INTRODUCTION

Breast cancer is a major health problem. It is estimated that 184,450 new cases of cancer breast were diagnosed in USA in the year 2008 which represents 26% of new cancer cases in females. In 2008, it is estimated that over a million women worldwide were diagnosed with cancer breast, of which 172,695 were classified as triple-negative ***(Swain, 2008).***

Triple-negative breast cancers are defined by a lack of expression of estrogen, progesterone, and ERBB2 receptors. This subgroup accounts for 15% of all types of breast cancer and for a higher percentage of breast cancer arising in African and African-American women. The triple negative subtype has characteristic epidemiological pattern. It is likely to arise in female, especially in premenopausal women with history of early menarche, higher parity, young age at full term pregnancy, short duration of breast feeding and higher body mass index. Also those who used medications to suppress lactation at a time have higher risk to develop basal-like tumor more than the luminal type ***(Milikan et al, 2008).***

Histologically, such cancers are poorly differentiated, and most fall into the basal subgroup of breast cancers, characterized by staining for basal markers (i.e. cytokeratin 5/6). Analyses of microarray gene-expression profiling data

show that they form a homogeneous group in transcriptional terms. Increasingly, research studies are identifying basal cancers on the basis of exhibiting this distinctive transcriptional profile. Histologically and transcriptionally, triple-negative breast cancers have many similarities to BRCA1-associated breast cancers, which suggests that dysfunction in BRCA1 or related pathways occurs in this subset of sporadic cancers ***(Cleator et al., 2007).***

The absence of specific treatment guidelines for this subgroup of triple-negative breast cancers are managed with standard treatment. However, such treatment leaves them results in a high rate of local and systemic relapse. Also, the triple negative disease has a characteristic pattern of the site of recurrence, the aggressive visceral metastasis are more common and bone relapse is less common ***(Smid et al., 2008).***

Recent studies highlight the frequency and aggressiveness of brain metastasis in triple negative cancer breast patient. From years 1989-2006, 3 thousands of cancer breast patients with brain metastasis were analyzed and triple negative pattern had the greatest risk factor to develop brain metastasis. The median survival among triple negative patients versus non triple negative was (4 vs 8 months, p = NS), and the interval between disease and development of brain metastasis was (22 vs 51 months, p < .0001) ***(Heitz et al., 2008).***

A Canadian group evaluated 1,500 women with cancer breast found increased incidence of distant recurrence and death among triple negative group compared with non-triple negative group. Also they found higher incidence of recurrence during the first 3 years following therapy with rapid declines thereafter ***(Dent et al., 2007).*** Although triple negative breast cancer is associated with poor outcome, it is not resistant to chemotherapy. In the adjuvant setting the CALGB 9344 study demonstrated higher benefit of adding taxanes to anthracycline in the double negative (ER/HER2) and over-expressed HER2 patients ***(Hayes et al., 2007).***

Triple-negative tumors do not respond to hormonal treatment or trastuzumab and can only be treated with chemotherapy. Fortunately, increasing evidence suggests that the triple-negative subgroup derives substantial and preferential benefit from chemotherapy. The Cancer and Leukemia Group B (CALGB) recently reviewed data from 3 randomized trials: 8541, investigating escalating dose intensity; 9344, exploring the addition of paclitaxel to the doxorubicin and cyclophosphamide (AC) backbone; and 9741, studying the impact of dose density. A combined analysis of over 6600 patients treated on these studies, stratified by hormonal receptor (HR) status, demonstrated greater reductions in risk of recurrence for the HR-negative subset, translating into larger absolute benefits in both disease-free and overall survival ***(Berry et al., 2006).***

Triple-negative breast tumors could contribute to the poor prognosis compared with luminal A breast cancer. Cisplatin and carboplatin are anti-cancer chemotherapy drugs that stop cancer cells from growing abnormally and is used to treat other cancers. Few studies have revealed that cisplatin-based therapy may be effective for this type breast cancer ***(Kaplan et al., 2007).***

AIM OF THE STUDY

The aim of this study is to assess the benefit of the addition of carboplatin to anthracyclins and taxenes in triple negative breast cancer patients as adjuvant chemotherapy.

REVIEW OF LITERATURE

Epidemiology & Risk factors:

Breast cancer is the most common cancer among women in the United States, the second most common cause of cancer death, and the main cause of death in women ages 45 to 55 years. In 2009, approximately 192,370 American women were diagnosed with breast cancer, and an estimated 40,170 women died of the disease ***(Jemal et al., 2009).*** In 2010, an estimated 207,090 new cases of breast cancer were diagnosed in the United States. Approximately 15% of all breast cancer cases are characterized as triple negative ***(Stead et al., 2010).***

An estimated 1 million cases of breast cancer are diagnosed annually worldwide. Of these, approximately 170,000 are of the triple-negative (ER–/PR–/HER2–) phenotype ***(Anders and Carey, 2009).*** Of these TNBC cases, about 75% are "basal-like" ***(Rakha et al., 2009).***

Breast and gynaenocological malignancies together constitute 44.9% of female cancers in Egypt, Gharbiah. Breast cancer is the most frequent cancer among Egyptian females. Over the three years 2000-2002, 1831 breast cancer cases were registered; 1810 females and 21 males with an average of 603 cases of female breast cancer per year. Breast cancer accounts for 35.7 % of all newly

diagnosed female cancers (5070 cases). The crude incidence rate for females was 33.1/100,000 female population. Standardized for age using world population, the rate was 41.9/100,000. Mean age at diagnosis in females was 49.3 years ranging between 18:93 years with a median of 49 years ***(Ibrahem et al., 2007).***

Compared to published worldwide rates, Egypt, Gharbiah occupies the 27th percentile rank. Rates lower than those of Egypt are reported from 50 registries all over the world. These remarkably large geographical differences are potentially explicable based on genetics or the influence of lifestyle and environment. Urban-Rural differences in breast cancer incidence across 8 years (1999-2006) in Egypt, Gharbiah showed 3-4 times higher rates in urban, (the more developed population). This higher rates in urban could be due to exposure to unknown risk factors like xenoestrogen ***(Ibrahem et al., 2007).***

Over the three years 2008-2010, 918 new breast cancer cases were registered at oncology department of Ain Shams University**.** Of those, approximately 20.4% (918 patients) have a triple-negative phenotype ***(Ain Shams University Registry, 2011).***

Several studies suggest that breast cancer subtypes vary by race and age. One of the largest descriptive analyses of TNBC is a population-based study of women with breast cancer from the California Cancer Registry.

The prevalence of TNBC by race and ethnicity depends on the demographics of the community Figure *(1*). Overall, most TNBC patients are Caucasian, but women of African American descent are proportionally 2 to 3 times as likely to have a triple-negative tumor ***(Parise et al., 2010).***

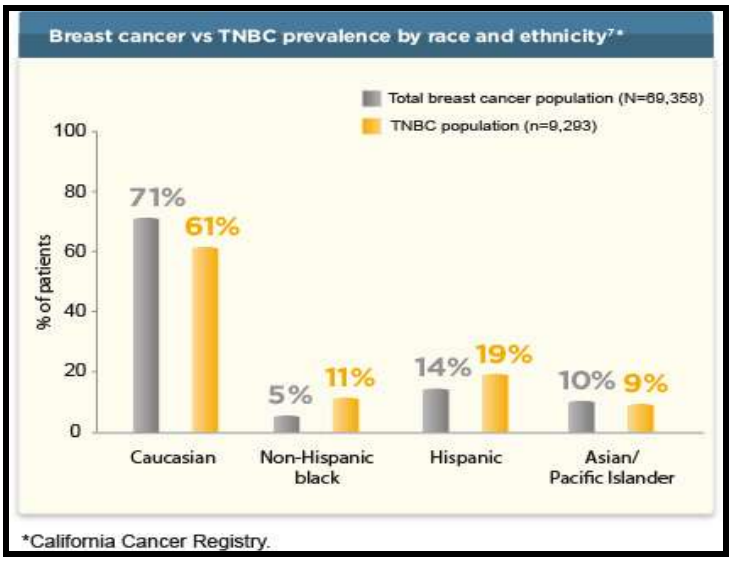

Figure (1): The prevalence of TNBC by race and ethnicity ***(Parise et al., 2010).***

Risk factors for TNBC have differed somewhat in various populations. However, compared with luminal tumors, triple-negative basal tumors are more likely to arise among women with a younger age at menarche, higher parity, younger age at full-term pregnancy, shorter duration of breast-feeding, use of medication that suppresses lactation, higher body mass index and waist-to-hip ratio and metabolic syndrome (Table 1) ***(Dolle et al., 2009).***

Epidemiological studies show the highest prevalence of TNBC among African American (AA) women, especially younger premenopausal African Americans ***(Morris et al., 2007).***This may, in part, explain a higher mortality rate despite a lower incidence of breast cancer overall among African Americans, though other factors like socioeconomic, cultural and treatment differences have been linked to this disparity as well ***(Smith et al., 2008).*** This racial disparity in survival, however, persists after adjustment for treatment distribution and access to health care ***(Polite et al., 2008).***

Table (1): Common risk factors for TNBC

Most common risk factors for TNBC[4]	
• Premenopausal	• High waist to hip ratio
• Young age at first pregnancy	• *BRCA1* mutation
• Parity ≥3	• Family history of breast cancer
• No or short duration of breast-feeding	• Use of lactation suppressants

(Dolle et al., 2009)

Familial and hereditary associations with TNBC suggest that genetics influence the etiology of these tumors. Eighty percent of patients with the *BRCA1* mutation have been identified as having TNBC. A larger percentage of

patients with TNBC have a family history of breast cancer and are more likely to be of African American descent than those who have other breast cancer subtypes ***(Kwan et al., 2009).*** Women with TNBC are significantly younger than women diagnosed with other breast cancer subtypes.25% are <46 years old versus 14% of all breast cancer patients ***(Parise et al., 2010).***

Little is known about the etiologic profile of triple-negative breast cancer. This is a breast cancer subtype associated with high mortality and inadequate therapeutic options. In a study, there were an assessment of the risk of TNBC among women 45 years of age and younger in relation demographic/lifestyle factors, reproductive history, and oral contraceptive (OC) use. In conclusion, significant heterogeneity exists for the association of OC use and breast cancer risk between TNBC and non-TNBC among young women, lending support to a distinct etiology ***(Jessica et al., 2009).***

Obesity may be differentially related to the risk of different subtypes given the various potential mechanisms underlying its association with breast cancer. Among women not currently using menopausal hormone therapy, body mass index (BMI) and weight were associated with the risk of luminal tumors. Neither BMI nor weight was associated with the risk of any tumor subtype among hormone therapy users. The positive relationship between

BMI and luminal tumors among postmenopausal women not using hormone therapy is well characterized in the literature. Although our sample size was limited, body size may also be related to the risk of postmenopausal triple-negative breast cancer among nonusers of hormone therapy ***(Amanda et al., 2008).***

Although none of the older epidemiologic studies were designed to identify risk factors by molecular subtype, recent re-analyses also raise interesting questions about traditional risk factors and whether some risk factors are stronger for one subtype versus another or even have opposite effects in different subtypes. For example, in contradistinction to luminal breast cancer, higher parity and young age at first birth may be risk factors for basal-like breast cancer, whereas lack of breast feeding and early age of menarche may be stronger risk factors than for luminal breast cancers ***(Millikan et al., 2008)***.

HISTOPATHOLOGY & MOLECULAR BIOLOGY

Triple-negative breast cancer (TNBC) is not a new type of breast cancer. In fact, the term has recently been coined to describe a subtype of breast cancer that lacks expression of the estrogen receptor (ER) and progesterone receptor (PR) and does not overexpress human epidermal growth factor 2 receptor (HER2) protein. TNBC is an important area of research for both researchers and clinicians alike because TNBC is a poor prognostic factor for disease-free and overall survival. No effective specific targeted therapy is readily available for TNBC ***(Roohi and Marilyn, 2010).***

The recent focus on this subgroup of tumors has arisen for two major reasons. First, unlike tumors that are estrogen receptor and/or HER2 positive, triple-negative tumors lack an established therapeutic target. As a result, conventional chemotherapy is the only effective systemic treatment for these patients and there is an urgent need for new treatment approaches. Second, recent developments in gene expression arrays have categorized breast cancer into distinct subgroups with different clinicopathological features (fig. 2 and tab. 2). One of these subgroups as defined by genetic clustering is the basal-like group of tumors (fig. 3) ***(Carey et al., 2006).*** Among the features of this basal-like subgroup defined by gene expression pattern is low expression of hormone receptor– and HER2-related genes, so most of these are triple-negative

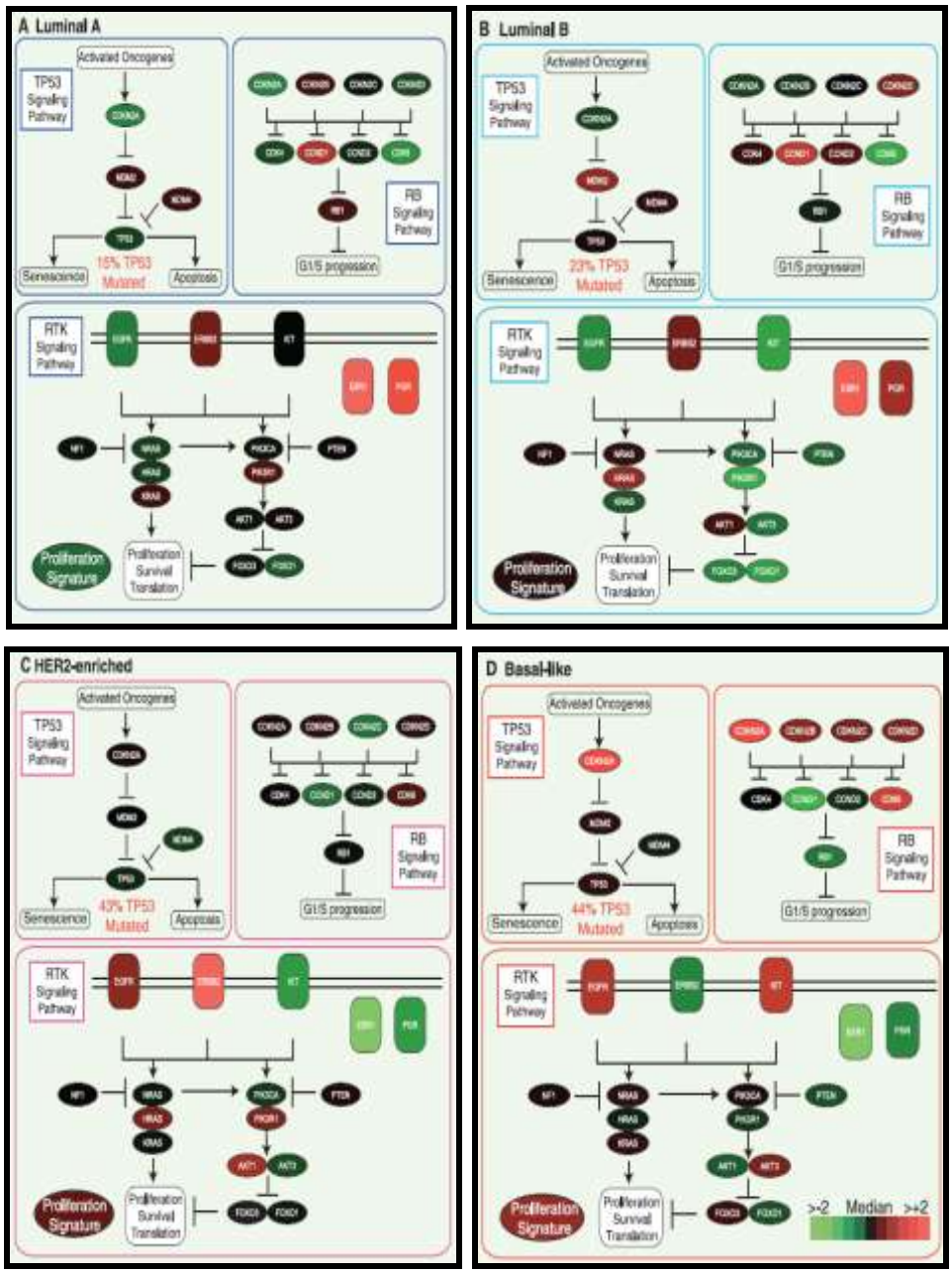

Figure (2): Pathway analysis of the intrinsic subtypes. TP53, retinoblastoma, and receptor tyrosine kinase signaling pathways are shown for many of the major genes within each pathway. Each gene is color-coded according to the average expression of that gene with each subtype. An average value for the ‘‘proliferation signature’’ for each subtype is also shown within the receptor tyrosine kinase (RTK) pathway box.TP53 mutation status is also shown for each subtype. These analyses highlight the triple-negative phenotype, the high expression of EGFR and c-KIT in basal-like tumors, and show their highTP53 mutation rates. Pathway analyses are shown for (A) luminal A and (B) luminal B(C) HER2-enriched and (D) basal-like tumors ***(Gauthier et al., 2007).***

Clinicians do not have either direct or indirect access to the molecular subtype. For this reason, breast cancers in the clinical setting are more typically categorized by routine immunohistochemistry (IHC) as triple negative breast cancer. It is crucial to note, however, that although most basal-like cancers are triple-negative breast cancer, there is moderate discordance between triple-negative breast cancer and basal-like breast cancer ***(Roohi and Marilyn, 2010).***

The highly heterogeneous immunohistochemical profile of TN breast carcinomas suggests that at least some of these neoplasms exhibit markers of myoepithelial derivation or differentiation (e.g. S-100 protein, smooth muscle actin, p63), and that they show a complex derangement of growth factor receptors with tyrosine kinase activity, and of the proteins regulating the cell cycle ***(Leibl et al., 2006)***.

Also, the immunophenotypical characterization of pure ductal carcinomas *in situ* (DCIS) of the breast has recently identified a variant of high-grade DCIS with the triple negative phenotype associated with expression of basal cytokeratins and of EGFR as a mutative precursor lesion of TN invasive carcinomas *in situ*. Accordingly, it is postulated that TNBC arise *de novo* from these precursor lesions, and are not the result of a de-differentiation process during the progression of pre-existing carcinomas. Though the vast majority of TN breast carcinomas are invasive duct

carcinomas of no special type and share many prototypical features, it should be emphasized that the triple negative phenotype is also a feature of some special types of breast cancer that have remarkably different morphological and clinical characteristics. These include the pleomorphic subtype of invasive lobular carcinomas, the myoepithelial carcinomas, the metaplastic carcinomas, the "oat cell" neuroendocrine carcinomas, the apocrine carcinomas, the medullary carcinomas, the secretory (juvenile) carcinomas and the adenoid-cystic carcinomas. It is important to identify these special types within the family of TN breast cancer, because some of these entities are associated with a better prognosis and do not benefit from aggressive chemotherapeutic regimens. This is particularly true for adenoid-cystic and medullary carcinomas, and for the low-grade metaplastic carcinomas (i.e. the low-grade adenosquamous carcinomas and the fibromatosis-like carcinomas). Apocrine carcinomas are almost invariably characterised by a triple negative phenotype, but their clinical outcome is more closely correlated with their histological grade and the disease stage ***(Reis-Filho and Tutt, 2008).***

The immunohistochemical profile of TN breast cancer has been extensively investigated and it is characterised by the variable expression of several markers, including cytokeratins 5,14 and 17 (at least one of these cytokeratins is expressed in the vast majority of TN tumors), vimentin (55%), P-cadherin (93%), EGFR (27−37%), PDGFR (31%), IGF-IR (36%), c-kit (11−38%), S-100 protein (22%), p63