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REVIEW PAPER

Metastatic and pathophysiological characteristics of breast cancer with emphasis on hereditary factors

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Highlights

- Breast cancer develops from the breast tissue and is the second leading cause of cancer deaths.
- Cadherin and integrin are could be considered in the metastasis procedure of breast cancer.
- BRCA1 and BRCA2 are the most important genes involved in breast cancer pathophysiology.
- Some other genes, including Her 2, p53, p21, bcl-2, etc. play the central role in breast cancer.

Graphical Abstract

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Abstract

Breast cancer is the most common type of cancer among women and the second leading cause of deaths after lung cancer. Each year, more than 180,000 new cases of breast cancer are diagnosed in the United States. The risk of breast cancer is low before the age of 35, but the high prevalence of this type of cancer is diagnosed after the age of 35. The risk of developing breast cancer in a woman's lifetime is about 10 and 5-10% with a familiar genetic basis. The accumulation of breast and ovarian cancers in certain families indicates that genetic variations are involved in developing these types of cancers. In 1994, two genes were identified to be linked to familial breast cancers. Gene variations in these two genes (BRCA1 and BRCA2) are found in most familial breast cancers, and variations in several other genes may also be involved in this cancer. The molecular functions of BRCA1 and BRCA2 are still unclear, although they could be involved in repairing damaged DNA or regulating the transcription of hormone-responsive genes. Mutations in these genes are predominantly autosomally transmitted by variable penetration. Women with BRCA1 variations are up to 50 percent more susceptible to breast cancer pending their lifetime. However, there are some other genes in which the variation may result in breast cancer occurrence. In this paper, we assessed some features of breast cancer to focus on hereditary aspects.

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Introduction

Based on World Health Organization (WHO), breast cancer is the most common cancer type in women and is the second cause of cancer-related death in women after lung cancer (1). It accounts for 22% of all women cancers (2). In Iran, breast cancer consists of 16% of all cancers and still ranks first. The fifth leading cause of death in Iranian women is common cancer in almost all provinces such as Mazandaran and Kermanshah (3, 4). Breast cancer is a multifactorial disease in which various genetic and environmental factors work in different ways. Our knowledge of how they work and the fundamental cause of the disease are still incomplete. A risk factor is any factor that grows the risk of developing a disease such as cancer. Of course, having risk factors does not mean that a person will get the disease, and not having them will not be a guarantee (5, 6).

Researches have not shown the definite cause of breast cancer, but it seems that this disease is influenced by factors such as the genetic structure of hormonal profiles and different life patterns (7). Some predisposing environmental factors of breast cancer are Geographical status, lifestyle, age of marriage and obesity (8). Genetic is a significant factor in breast cancer, so the risk of disease for a woman with one or more first-degree relatives with this cancer is three and ten times higher, respectively (9). According to another source, the risk of breast cancer for women up to the age of 80 with any first-degree relatives suffering cancer will be 7.8%, and for women with one or two first-degree relatives is 13 and 21%, respectively (10). Finding the relevant agents of this disease, including its genetic factors, will provide important information that helps researchers and physicians find solutions to prevent, treat, or increase life expectancy with the least physical and mental problems for patients (11).

BRCA1 and BRCA2 are two primary genes involved in breast cancer. These genes are the dynamic managers of the integrity of the genome. Mutations in these genes are correlated with cancer development in several organs, such as the ovary and breast. The BRCA1/2 genes mutations mainly elevate duration risk to the development of cancers of the ovary and breast, and these mutations are commonly detected in the hereditary ovary and breast cancers (12). Also, deregulation and changed expressions of BRCA1/2 could result in sporadic breast cancer. Significantly, both proteins play a role in DNA repair and regulation of gene transcription in DNA damage events. Thus, defects of BRCA1/2 result in the accumulation of genetic changes and eventually impact cancer development. Both BRCA1/2 have provided vital signs for their activities in tumor suppression, definitely for breast cancer (13). In this review, we describe the pathophysiological characteristics and metastasis of breast cancer, focusing on its genetic aspects.

Breast cancer metastasis

Breast cancer is the most common cancer, could affect other parts of the body. This migration from the origin to another is known as metastasis, which is the main cause of cancer death. Cancer can spread in several ways. Cancer cells, or small packages of cells, can invade healthy tissue near the site of origin. They may also migrate to other body regions through the lymph or blood vessels and attack healthy tissues. Although most cancers can spread almost anywhere, bone is the most common site for breast cancer metastasis, so that up to 75% of breast cancer patients with metastatic cancer have bone involvement (14, 15).

In cancer metastasis, cells must pass the basement membrane and enter the blood circulation or lymphatic system. There are specific genes that command the production of adhesive proteins. If these genes are mutated, proteins are produced that will not be able to function normally. Thus, cells lose their natural adhesion to each other and the basement membrane. As a result, they go outside their natural limitations (16, 17, 18).

Researchers have shown that the normal function of these adhesive molecules is gradually reduced in advanced tumors that cause the onset of metastasis, which is one of the most dangerous stages in the development of cancer. Removing a malignancy before it enters this dangerous stage will significantly reduce patient mortality (19). Among the adhesive proteins, cadherin and integrin are the two most well-known types, which have been the subject of many biological types of research on breast cancer (20). These cells can only raise

and increase if they have certain abilities like produce new blood vessels. The mechanism of metastasis is multifaceted, and its ability differs according to the target tissue (21).

Pathophysiology of breast cancer

Breast cancer, like other cancers, is triggered by contact between an environment and a defective gene. Cell division in normal cells stops after the desired number; then cells enter their tissues by attaching to other cells (22). However, in cancer cells, due to the variation, the ability to stop division is lost; as a result, the cell cannot attach to other cells and be placed in its tissue (23). Normal cells are doomed to cell death when they are no longer needed, but until then, these cells are protected from apoptosis by several proteins and pathways (24). One of these pathways is the mTOR/AKT/PI3K pathway (the intracellular signalling pathway that is important in cell cycle regulation), and the ERK/MEK/Raf/Ras pathway (A group of intracellular proteins that are involved in leading signals from the receptor on the cell surface into the nucleus) is another one (25). Sometimes some of the genes involved in the protective pathways mutate into permanent and stable genes that are not capable of apoptosis. This type of variation, along with other ones, causes cancer (26). Usually, the Phosphatase and tensin homolog (PTEN) protein blocks the PI3K/AKT/MTOR pathway when the cell is ready for apoptosis.

In some breast cancers, the gene that makes the PTEN protein is changed. Therefore, the PI3K/AKT/MTOR pathway remains active, and the cancer cells will not be able to apoptosis and become immortal (27). Experiments show that variations that can lead to breast cancer are associated with high estrogen levels. Immune system defects that are naturally responsible for killing malignant cells through a person's life and anomalous signalling of growth factors in the interaction between stromal cells and epithelial cells can enable the growth of cancerous cells (28).

Genetic factors of breast cancer

All breast cancer cases are not inherited, and the hereditary type accounts for just a small percentage (5-10%) of all cases. In fact, in most cases, the disorder begins in the individual and is not related to higher generations (29). These are called "unilateral breast cancers." About 70% of breast cancers are non-hereditary, but family history is a very important risk factor for breast cancer. Women with a family history are at higher risk for disease (30). Thus, the risk of breast cancer in a woman with an infected sister or mother is 1.5 to 3 times higher, for instance, in a woman whose mother has breast cancer in comparison with a woman who has no family history of breast malignancy, the age of onset is lower (31).

In two-thirds of these cases, inherited variations in the BRCA1 and BRCA2 genes (an autosomal dominant genetic pattern) increase breast cancer and ovarian cancer (32). In 40% of familial breast cancer cases, a variation in BRCA1 and 30% of this type of breast cancer, a variation in BRCA2 gene was observed (33). While both BRCA1 and BRCA2 genes are tumor suppressor genes that control cell growth, death and differentiation, they are also involved in DNA repair. The protein products of these genes are called caretaker, which maintains genomic integrity (33).

In proto-oncogenes, variations in one allele are sufficient to alter gene function in uncontrolled cell growth; unlike in tumor suppressor genes, both alleles must mutate to disrupt gene function. Therefore, when an abnormal BRCA1 or BRCA2 gene is inherited, a person gets breast cancer when another allele is mutated too (34). So far, more than 700 types of BRCAl variations and 300 types of BRCA2 variations have been identified, which in addition to increasing the risk of breast cancer and ovarian cancer, lead to other cancers, including breast cancer in men, fallopian tube cancer and prostate cancer. BRCA2 variations also increase the risk of melanoma and stomach cancer (31).

Somatic variations involved in breast cancer

Over the past decades, the theory has appeared that somatic variations are the primary reason for cell cancer in most malignancies. Most cases of breast cancer were reported in women who had no family history of the

disease. Also, a review of the history of breast cancer in some families showed that heredity is an essential factor in breast cancer. Breast cancer is a complex genetic disease whose phenotype is due to connections between specific genes and environmental factors (35, 36).

That cancer is a genetic disease should not be confused with the fact that cancer is a disease. Although cancer is caused by the inheritance of a defective gene from parents such as retinoblastoma, this is an exception to the general rule that cancer is not inherited. However, all cancers, including breast cancer, are genetic, that is, and they are triggered by the abnormal functioning of genes (37).

Essential genes in cell cancer

BRCA1 and BRCA2

The BRCA1 gene was identified in 1990 on chromosome 17 (17q21) and the BRCA2 gene in 1994 on chromosome 13 (13q12-13). The structure of this protein was illustrated in Figure 1. There are numerous variations in the normal BRCA1 and BRCA2 alleles (38). These variations alter the transcriptional structure of these two genes, leading to the production of abnormal proteins. Variations in the two genes mentioned above were reported in 5-10% of total cancers of the breast. 40% of breast cancers with a family history had a variation in the BRCA1 gene, and 30% had a variation in the BRCA2 (39). In male cancers, variations in the BRCA2 gene are more common than in BRCA1. BRCA1 mutant allele carriers have a worse prognosis than BRCA2 mutant carriers, even if diagnosed early, which is probably the main reason for the different breast mass structure of these groups. People with breast cancer with a variation in BRCA1 often have axillary lymph node problems in the early stages with a negative situation in estrogen receptor (ER-) and progesterone (PR) receptors. BRCA1 and BRCA2 are genes involved in DNA repair (40).

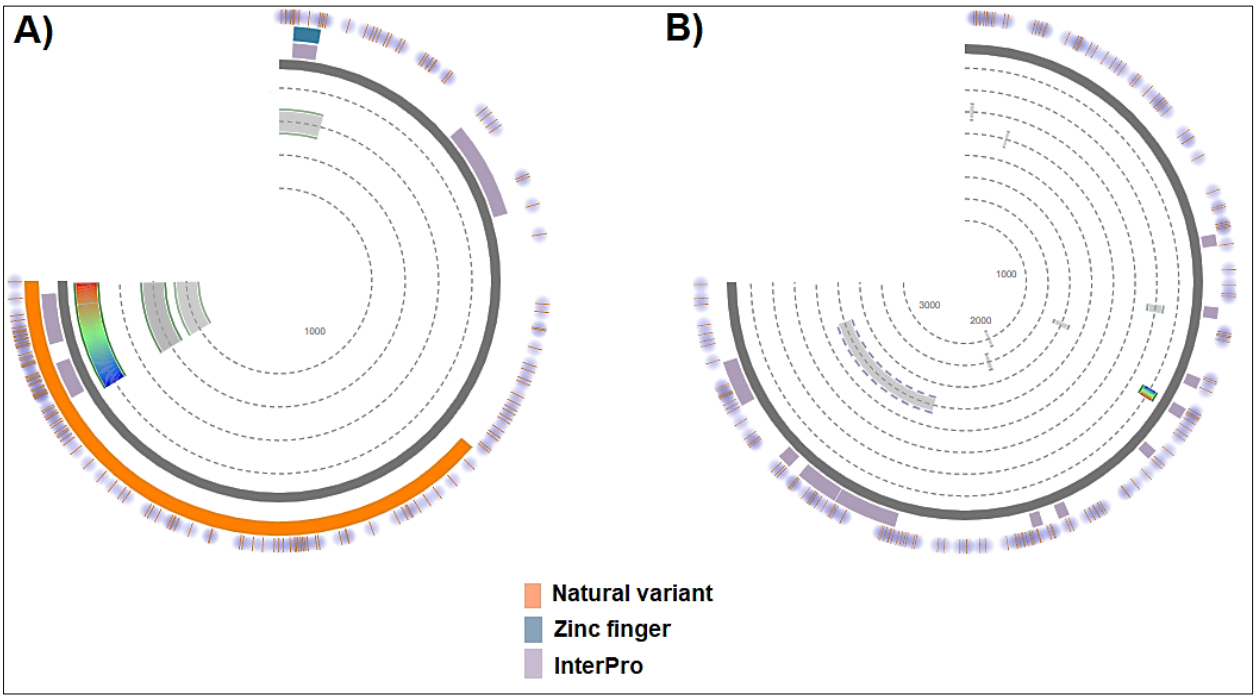

Figure 1. Protein structure homology models. The overview of BRCA1 (A) and BRCA2 (B) gene structures. The natural variants, zinc finger, and InterPro information for the two mentioned proteins are illustrated in unique colors. The figure was deduced from the Expasy server and was modified by the authors.

Her 2 and C-erbB-2

These genes, which are part of proto-oncogenes, include erbB1 (B1/EGFR), erbB2 (Her2/neu), erbB3 (Her3), and erbB4 (Her4), produce protein products that belong to the tyrosine kinase receptor family. In 20 to 30% of invasive breast tumors, we see an increase in copies of this gene, and there seems to be an association between

increased copies of this gene and the invasiveness of breast cancer. ErbB2 gene amplification is associated with lymph node involvement and non-recurrent survival in breast and ovarian cancers (41). Increased erbB2 expression is associated with a growth in the degree of tumor in the negative state of estrogen and progesterone receptors and causes bone marrow metastasis (42, 43).

c-Myc

The c-Myc is a nuclear protein and a component of proto-oncogenes that plays a vital role in regulating cell growth and proliferation. C-Myc mRNA overexpression is associated with inflammatory carcinoma (44). Deregulation of MYC could play a role in the progression and development of breast cancer. Several mechanisms contributed to the deregulation of MYC in breast cancer, consisting of transcriptional regulation, gene amplification, and mRNA and protein stabilization, associated with loss of tumor inhibitors and stimulation of oncogene paths. Breast cancer is categorized into at least 5 subgroups according to gene expression profiles, and each subgroup has different biological properties and clinical consequences. The BRCA1 prevents MYC's transforming and transcriptional action. Lack of BRCA1, along with overexpression of MYC results in breast cancer development (45).

Cyclin

Cyclins are a family of genes that could regulate the cell progression via the cell cycle by triggering cyclin-dependent kinase (CDK) proteins or a group of proteins essential for cell cycle synthesis (46). If the cyclins bind to the related kinases, including the p34/cdc2/cdk1 complex, they create the maturation-promoting factor (MPFs). MPFs trigger other proteins via phosphorylation procedure. The phosphorylated molecules are then responsible for definite actions throughout cycle division, including remodeling chromatin and microtubule formation (47). Many types of cyclins play a different role in cell division and also in cancer development. Increased expression of B1 cyclin, cyclin E and overexpression of D cyclin was detected in studies on breast cancer cell line and breast biopsies. The cyclin family, including D1 and E, control the cell cycle and activate in the G1 stage of the cell cycle (48). The role and schematic representation of the cell cycle and its regulatory proteins are shown in Figure 2.

EGFR, IGF-I and IGF-II

Epidermal growth factor receptor (EGFR) gene product is a glycoprotein with a molecular weight of 170KD, which is found in many cell types, including breast cancer cells. In addition, some growth factors bind to and are activated by EGFR, which include altered epidermal growth factor receptor (EGFR-α), epidermal growth factor, and amphiregulin (49).

The insulin-like growth factor (IGF) family and the normal growth and development of the breast also play a role in the development of cancer. The IGF family, especially IGF-I, plays an important role in cell division, metastasis, and inhibiting apoptosis in breast cancer cells (50, 51).

Waf1/cip1, Tenascin and CD44

The Cip / Kip gene family includes p21 / WAF1 / CIP1, p27 Kip1, p57 Kip2 proteins, which negatively regulate the activity of cyclin-CDK complexes in the G1 phase and, to a lesser extent Cycline B/CDK1 (52, 53).P21 (a product of the CDKNA1 gene), located on chromosome 6p21.2, inhibits cell cycle progress in two ways: stress-induced p53-dependent ending and p53-independent ending (54).

Tenascin is an extracellular matrix glycoprotein that has been considered a regulator of cell migration and organogenesis. Tenasine is strongly associated with ductal and lobular breast cancers, and its other expression is associated with the degree of tumor differentiation (55). The product of CD44 is a transmembrane glycoprotein that has several isoforms. In one study, v6 isoform was observed in 84% of primary breast tumors and 100% of cases of lymph node metastasis (55).

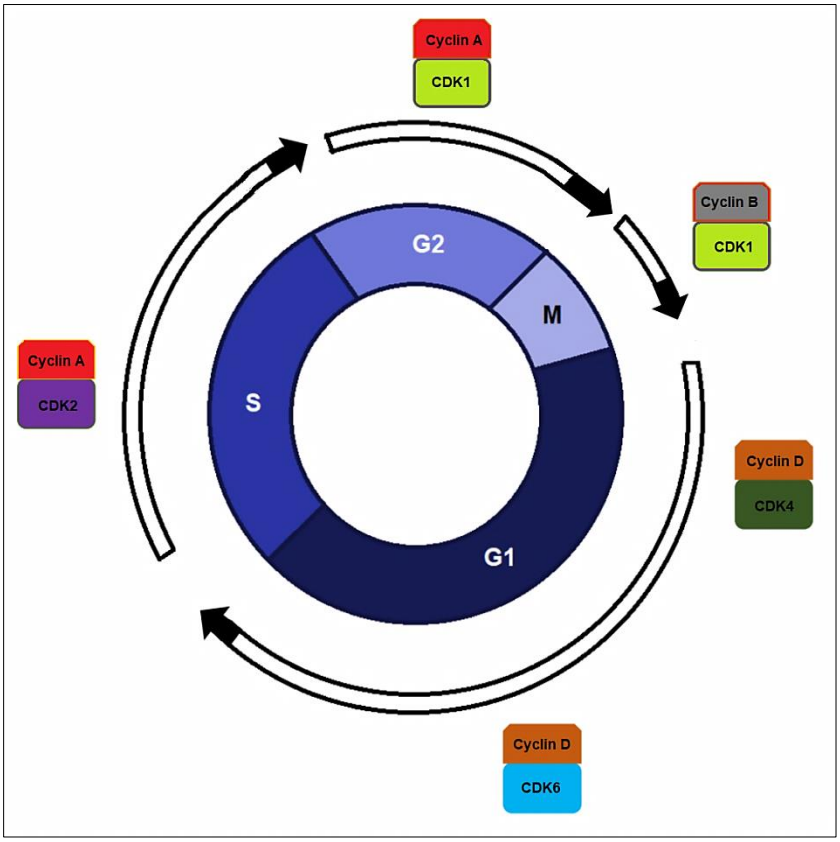

Figure 2. Cell cycle and its regulator. The cell cycle consists of four phases, including G1, S, G2, and M. The special cyclins and CDKs for each step are different. For example, cyclin D and CDK4 and cyclin D and CDK6 are involved in the G1 phase. This cycle is disrupted in the cancerous process.

Rb, p53, and p21, and bcl-2

Rb gene is located on the extensive arm of chromosome 13. In approximately 25% of breast cancers, the absence of alleles on chromosome 13 is found in the Rb gene region (56). Retinoblastoma is a tumor-inhibitor that, in the non-phosphorylated state, binds to E2F transcription factors and stops the cell cycle in the G1 stage. Rb variations have been observed in advanced breast cancer cases or in breast aneuploid cancers, which demonstrates that Rb variation is not the trigger for breast cancer but is a phenomenon that occurs during genetic instability (57).

The p53 is a tumor protein (TP) and a regulatory transcription factor in the cell cycle, so it acts as a tumor inhibitor.P53 is considered an expert genomic protector because of its role in sustaining cell balance by preventing gene variation (58).P53 is located on the short arm of chromosome 17, and its deletion is common in primary breast cancer (59).

P53 plays a vital role in cell cycle control. The normal function of this gene not only detects DNA damage but also allows the cell to enter a stop phase to repair the damage. If the cell fails to repair the damage, P53 inhibits the transfer of mutated genes to daughter cells by inducing programmed death (60). P53 variations are mainly acquired, but the mutated gene is inherited from parents in rare cases causes-Fraumeni syndrome. People with this syndrome are at risk for various cancers, including breast cancer, at an early age.

The p21 is the primary mediator which through it, P53 induces cell growth arrest. In addition, p21 induces cell death. In addition, the bcl-2 gene is a proto-oncogene, which regulates the mitochondrial pathway of apoptosis. It can play a stimulatory or inhibitory role in apoptosis. There is a weak association between bcl-2 gene expression and breast cancer (61-63). However, a detailed study of this dilemma requires a more detailed and comprehensive study of the genome in this regard, as has been done for some disorders and inadequacies.

Conclusion

Breast cancer is a type of cancer that starts in the breast tissue. There are many known risk factors for breast cancer. Lifestyle risk factors including alcohol consumption, smoking, eating unhealthy foods, being overweight, inactivity and exercise are a group of risk factors for this disease. Environmental risk factors such as UV rays, pollution, pesticides and toxins are other risk factors. The disease also depends on other factors such as gender, race, age and skin color. Hereditary risk factors, including specific mutated genes, can also increase the risk of breast cancer in carriers of these variations. The BRCA1 and BRCA2 genes, Her 2 and C-erbB-2, c-Myc, cyclin, EGFR, IGF-I and IGF-II, Waf1 / cip1, Tenascin, CD44, bcl-2, Rb, p53, p21 are the most important genes involved in this disease. Meanwhile, BRCA1 and BRCA2 genes are more important than other genes and play a key role in breast cancer. These genes are responsible for 20% of inherited breast cancers.

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