels were associated with an increased risk of breast cancer among nondiabetic, postmenopausal women who did not take menopausal hormone therapy (HR for highest versus lowest quartile of insulin level 2.40, 95% CI 1.30-4.41) ***(Ganter et al., 2009).***

Reproductive factors: Earlier menarche or later menopause Younger age at menarche is associated with a higher risk of breast cancer ***(Coldit et al., 2000).***

Infertility: The relation between infertility and breast cancer risk is controversial. Several epidemiologic studies implies that infertility due to anovulatory disorders decreases the risk of breast cancer ***(Preutice et al., 2006).***

Absence of breastfeeding: A protective effect of breastfeeding has been shown in multiple studies ***(Jernström et al., 2005).***

A large pooled analysis that included individual data from 47 epidemiologic studies (50,302 women with invasive breast cancer and 96,973 controls) estimated that for every 12 months of breastfeeding, there was a 4.3 percent reduction in the relative risk of breast cancer ***(The Lancet, 2002).***

Personal history of breast cancer: History of ductal carcinoma in situ (DCIS) or invasive breast cancer increases the risk of developing cancer in the contralateral breast. A 2010 study using Surveillance, Epidemiology, and End-Results (SEER) data that included almost 340,000 women with a primary breast cancer found the incidence of invasive contralateral breast cancer was 4 percent during an average follow-up of 7.5 years ***(NICH et al., 2011).***

Family history of breast cancer: The risk is directly related to the number of female first-degree relatives with and without cancer. As an example, in a pooled analysis using data from over 50,000 women with breast cancer and 100,000 controls, the risk of breast cancer was ***(NICH et al., 2011):***

- Increased almost twofold if a woman had one affected first-degree relative
- Increased threefold if she had two affected first-degree relatives

Physical inactivity: Regular physical exercise appears to provide fair protection against breast cancer, particularly in postmenopausal women ***(Maruti et al., 2008).*** A 2011 review of epidemiologic studies estimated that risk of breast cancer was reduced by 25 percent among physically active women compared with women who were the least active ***(Lynch et al., 2011).***

Alcohol: Apparently there is significant dose-response relationship between alcohol consumption and an increased risk of breast malignancy, which begins with alcohol intake as low as three drinks per week.

Smoking: Multiple studies suggest there is a modestly increased risk of breast cancer in smokers ***(Johnson et al., 2011),*** although others have not ***(Al Delaimy, 2004).*** Increased risks are most consistent in studies that evaluated early

initiation, longer duration, and/or higher pack-years of smoking. In a 2011 report from the Women's Health Initiative Observational study of almost 80,000 women, nonsmokers who reported extensive exposure to cigarette smoke (defined as ≥10 years' exposure in childhood, ≥20 years' as an adult at home, or ≥10 years' occupational exposure) had a higher risk of breast cancer compared to those who were not exposed to cigarette smoke (hazard ratio [HR] 1.32, 95% CI 1.04-1.67) ***(Luo et al., 2011).***