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ORIGINAL PAPER

Breast Cancer: Epidemiology and Etiology

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Abstract Breast cancer, the most frequently occurring cancer in women, is a major public health problem, with 1,384,155 estimated new cases worldwide with nearly 459,000 related deaths. Breast cancer is highly heterogeneous in its pathological characteristics, some cases showing slow growth with excellent prognosis, while others being aggressive tumors. Current predictions and statistics suggest that both worldwide incidence of breast cancer and related mortality are on the rise. According to 2012 GLOBOCAN statistics, nearly 1.7 million women were diagnosed with breast cancer with 522,000 related deaths—an increase in breast cancer incidence and related mortality by nearly 18 % from 2008. According to American Cancer Society, one in eight women in the United States will develop breast cancer in her lifetime. It has been predicted that the worldwide incidence of female breast cancer will reach approximately 3.2 million new cases per year by 2050. These numbers reflect the magnitude of breast cancer incidence, its effect on society worldwide and the need for urgency for preventive and treatment measures. While technological advances in medical sciences and health care have made it possible to detect the disease early and to start the treatment early on to prevent the progress of the disease into a metastatic state, there are several unanswered questions with regard to the molecular mechanisms that underlie the aggressiveness of certain forms of this disease. Epidemiological studies suggest that addressing socio economical issues is utmost important, so that all women have equal access to medical care from screening to advanced treatment, and only such decisive action can help reduce the worldwide burden of breast cancer.

Keywords Breast cancer · Epidemiology · Etiology

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Introduction

Breast cancer is highly heterogeneous in terms of its etiology and pathological characteristics, some cases showing slow growth with excellent prognosis, whereas other cases taking a highly aggressive clinical course [1]. Breast cancer, the most frequently occurring cancer in women, is a major public health problem, with 1,384,155 estimated new cases from population-based cancer registries in 2008 worldwide [2] with nearly 459,000 related deaths [3]. It is alarming to note that GLOBOCAN statistics for 2012 show that approximately 1.7 million women were diagnosed with breast cancer in that year, with 522,000 related deaths—an increase in breast cancer incidence and related mortality by nearly 18 % from 2008. Besides this, among the total cancer cases, breast cancer incidence represented about 11 % in 2008 while this number jumped to 12 % in 2012. According to American

Cancer Society, one in eight women in the United States will develop breast cancer in her lifetime and approximately 232,340 new cases of invasive breast cancer and 39,620 breast cancer deaths were projected for 2013 among US women [4]. It has been predicted that the worldwide incidence of female breast cancer will reach approximately 3.2 million new cases per year by 2050 [5]. These numbers reflect the magnitude of breast cancer incidence, its effect on society worldwide and the need for urgency for preventive and treatment measures.

Morphological and Molecular Classification of Breast Tumors

Clinically, breast cancer classification is done on the basis of tumor morphological characteristics into different types and these include infiltrating ductal carcinoma of no special type, and a large number of 'special types' such as infiltrating lobular carcinoma, tubular, mucinous, medullary, and adenoid cystic carcinoma. Histological grade, including the degree of cellular differentiation, nuclear pleomorphism, and mitotic count help in further sub-classification of breast tumors. Breast tumors such as smaller size tubular carcinomas are typically associated with earlier stage at presentation, compared with infiltrating ductal carcinomas. It is also noted that breast tumors of high histological grade are generally large at presentation and are associated with local or distant metastasis, compared with tumors of low histological grade. Breast tumors have also been identified into five different subtypes based on the expression of estrogen receptors (ER) and progesterone receptors (PR), and Her2 oncogene. Overall, the ER positive tumors are more common than the ER-negative tumors. Also, the ER positive tumors are smaller and low grade and lymph node negative unlike the ER negative tumors [6]. Thus, there are two ER/PR-positive subgroups, Luminal A and Luminal B, and three ER-negative subgroups. One of the ER negative type is characterized by elevated expression of Her2 and related genes, and thus termed as the Her2 subtype; the second ER negative type is associated with high expression of genes normally identified with myoepithelial or basal cells, termed basal-like subtype; and a third ER negative group that shows a varied gene expression profile is termed normal-like subtype [7]. Both Her2 and basal-like subtypes of ER negative breast tumors clinically exhibit significantly poorer outcome than the luminal and normal-like groups [8]. It has been observed that prognosis is worse in a stage-independent manner for both Her2 and basal-like subtypes of ER negative breast tumors [9] and that both subtypes are also associated with more advanced stage at presentation [10]. Both Her2 and basal-like breast tumors were found to contain a greater percentage of stem cell-like cells, which seven may contribute to their aggressive clinical behavior [11]. Her2 oncogene is related to epidermal growth factor receptor family and is overexpressed in approximately 20 % of the breast tumors [12]. PR negativity among all ER positive tumors independently predicts Her2 positivity [13].

Breast tumors that do not express either ER, PR, or Her2 are called triple negative breast cancers (TNBC) and approximately 15 % of the breast cancers fall into this category [14]. The incidence of TNBC is generally higher in younger women, African-American women, and in patients with mutated BRCA1 [15, 16]. TNBCs are often larger and grade III tumors with aggressive phenotype and poorer outcomes [16–18]. Interestingly, it has been observed that even though the risk for estrogen receptor-positive tumors is lower by 12 % in postmenopausal women who gave birth to more than two children, they had a 46 % higher risk of developing TNBC [19].

Besides the above subtypes, there is another form of breast cancer known as inflammatory breast cancer (IBC) that is clinically and biologically distinct. IBC has the characteristic presence of tumor emboli in dermal lymphatic channels and there is generalized breast tenderness [1] and frequently presents at an advanced stage. At presentation, majority of the IBC patients have axillary lymph node involvement at diagnosis and up to 35 % show distant metastases. Nearly 50 % of IBC have elevated level of Her2, compared with 20 % in non-IBC breast cancers and this likely contributes to the high degree of metastases at presentation [20]. The high degree of early metastases in IBC can also be due to the highly angiogenic and angioinvasive nature of these tumors and expression of elevated levels of pro-angiogenic factors [21]. There is also increased expression of genes associated with the basal-like phenotype, vascular associated genes, and immune-related genes in IBC. Genes involved in cell migration and invasion, such as integrin β4 and VASP, and ARNT, which encodes the β subunit of hypoxia-inducible factor 1 (HIF1) that play a role in angiogenesis are also up-regulated in IBC.

Genetic and Epigenetic Factors that Influence Tumor Behavior

A combination of information from studies on epigenetic traits of the disease and the risk of breast cancer is often important for promoting cancer prevention at three levels, first by identifying risk factors and their mode of action, second by establishing markers of early disease, and third by establishing markers of disease progression and drug resistance [22]. Micro-RNA miR-21 controls the expression of several genes that regulate tumor progression, including RAB6A, a member of the RAS oncogene family, TGFβ-induced protein, TGFβ receptor II and Bcl2 [23, 24]. It has been suggested that miR-21 likely exerts its

oncogenic effect by regulating the expression of tumor-suppressor gene PTEN, which is down-regulated in many types of breast cancer [25]. More recently it has been shown that miRNA hsa-MiR-21 (miR-21) is up-regulated in breast cancer and significantly associated with advanced stage at presentation [23, 24] and the increased levels of miR-21 are correlated with poor survival. Besides this, the levels of miR-34a, miR-93, and miR-373 were found to be higher in serum from breast cancer patients as compared to healthy individuals, and their levels were even higher in patients with metastases [26]. A direct relationship between the blood levels of miR-195 and let-7a levels and breast cancer was seen as these miRNAs were elevated by 19- and 11-fold, respectively, in breast cancer patients, and decline to normal levels after tumor resection [27]. Epigenetic studies revealed that breast cancer subtypes display different LINE-1 methylation profiles and are epigenetically distinct. Silencing of the estrogen receptor and inactivation of BRCA1 and BRCA2 can occur through methylation [28] and other epigenetic mechanisms, and the frequencies of this epigenetic involvement can vary from 17 to 60 % [29]. Similarly, RASSF1A and HIN1 were found to be hypermethylated in 65–85 % of breast tumors. A meta-analysis of nine studies that included a total of 3,205 patients reported that hypermethylation of the BRCA1 gene is a high risk factor for developing breast cancer (HR 3.92) [29].

Dominant gene mutations appear to be present in only small number of breast cancers and the most common mutations are in BRCA1 and BRCA2 genes. It is suggested that gene variations due to single-nucleotide polymorphisms likely explain the heterogenous nature of breast cancer and the differences among individuals with regard to tumor behavior [30]. An important gene family, that commonly shows this type of genetic variations that are functionally relevant, is the matrix metalloproteinase family [1]. While SNPs that lead to high expression of MMP-1 and MMP-9 correlate well with advanced tumor stage [31], SNPs that lead to elevated expression of MMP-8 were found to act as tumor suppressors [32]. In line with this, it has been observed that SNPs that cause down regulation of MMP-8 lead to enhanced breast cancer metastasis [33]. Breast tumors arising due to genetically transmitted abnormalities, including BRCA1/2 and TP53 mutation, generally cluster to the younger age group (<45 years age), and these tumors display a more aggressive phenotype.

Age and Reproductive Factors

Many studies indicated that at the time of diagnosis of breast cancer, younger age poses an adverse risk factor and that young women present with larger tumors at more advanced stage and more frequently as lymph node positive with poorer survival [34]. The approximate threshold for the differing prognosis with worse outcome of younger age presentation of breast cancer is about 45 years. It is estimated that the average probability of a 30-year-old woman to develop breast cancer over a 10-year period is 1 in 232 (0.43 %), about 10 times less than that for a 70-year-old woman, with 1 in 27 probability (3.74 %) [35]. After a slow increase from 1975 to 1990 (0.4 % annually), breast cancer death rates per year decreased by 2.2 % during 1990–2007 for women of all ages. This decline was higher among women younger than 50 years (3.2 % per year) than in older women [36].

Our understanding of many of the breast cancer risk factors, especially reproductive factors, has evolved over the last several years. Increased pregnancy with child birth can potentially decrease the risk, for example each birth can potentially reduce the risk of breast cancer, particularly ER positive type, by 7 % [37]. This protection by pregnancy is probably due to the process of breast tissue differentiation following pregnancy [1]. Conversely, as mentioned above, increased number of childbirths can significantly elevate the risk of post-menopause TNBC. However, delayed child bearing and birth could increase the risk such that, every 1-year increase in age at first birth and also at first menstruation can increase the risk of breast cancer by 1.7 and 5 %, respectively [35]. Apparently, increased use of post-menopausal hormones among women contributed significantly to the steady rise in incidence of ER/PR-positive breast cancer observed before 1980, since these hormones could promote the growth of these otherwise indolent but hormonally responsive tumors [38]. The sharp decline in the breast cancer incidence could be due to the increased awareness of public and physicians about the effects of post-menopausal hormones followed by their reduced usage.

The all stages combined breast cancer incidence continues to increase in White women age 50 and older, whereas the disease trend is stable for the same age group African-American women. On the other hand, the disease trend is stable in White women under age 50 years, while it is decreasing for African-American women of same age. An interesting statistical anomaly is that because women aged 50 years and older represent ~73 % of female population, the overall incidence rates appear to be substantially higher for women age 50 and older (375.0 per 100,000 females) compared with women younger than 50 years (42.5 per 100,000 females), even though ~23 % of breast cancers are diagnosed in women younger than 50 years. Racial differences are markedly evident in many studies, which showed despite lower incidence rates for breast cancer in African-American women, the mortality rates are 37 % higher than in White women [39]. Gene

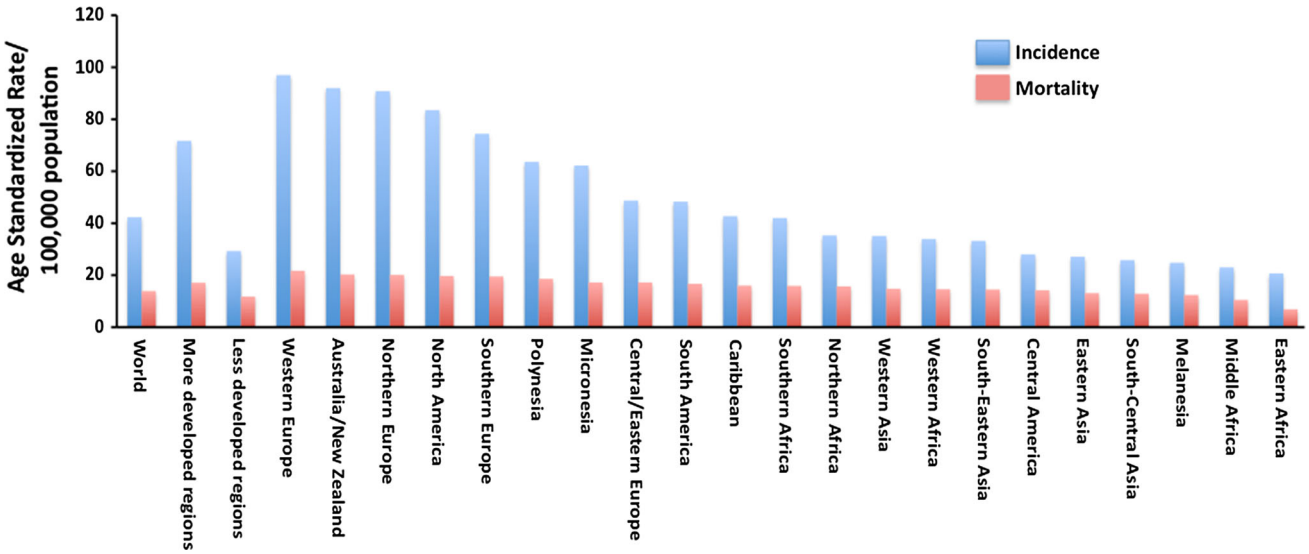

Fig. 1 Estimated age-standardized rates based on 2008 GLOBOCAN data for incidence and mortality of female breast cancer by world region

expression profiling indicated a higher frequency of the basal-like subgroup, which is known to confer a poorer prognosis and is also over-represented in BRCA1-mutated breast cancer in young African-American women [40]. Similarly, it has been noted that in the USA, while breast cancer death rates have been declining since the early 1990s for all women except American Indians/Alaska Natives, among whom rates have remained stable [36]. It has been estimated that the average annual female breast cancer death rate between 2003 and 2007 was highest in African-Americans (32.4 deaths per 100,000 women) and lowest among Asian Americans/Pacific Islanders (12.2 deaths per 100,000 women). Also, African-American women have the lowest 5-year breast cancer survival rate (77.5 %) of any racial or ethnic group (Fig. 2), whereas Asian American/Pacific Islander women have the highest 5-year breast cancer survival rate (90.3 %) [36].

It is well recognized that while the breast cancer incidence is higher in developed countries and also in women of higher socioeconomic status, the mortality due to breast cancer is higher in women from poorer countries and also from lower socioeconomic status [41]. This can be partly because of the lower screening rates in poor women compared with relatively affluent women, despite much progress in increasing mammography utilization. For example, in 2008, about 21 % more non-poor women had undergone screening than the poorer women [36].

Breast Cancer Incidence and Mortality

In 2008, nearly 1.4 million women were diagnosed with breast cancer worldwide with ~459,000 breast cancer related deaths. While the incidence rates were higher (71.7/100,000) in more developed countries compared to less developed countries (29.3/100,000), the corresponding mortality rates were 17.1/100,000 and 11.8/100,000, respectively, indicating that the deaths due to breast cancer are nearly 17 % higher in the less developed countries (Fig. 1). Thus, the 5-year relative survival estimates range from 12 % in Africa where the incidence is lower to almost 90 % in the United States, Australia and Canada, where the incidence is much higher [3] (Fig. 2). The international incidence of female breast cancer will probably reach ~3.2 million new cases per year by 2050 [5]. Breast cancer incidence rates are expected to further increase within many less developed countries due to longer life expectancy coupled with the adoption of a more ''westernised'' lifestyle, less physical activity, and delays in childbearing [42]. The large predicted increase in the incidence throughout parts of Asia due to an increasingly ''westernised'' lifestyle will influence the worldwide breast cancer burden in future.

Even though breast cancer incidence has been increasing throughout the world, there are significant inequalities between rich and poor countries, with the incidence rates remaining highest in more developed regions, while mortality rates are much higher in less developed countries. For example, in western Europe, breast cancer incidence is >90 new cases per 100,000 women annually, compared with 30 per 100,000 in eastern Africa, even though the breast cancer mortality rates in these two regions are the same [3]. Since the 2008 estimates, by 2012, breast cancer incidence has increased by more than 20 %, while mortality has increased by 14 %. Breast cancer is also the most common cause of cancer death among women (522,000 deaths in

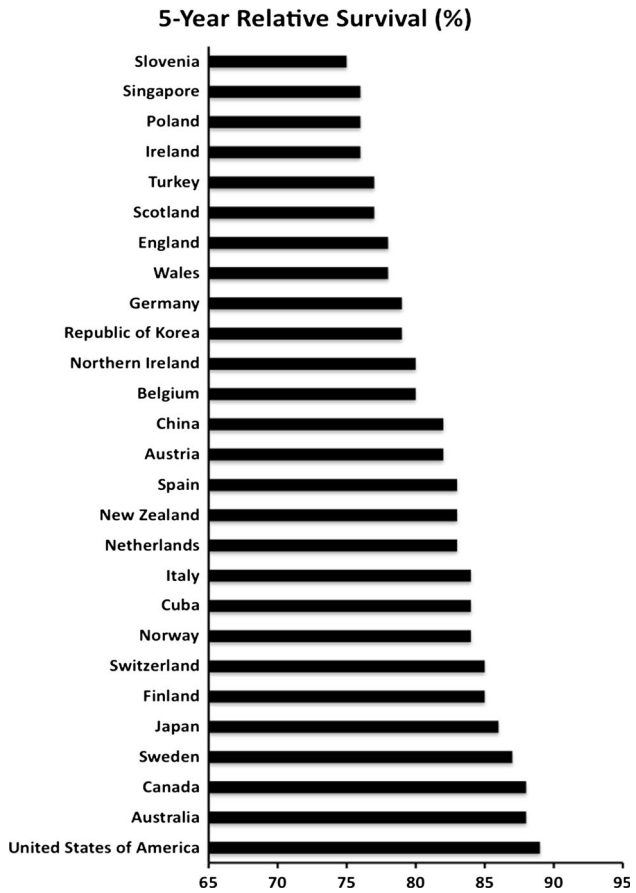

Fig. 2 Estimates of 5-year relative survival for female breast cancer patients in selected countries

2012) and the most frequently diagnosed cancer among women in 140 of 184 countries worldwide.

Before the 1990s, China had a low incidence of breast cancer, but since then its incidence has increased more than twice as fast as the remaining global rates [43]. Breast cancer is now the most frequently diagnosed cancer in Chinese women and is the sixth leading cause of death. By 2008, the incidence of breast cancer in China and its magnitude became so staggering that China accounted for 12.2 % of global cases and 9.6 % of related deaths [43]. Annual breast cancer diagnoses in China are approximately half of those in the European Union and are similar to the number of cases in the USA and unless steps are taken to slow this trend, incidence of breast cancer in China is predicted to rise in women aged 55–69 years from <60 cases to >100 cases per 100,000 women by 2021, reaching 2.5 million cases by 2021. GLOBOCAN estimates that breast cancer is the most frequent cancer in Chinese women, with an age-standardized rate (ASR) of 21.6 cases per 100,000 women and it is the most common cancer among urban women and the fourth most common cancer in rural areas according to the Chinese National Central Cancer Registry.

Conclusions

Current predictions and statistics suggest that both worldwide incidence of breast cancer and related mortality are on the rise. While technological advances in medical sciences and health care have made it possible to detect the disease early and to start the treatment early on to prevent the progress of the disease into a metastatic state, there are several unanswered questions with regard to the molecular mechanisms that underlie the aggressiveness of certain forms of this disease. Besides, the epidemiological studies strongly indicate that addressing socio economical issues is utmost important, so that all women have equal access to medical care from screening to advanced treatment and only such decisive action can help reduce the worldwide burden of breast cancer that is single handedly responsible for the millions of "years of female life lost" according to World Health Organization.

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