INTRODUCTION

Breast cancer is the most common cancer among US women, accounting for 29% of all newly diagnosed cancer cases and the second most common cause of death after lung cancer. The American cancer society estimated that the number of new cases of breast cancer patients in 2014 would be 232,670 females and 2,360 males while estimated number of deaths is 40,000 and 430 in females and males respectively. ***(American Cancer Society, 2014)***

The development of breast cancer has been associated with numerous risk factors, including genetic, environmental, hormonal influences yet 75%of women with this cancer have no readily identifiable risk factors ***(Jardines L. et al., 2014).*** Breast cancer is an age-related disease. Second to female gender, advancing age is the most important risk factor for breast cancer. In USA, approximately 50% of breast cancer occurs in women 65 years or older and more than 30% occurs in age more than 70. While in Egypt, the peak incidence of breast cancer occurs in the age group from 40-59 years. ***(Zeeneldeen et al., 2012)***

Moreover, obesity, exposure to ionizing radiation, and proliferative breast disease as atypical hyperplasia are all risk factors. Hormonal factors as early menarche, late menopause, null parity, late first full term pregnancy, and lack of breast feeding which all represent exposure to endogenous estrogen.

In addition, exposure to exogenous estrogen in cases of hormone replacement therapy is a known etiologic factor ***(Pegram et al., 2012)***

Family history is by far one of the commonest risk factors. Only 5–10% has a strong inherited component with only 4–5% being due to high penetrance genes as BRCA1 and BRCA2 mutations. Individuals with a family history in most of the developed countries are referred to family history clinics for an assessment of their breast cancer risk ***(Lallo et al., 2012).***

Regarding histopathological classification of breast cancer, it could be broadly categorized into in situ carcinoma and invasive (infiltrating) carcinoma. Breast carcinoma in situ is further sub-classified as either ductal or lobular. Similar to in situ carcinomas, invasive carcinomas are a heterogeneous group of tumors differentiated into histological subtypes. The major invasive tumor types include infiltrating ductal, invasive lobular, ductal/lobular, mucinous (colloid), tubular, medullary and papillary carcinomas. ***(Malhotra et al., 2010).***

Histological tumor grade is based on the degree of differentiation of the tumor tissue. According to the Nottingham Grading System; which is based on the evaluation of three morphological features: (a) degree of tubule or gland formation, (b) nuclear pleomorphism, and (c) mitotic count. Grading has a very important prognostic factor in breast cancer ***(Rakha, 2010)***

All breast cancers should be evaluated by immunohistochemistry (IHC) staining for estrogen and progesterone receptor status and HER2 over expression. Breast cancers expressing high level of Ki67, a nuclear marker for cell proliferation, are associated with worse outcomes ***(Cheang et al., 2009)***.

Breast cancer may be presented in the form of a breast lump, nipple discharge, skin changes (peau d'orange), axillary lymphadenopathy, and nipple retraction. Paget's carcinoma and inflammatory breast cancer are also presentations of breast cancer.In some cases patients are presented late with symptoms of metastasis ***(Pegram et al.,2012).***

The diagnosis of breast cancer is based on history and clinical examination, in combination with imaging and confirmed by pathological assessment. ***(Saslow et al., 2004).***

All breast cancer patients should be assigned proper clinical stage and if appropriate evaluation available, a pathological stage as well. Proper staging allows for identification of local and systemic treatment options and provides baseline prognostic information. The most widely used system to stage breast cancer is The American Joint Committee on Cancer AJCC which is based on the tumor size (T), nodal involvement (N) and presence of distant metastasis (M). The AJCC has implemented a revision of the cancer staging manual (7^{th} edition) containing some changes and

additions to the TNM staging system, effective from January 2010 ***(Edge et al., 2010).***

The prognosis of breast cancer has become relatively good, with current 10-years relative survival about 70% in most western populations conventional prognostic factors of survival, such as tumor size, lymph node status and grade, remain the most important determinants of 10-years survival for breast cancer patients, other tumor related characteristics as histopathological type and lymphovascular invasion are important as well. Patient characteristics include age at diagnosis, co-morbidities, performance status play an important role. Hormone receptor status and HER2 over-expression have both a prognostic and predictive values thus making their identification at diagnosis of utmost importance ***(Soerjomataram et al., 2008).***

Treatment of breast cancer implies treatment of local disease either by surgery or radiotherapy or both, and treatment of systemic disease by cytotoxic chemotherapy, hormonal therapy, or combination of these.

The need for and selection of treatment modality depends on the various prognostic and predictive factors including tumor histology, clinical and pathological characteristics, lymph node status, hormone receptor and HER2 status, staging, menopausal status, age and other comorbidities. Treatment should be individualized and patient preference should be included in the treatment decision ***(Gradishar et al., 2014).***

AIM OF THE WORK

The aim of this work is to retrospectively analyze the clinical and epidemiological features of Breast Cancer at our Clinical Oncology Department, Ain Shams University in five years duration (from 2010 till 2014).

Study risk factors, most common presentations, pathology, staging, and prognostic factors.

Eventually coming up with statistical data that is customized to our patients will help us define the magnitude of the problem in our department and help us deal with that problem.

Chapter 1

EPIDEMIOLOGY AND ETIOLOGICAL FACTORS

Epidemiology

Breast cancer is the most common cancer among US women, accounting for 29% of all newly diagnosed cancer cases and the second most common cause of death after lung cancer. The American cancer society estimated that the number of new cases of breast cancer patients in 2014 would be 232,670 females and 2,360 males while estimated number of deaths is 40,000 and 430 in females and males respectively***(American Cancer Society, 2014).***

Moreover, according to the Surveillance, Epidemiology and End Results program statistics, breast cancer accounts for 6.8 % of all cancer deaths, with a median age at diagnosis of 61 years and median age at death of 68 years ***(Howlader et al., 2014).***

While in Egypt, and according to the results of the population-based cancer registry, the estimated incidence rates of breast cancer among females in Lower, Middle, and Upper Egypt are 33.8%, 26.8% and 38.7% respectively ***(Amal et al., 2014).***

Breast cancer is an age-related disease. Second to female gender, advancing age is the most important risk factor for breast cancer. In USA, approximately 50% of breast cancer occurs in women 65 years or older and more than 30% occurs in age more than 70. While in Egypt, the peak incidence of

breast cancer occurs in the age group from 40-59 years ***(Zeeneldin et al., 2012).***

One of the highly challenging clinical situations met in breast cancer population, is the gestational or pregnancy associated breast cancer, defined as, breast cancer that is diagnosed during pregnancy, in the first postpartum year, or any time during lactation. Since the well being of the mother and the fetus both must be taken into consideration before starting any treatment plan. In addition, prospective studies in this aspect are very few, and much of the clinical evidence is limited to retrospective studies and case reports. Up to 20% of breast cancers in women under age 30 are pregnancy-associated, compared to less than 5% in women under age of 50 ***(Anderson et al., 1996).***

All around the world the incidence of this cancer shows varied rates. The rates are low in less-developed countries and greatest in the more-developed countries. Breast cancer is related to age with only 5% of all breast cancers occur in women less than 40 years old ***(Manda, 2014).***

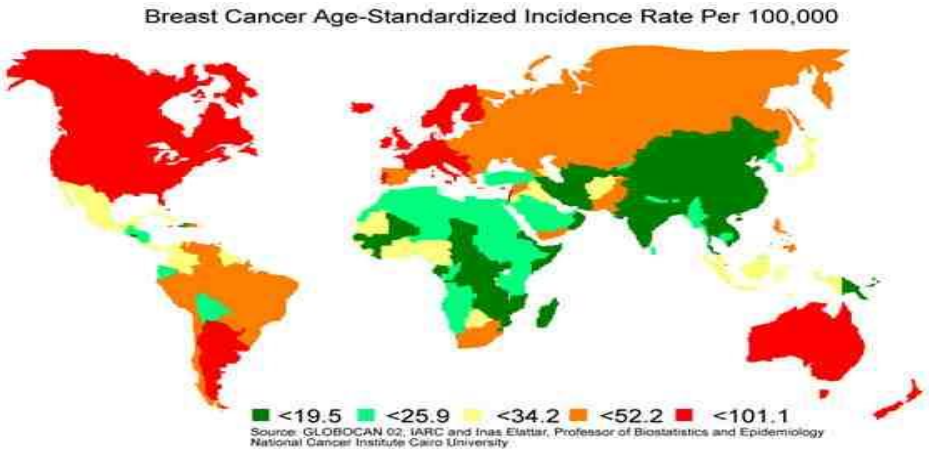

Figure (1): Breast cancer Age-Standardized Incidence Rate per 100,000 ***(Manda, 2014).***

Regarding ethnicity, breast cancer is highest among white females. Age-standardized rates for White females with breast cancer range from 122.4 to 125.7 per 100,000. Rates for Asian females are significantly lower, ranging from 59.7 to 92.3 per 100,000 and the rates for Black females are also significantly lower, ranging from 68.8 to 107.9 per 100,000 ***(Collaborative Group on Hormonal Factors in Breast Cancer, 2001).***

Generally, the highest incidence rates are found in Switzerland, U.S. whites, Italy, and many other European countries, whereas low rates are found in Africa, Asia, and South America. This difference reflects the long-standing high prevalence of reproductive factors associated with increased risk of breast cancer, including early menarche, late child bearing, fewer pregnancies, use of menopausal hormone therapy, as well as increased detection through mammography. In addition to these factors, the high breast cancer incidence rates in Israel may

reflect the disproportionately high prevalence of BRCA1 and BRCA2 mutations in the Ashkenazi Jewish population ***(Jemal et al., 2010).***

Etiology and risk factors

The development of breast cancer has been associated with numerous risk factors, including genetic, environmental, hormonal influences yet 75%of women with this cancer have no readily identifiable risk factors ***(Jardines et al., 2014).***

Among the well-documented risk factors for breast cancer development is the presence of a familial history of breast cancer, reproductive factors associated with prolonged exposure to endogenous estrogens, such as early menarche, late menopause and late age at first childbirth. Exogenous hormones such as oral contraceptives and hormone replacement therapy also exert a higher risk. Furthermore, alcohol use, and body mass index, as well as exposure to ionizing radiation are among the modifiable risk factors for breast cancer ***(Lacey et al., 2009).***

Hereditary breast cancer And Family history

The risk associated with a positive family history of breast cancer is markedly affected by the number of first degree relatives having breast 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 increased by a twofold if a woman had one affected first-degree relative and

by three fold if she had two affected first-degree relatives. Moreover, the age at diagnosis of the affected relative influences that risk as well. A female has a threefold higher risk if the first degree relative was diagnosed before the age of 30 (RR 3.0, 95% CI 1.8-4.9), on the other side, she has only 1.5-fold increased risk if the affected relative was diagnosed after age of 60 ***(Collaborative Group on Hormonal Factors in Breast Cancer, 2001).***

Although a family history of breast cancer is common in 10% of females diagnosed with this cancer, yet, not all is associated with germ line (inherited) genetic mutations. The majority of hereditary breast cancer is associated with mutations in two genes, breast cancer susceptibility gene 1 and 2 (BRCA1 and BRCA2) ***(Foulkes, 2008).***

BRCA1 and BRCA2 germ line mutations explain almost 25 % of the inherited cases of breast cancer. BRCA1 accounts for around 15 % of the inherited breast cancers and 45 % of the families with breast and ovarian cancer. However, most of the families with less than six cases of familial breast cancer and no ovarian cancer or male breast cancer do not carry BRCA1 or BRCA2 mutations that can be detected using routine sequencing protocols. Non-BRCA hereditary breast cancer accounts for 67 % of breast cancer cases in families with only female breast cancer and four or five affected members ***(Eugenia, 2014).***

Other hereditary syndromes that demonstrate an increased susceptibility to breast cancer include Li-Fraumeni, Cowden, Lynch (also known as hereditary non-polyposis colorectal cancer [HNPCC]) and Peutz-Jeghers syndromes. They all share some characteristics as; early age at onset of breast cancer (usually before 50s), increased incidence of other cancers, and a higher incidence of a bilateral disease ***(Daly et al., 2010).***

Li Fraumeni Syndrome (LFS) caused by germline mutations in the TP53 tumor suppressor gene, breast cancer is the most common tumor among women with TP53 mutations. The risk of breast cancer in women with LFS is approximately 49% by age 60, with significant risk before age 40. The frequency of TP53 mutations in population-based series of young onset breast cancers (age <30 years at diagnosis) ranges from <1% to approximately 7%. It also features soft tissue and bone sarcomas, brain tumors, leukemias, and adrenal cortical carcinomas and a wide spectrum of other malignancies ***(Masciari et al., 2012).***

Cowden syndrome is a rare genetic disorder related to a mutation in PTEN gene, increasing the cellular proliferation of ectodermal, mesodermal and endodermal tissues. Its most featured characteristics is the occurrence of multiple hamartomas in the skin, breast, thyroid, gastrointestinal tract, endometrium and brain, as well as an increased risk for

malignant tumors of the breast, thyroid, endometrium and skin ***(Tutluer et al., 2012).***

Peutz-Jeghers syndrome is characterized by peri-oral pigmentation, hamartomatous polyposis and a predisposition to benign and malignant tumors of the gastrointestinal tract, breast, ovary, uterine cervix and testis. It occurs through inactivating germ line mutations of the STK11 gene functioning through the inhibition of the mTOR pathway. Patients with this syndrome have a 30–50 % risk of developing breast cancer ***(Taheri et al., 2013).***

Hereditary diffuse gastric cancer syndrome is an inherited cancer susceptibility syndrome caused by a germ line mutation in CDH1 gene important for cell-to-cell adhesion. It is suspected by more than two cases of diffuse gastric carcinoma in first degree relatives, with at least one documented case of diffuse gastric carcinoma before the age of 50 years, or multiple cases of gastric cancer of which at least one is identified as diffuse gastric carcinoma before the age of 50 years ***(Becker et al., 1994).*** Females with familial diffuse gastric cancer have an increased risk of almost 50 % of also getting lobular breast cancer ***(Keller et al., 1999).***

Hormonal factors:

Those include early menarche and late menopause and parity studies, which all represent exposure to endogenous

hormonal factors. The relationship between those factors and the risk of breast cancer was analyzed in a series of studies using subjects from the "Breast Cancer Detection Demonstration Project". This was a multicenter breast cancer screening program involving over 280,000 women at 29 centers. Information about reproductive variables (timing of menarche and menopause, number and timing of children) was obtained from home interviews conducted by trained nurse interviewers. Case-control data were ultimately obtained from 2,908 breast cancer patients and 3,180 controls matched for ethnicity and age ***(Singletary, 2003).***

These data indicated that early menarche increased the risk of breast cancer by a RR of 1.3 comparing females who began menstruating before the age of 12 to those who began after the age of 15. At the other end of the reproductive period, late menopause until age of 55 or after showed a RR of 1.22 compared with those who experienced menopause before the age of 45. As support for this idea, it has been observed that women who have bilateral oopherectomy before the age of 40 show a 45% reduction in risk compared with women who undergo a natural menopause at the age of 50 to 54 years ***(Brinton et al., 1988).***

The association between parity and breast cancer risk also has been a subject to different meta-analyses, being more obvious in estrogen receptor (ER) and progesterone receptor (PR) positive tumors. Overall, women who have had any

children have a 30% lower breast cancer risk than nulliparous women. Moreover, breast cancer risk decreases by 7% for each live birth ***(Ma et al., 2006)***.

The relationship between oral contraceptives (OCs) and the increased risk of breast cancer has been the subject of intense research. The Collaborative Group on Hormonal Factors in Breast Cancer pooled together data from almost all studies of breast cancer risk in relation to OC use published up to the mid-1990s. It concluded that women who were current or recent users of OCs had a slightly increased risk of developing breast cancer. However, ten years or more after stopping OCs, their risk of developing breast cancer returned to the level at which it would have been if they had never used them ***(Dumeaux et al., 2005).***

Overall, the collaborative study found that women who used OCs had a very slight increased risk of breast cancer compared with never-users. The risk was limited to current users and those who had used hormonal contraceptives within 10 years. While the only subgroup that appeared to be at higher risk than others was women who started using hormonal contraception at a very young age before age of 20. ***(Kilbourne-Brook et al., 1997).***

The relative risk (RR) for breast cancer in relation to years since last use of oral contraception, as calculated by the collaborative group on hormonal factors in breast cancer, were;

RR=1.24 for current users, 1.15 for 1-4 years since last use, 1.07 for 5-9 years, 0.98 for 10-15 years and 1.01 for 15-19 years ***(Collaborative Group on Hormonal Factors in Breast Cancer, 1996).***

In order to establish the evidence of the risk of hormone replacement therapy (HRT), the Collaborative Group on Hormonal Factors in Breast Cancer has brought together and reanalyzed about 90% of the worldwide epidemiological evidence on the relation between risk of breast cancer and use of HRT. Data on 52,705 women with breast cancer and 108,411 without breast cancer from 51 studies in 21 countries were collected, checked and analyzed centrally. Results showed that among current users of HRT or those who ceased use 1 to 4 years previously, the RR of breast cancer diagnosis increased by a factor of 1.023 (95% confidence interval [CI] 1.011–1.036; 2P = 0.002). For women who had used HRT for 5 years or longer (average duration of use 11 years) the RR was 1.35 (95% CI 1.21–1.49; 2P = 0.00001) for each year of use. Five or more years after cessation of HRT use, there was no significant excess of breast cancer overall or in relation to duration of use. In North America and Europe, the cumulative incidence of breast cancer between the ages of 50 and 70 in never-users of HRT is about 45 per 1,000 women. The cumulative excess numbers of breast cancers diagnosed between these ages per 1,000 women who began use of HRT at age 50 and used it for