Breast Cancer: Genetics, Risk factors, Molecular Pathology and Treatment

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ABSTRACT

Breast cancer within incident of one million new cases each year has become one of the most common malignancies and leading cause of death among females. This disease is comprised of about 18% of women cancers. The availability of early detection and improved treatments may decrease the mortality rates which reflected in the United States and many other western countries. Breast cancer in over the past 20 years may also have contributed to the Increasing age, nulliparity, positive family history of breast cancer, and use of menopausal hormone therapy were positively risk factors associated with breast cancer. Therefore, studying this malignity is prominent due to its mortality world wild. Evaluation and study of different aspects of breast cancer have been established during past decays which, in this review, it is presented and discussed.

Keywords: Breast Cancer, Genetics, Molecular Pathology, Treatment, Risk Factors

INTRODUCTION

Breast cancer, the most widespread malignant disease between women in Western countries, has poor prognosis following metastasis [1]. Breast cancer emerges when an unregulated growing of abnormal cells in different parts of breast tissue begins. This may develops in milk ducts and glands of breast. There are two main types of breast cancer: ductal carcinoma and Lobular carcinoma. In rare cases, breast cancer can start in other areas of the breast [2]. Normally the highest rate is found in the typically 'westernized' countries of North America and Europe, while much lower rates are observed in Asian and African population [3]. According to recent statistics published by the American Cancer Society, 89% and 82% of women diagnosed with invasive breast cancer in the United States will still be alive 5 and 10 years after diagnosis, respectively [4]. The rate of breast cancer epidemics in United Kingdom has its highest score within two per 1000 women in their fifties which are the most capable of this type of cancer [5]. Generally low breast cancer incidence in Asian women has been reported [6]. Breast cancer occurrence is high in adolescence with the age of 40 to 50 which are the most adequate. Although, many studies have been conducted, patient-age-dependent differences in the biology and clinical outcomes of breast cancer have still not been definitively specified. Some younger women (mostly those 35 years old) have a more aggressive form of the disease characterized by larger, higher-grade tumors with vascular invasion, increased rate of aneuploidy, and higher S-phase fractions (SPFs) [7]. There are lots of risk factors associated with the cause of breast cancer development such as age, life style, obesity, family background, race, estrogen hormone as the therapeutic agent, reproductive factors(age of pregnancy, marriage and breast feeding), genetic mutations in BRCA1 and BRCA2 and other genetic factors [8-10]. In this review, different aspects of breast cancer have been studied.

Breast Cancer Epidemiology

Breast cancer is the most leading cause of cancer related -death in women in the world, with an estimated 1.4 million new breast cancer cases and 458,000 deaths in 2008 [11].The incident and morality rates of breast cancer vary internationally by more than 5-fold and it is very high in civilized populations. 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. The rates in U.S. Hispanics and Asians are substantially higher compared with the rates in most cancer registries in Asia and Latin America. Regional patterns in mortality rates are generally similar to the incidence patterns, although U.S. whites, Hispanics, and Asian-Pacific Islanders and Australia have relatively low rates, whereas U.S. blacks and Trinidad and Tobago have the highest rates.

The high breast cancer incidence rates in white women in the United States and in most European countries reflect 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 [12, 13]. Beside these factors, the high breast cancer epidemiology is in Israel may reflect the disproportionately high prevalence of BRCA1 and BRCA2 mutations in the Ashkenazi Jewish population. The lifetime risk of being diagnosed with breast cancer in women with BRCA1 or BRCA2 mutation is about 50% [14], compared with 13% in all U.S. women [15]. The relatively low mortality rates in the United States and many other western countries reflect the availability of early detection and improved treatments. Breast cancer incidence rates in the United States have decreased since the early 2000s largely due to reduction in the use of menopausal hormone therapy [16-18]; decreases in utilization of mammography [19] or decreases in the number of preclinical cases found by screening over the past 20 years may also have contributed to the decrease in the incidence rates [20, 21].In Iran, it is one of the most frequent malignancies among women and ranks the second most common cancer [22, 23].

Breast Cancer Classification

Breast cancer is divers due to its morphology and histology. Each of these aspects influences treatment response and prognosis. It can begin in different areas of the breast; the ducts, the lobules, or in some cases, the tissue in between [24]. As it is mentioned above there are different types of breast cancer that, two main category of breast cancer are as below:

- Ductal carcinoma starts in the tubes (ducts) that move milk from the breast to the nipple. Most breast cancers are of this type.
- Lobular carcinoma starts in the parts of the breast, called lobules that produce milk.

In rare cases, breast cancer can start in other areas of the breast [2]. Breast cancer can be invasive or noninvasive. Invasive means it can spread through milk duct and lobules to other tissues. Invasive means it has not yet spread to other breast tissue. Noninvasive breast cancer is called "in situ".

- Ductal carcinoma in situ (DCIS), or intraductal carcinoma, is breast cancer in the lining of the milk ducts that has not yet invaded nearby tissues. It may progress to invasive cancer if untreated.
- Lobular carcinoma in situ (LCIS) is a marker for an increased risk of invasive cancer in the same or both breasts [25].

Risk Factors

There are lots of risk factors associated with breast cancer (see table 1). Family history is one of them; it is known to be one of the prominent risk factors for this malignancy. For instance, meta-analysis of familial breast cancer studies gives lifetime risk ratios of 1.80 in families with one affected first-degree relative, 2.93 in families with two affected relatives, and 3.90 in families with three affected relatives. The familial pattern of the disease provides clear evidence for the important role of genetic variation in determining risk [26]. The ratio of breast cancer is the highest in young people. A notable early achievement in the genetic dissection of the disease was linkage mapping, using breast cancer family data, of the *BRCA* and BRCA genes. Rare mutations in these genes confer high relative risks to carriers of 10- to 20-fold, corresponding to a 30%–60% risk by the age of 60 years, compared with 3% for the general population [27].The possibility of an underlying breast cancer almost occurs at any age [28]. Another thing is age; the risk of developing breast cancer increases with age. Most advance cases of breast cancer commonly are found in elderly. Living up to age 95, about one in eight would be diagnosed with breast cancer during their lives However, the actual lifetime risk is lower than that, due to the fact that 90% of women die before age 95, mostly from heart attacks, strokes, or other forms of cancer. The possibility of breast cancer rises as

getting older, but breast cancer tends to be more common in younger people [29, 30]. In addition, other factors such as diet and physical activity can do a lot with this type of cancer. For example, it has been reported that, physical activity can improve quality of life, decrease fatigue and reduce all-cause and breast cancer-specific mortality in breast cancer survivors. The beneficial effects of physical activity may regulate circulating levels of insulin, insulin growth factors (IGFs) I and II and their binding proteins (IGFBPs), or inflammatory biomarkers [4]. Evidence suggests that fruits and vegetables, low-fat dairy products, fish, monounsaturated and polyunsaturated fatty acids, vitamin D, calcium, and phytoestrogens may lessen the risk of breast cancer, while high consumption of fried meat, saturated fatty acids is associated with increased risk of breast cancer[31 , 32].

Table 1: Associated risk factors with breast cancer

Risk factors			References
Gender	Women	150	33
	men	1	
Physical activity			35
Genetic (About 5 to 10%)			36
Dietary	Alcohol		37
	Fat		38
	High fiber		39
Hormones			40
childbearing			12, 13
Viruses			41
Proliferative breast lesions			42
Long-term use of oral contraceptives			43
Height, Weight, Age			44
Heritability of Mammographic Density (1.8 to 6.0 time)			45

Gender and Physical activity

Breast cancer is more likely in women population than men. For every 150 cases of female breast cancer, there is one case of male breast cancer [33]. In developed countries, about 99% of breast cancer cases are diagnosed in women. In addition to this, white women aged 50 years and older have experienced higher prevalence rates than their non-white counterparts [33]. Whilst, breast cancer incidents in male's European population is one or less per 100 000. Male breast cancer has high prevalence at the age of 71 years. There are no randomized data giving information on the optimal therapy for male breast cancer patients, thus limiting firmer conclusions [34]. Men diagnosed with breast cancer are commonly older than women with breast cancer. They are more expected to be diagnosed with hormone-receptor positive tumors, with about six out of seven cases being estrogen-receptor positive. On the whole prognosis is worse for men than for women [30]. Physical activity is an another prominent factor; there is some evidence from available RCTs that physical activity intervention may result in beneficial changes in insulin levels, IGFI and IGFBP, as well as inflammatory biomarkers in breast cancer survivors. However, available studies are generally small, and the evidence is not consistent. For that reason, further larger RCTs on physical activity and biomarkers in breast cancer survivors are warranted. Some studies show that, about 50% risk reduction in breast cancer death in women who engaged in moderate intensity physical activity before and after their diagnosis of breast cancer [35].

Genetic Factors

Genetic and lifestyle/environmental factors are implicated in the etiology of breast cancer. The genetic factor of the disease is reflected on a tendency to cluster in families, even thought this could also reflect shared life-style and environment [36]. About 5 to 10% of breast cancer cases are associated with a hereditary inclination, characterized by young age at diagnosis and/or multiple relatives with breast, ovarian and/or prostate cancer [46]. The genetic factors known to be involved in breast cancer risk consist of about 30 genes [20]. Two autosomal dominant genes, BRCA1 on 17q21 and BRCA2 on 13q12, make up for almost 15% of the cases of familial breast cancer [47, 48] which, loss of heterozygosity of these normal alleles is frequently observed [46].

In addition to this, women who carry a destructive BRCA mutation have a 60% to 80% risk of developing breast cancer in their lifetimes [49].

On the other hand, other gens beside BRCA may be associated with breast cancer. For instance, the presence of *NBR2*, near breast cancer gene 1, has been discovered, and research into its contribution to breast cancer pathogenesis is ongoing [50]. Moreover, genetic variation in genes involved in estrogen synthesis, metabolism and signal transduction have been suggested to play a role. Estrogen influences the growth, differentiation and

function of breast tissue, exerting its biological effect through binding to estrogen receptors (ERs). ERs belong to a family of transcription factors, the nuclear receptor super family, responsible for mediating the effects of steroids on development, reproduction, proliferation, cellular homeostasis and gene expression [51]. These estrogen gen polymorphisms are linked to the metabolism of carcinogens (CYP1A1, CYP1B1, CYP17, CYP19, COMT, NAT2, GSTM1, GSTP1, GSTT, . . .), to estrogen, androgen and vitamin D action (ESR1, AR, VDR), to co-activation of gene transcription (AIB1), to DNA damage response pathways (CHEK2, HRAS1, XRCC1, XRCC3,XRCC5) [51]. Sequence variants of these genes that are relatively common in the population may be associated with a small to moderate increased relative risk for breast cancer. Combinations of such variants could lead to multiplicative effects. In addition to this, PON1 M and Q alleles are associated with a higher risk of breast cancer. Persons having MM and QQ genotypes have a lower level and lower detoxification activity of the PON1 enzyme, which may enhance the vulnerability of the breast to genetic damage by reducing the ability to detoxify inflammatory oxidants, as well as dietary carcinogens [44].

Dietary factors

Alcohol

Alcohol appears to be a risk factor for breast cancer in women [37]. Findings indicate that, among lifestyle factors, alcohol consumption is constantly linked to increased risk for breast cancer in both premenopausal and postmenopausal women, aside from of the kind of alcoholic drink consumed. The percentage of breast cancer attributable to alcohol consumption between U.S. women has a population attribute to the risk of 2.1%, accounting for about 14,000 women yearly [52]. One or two drinks each day increases the relative risk to 150% of normal, and six drinks per day increases the risk to 330% of normal The primary mechanism through which alcohol causes breast cancer may be by increasing estrogen levels [53].

Fat intake

It is believed that, modification of dietary fat and fiber could help prevent cancers of the breast [38]. There is a controversially about this subject that, whether fat intake is related to breast cancer or not? For many years high energy intake, most of all high fat intake was considered the critical explanation for the regional differences in breast cancer incidence. Mainly the consumption of animal fat and saturated fatty acids was accused of a contributory association with breast cancer. However, some studies show that, there is not significant relationship between fat consumption and breast cancer risk. Animal fat, generally regarded as ‘‘unhealthy’’, was not found to be considerably related to breast cancer possibility [54].

High fiber foods

Some studies have been suggested that, a high consumption level of fruit and vegetables as healthy diet can effect against hypertension, obesity and coronary heart disease and even cancer [39]. However, according to other studies Brassicas vegetable intake (broccoli, cauliflower, cabbage, kale and Brussels sprouts) was inversely related to breast cancer growth. The relative risk among women in the highest decile of Brassica vegetable consumption (median, 1.5 servings per day) compared to the lowest decile (virtually no consumption) was 0.58. That is, women who consumed around 1.5 servings of Brassica vegetables per day had 42% less risk of developing breast cancer than those who consumed virtually none [55]. In addition, other studies show that, the possible relationship of fruits and vegetables with risk of breast cancer has normally been much weaker and less reliable [56].

Hormones and childbearing

Some evidences suggest that steroid hormones are implicated in the risk of breast cancer [40]. steadily increased blood levels of estrogen are associated with an increased risk of breast cancer, as are increased levels of the androgens androstenedione and testosterone (which can be directly transformed by aromatase to the estrogens estrone and estradiol, respectively). Increased blood levels of progesterone are associated with a decreased risk of breast cancer in premenopausal women [57].A number of circumstances which increase exposure to endogenous estrogens including not having children, delaying first childbirth, not breastfeeding, early menarche (the first menstrual period) and late menopause are suspected of increasing lifetime risk for developing breast cancer [58]. Several studies put forward that total breastfeeding time reduces breast cancer possibility. However,

some other researches indicate that there is no significant connection between age at first childbirth and number of children in breast cancer incident [59].

Viruses

Several kinds of viruses have become major suspects as etiological agents for human breast cancer. Unraveling the relationship between viruses and breast cancer incident is prominent for better understanding of its etiology, early detection and possibly prevention. Human Papilloma viruses, mouse mammary tumor virus and Epstein-Barr virus are the main candidate viruses as causes of human breast cancer. Human Papilloma viruses and the mouse mammary tumor virus have hormone responsive elements that appear to be associated with enhanced replication of these viruses in the presence of corticosteroid and other hormones [41]. Moreover, Epstein-Barr virus (EBV) contribution in breast carcinogenesis is still controversial .According to one study, by acting as a promoter for the development of PIBC; it could contribute to progression of breast cancer [60].

Molecular Pathology

As breast cancer is one of the heterogeneous diseases including clinical, morphological and molecular aspects, molecular biology of the disease is prominent to examine. This heterogeneity cannot be explained only by clinical parameters such as tumor size, lymph node involvement, histological grade, age; or by biomarkers like estrogen receptor (ER), progesterone receptor (PGR) and epidermal growth factor receptor 2 (HER2) regularly used in the diagnosis and treatment of patients. Moreover, technological breakthroughs and in particular high throughput approaches like proteomics technology [61], have allowed scientists to investigate deeply in the nature of breast cancer which shows that, there is a systematic interconnection of several signaling pathways and that both the cellular microenvironment, and the innate characteristics of the patient influence disease pathophysiology, outcome and treatment response. These findings indicate that, there might be more than one disease relating to breast cancer, and that each patient entails a particular case where personalized medicine could play a key role in treatment strategy [62, 63].

Metastasis

The risk of developing distant metastatic may remain after management of the primary tumor. Despite advances in surgery, chemotherapy and radiation therapy, breast cancer still lacks effective treatment, and it might not be controlled in preventing relapses. In addition, they are the most lethal form of breast cancer relapses and are associated with a high rate of mortality, and increased costs for care [64]. Mortality is approximately invariably due to metastasis. For instance, among 25% and 50% of patients diagnosed with breast cancer will ultimately develop deadly metastases, frequently decades after the time of diagnosis and removal of the primary tumor. The prognosis for patients with metastatic breast cancer is normally unfavorable, with an average 5-year survival rate of only about 25% [65].The different histological subtypes of breast cancer (e.g. ductal, lobular, basal like) and molecular marker expression (e.g. estrogen receptor, ER; progesterone receptor, PR; human epidermal growth factor .receptor 2, HER2) have strong prognostic and predictive values. For example, triple negative breast cancers (i.e. ER-, PR-, HER2- negative) are associated with a significantly increased risk of progression and metastasis formation. In spite of intense clinical research efforts, only limited advances have been obtained in the management of breast cancer metastases. Lymphatic organs are pro of metastasis. The HER2 gene encodes the receptor tyrosine kinase HER2 and is often over-expressed or amplified in breast cancer. Up-regulation of HER2 contributes to tumor progression. In fact, HER2 plays a role in increasing proliferation and survival of the primary tumor and distant lesions which upon completion of full transformation cause metastases [66].

Treatment strategies

Different strategies may be use in treating breast cancer. The first strategy is to eradicate of established metastases by adding novel modalities to current treatments, such as immunotherapy or targeted therapies. A second way is to prevent tumor cell dissemination to secondary organs by targeting specific steps leading the metastatic cascade and organ-specific tropism. A third one is to block the colonization of secondary organs and subsequent cancer cell growth by impinging on the ability of distributed cancer cells to adapt to the novel microenvironment. To achieve the

best results it could be necessary to unite these strategies. These advances entail a deeper understanding of the specific genetic events occurring in cancer cells and of the host responses that co-operate to promote metastasis formation. In particular the crosstalk between disseminated cancer cells and the host microenvironment is emerging as a critical determinant of metastasis. Therefore, the identification of tissue-specific signals involved in metastatic progression will open the way to new therapeutic strategies [67].

CONCLUSION

As breast cancer is one of the most common cancers among women over the world [68], so there should be more accurate therapy for it. To achieve this goal, deep examination of this disease is highly needed. Therefore, molecular biology studies of this disorder could be possibly helpful due to its potential for bringing a deep insight of the illness.

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