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Breast Cancer: From Molecular Subtypes to Metastasis

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Abstract: Breast cancer is the most common cancer among women and is the leading cause of female mortality worldwide. According to the American Cancer Society, 13% of women (1 in 8 women) will have been diagnosed with breast cancer at least once in their lifetime. Although breast cancer is more common in women, men are also susceptible to breast cancer, but to a much lesser extent. Only 0.12% of men (one in 833 men) are diagnosed with breast cancer. Breast cancer is caused by the interplay between genes and specific environmental factors. The classification of breast cancer into different molecular subtypes that are different from each other affects the choice of the type of treatments. A number of recent studies have shown a significant relationship between breast cancer molecular subtype and metastatic status. The metastasis is a process of biological actions that must be completed by cancer cells to exit the primary tumor and develop a new tumor at a distant site. Certain breast cancer molecular subtypes are more likely to cause metastases in certain organs of the body than others. Primary and secondary breast cancer of the triple-negative molecular subtype is often the worst, followed by the HER+ molecular subtype.

Keywords: Breast cancer, Breast cancer molecular subtypes, Metastasis

Introduction

When the body grows or some of its cells die, new cells are produced to replace the old cells. During this process, the number of new cells is always equal to the number of dead cells. If this biological process is disrupted and the new cells multiply more than the normal level, the body will fight against them through the mechanisms that control cell growth. When these cells are able to evade the body's mechanisms, cancer will occur. If cancer is not detected and treated, these abnormal cells will continue to grow and divide. The reason they are able to form a cancerous tumor is because these cancer cells have acquired characteristics such as their ability to evade growth inhibition or cell death mechanisms, their constant release of growth signals, their genetic instability, and their ability to induce angiogenesis and metastasis (Eroles et al., 2012).

The incidence of breast cancer is increasing every year and the incidence of breast cancer is the highest among all malignant tumors in women. In 2021, the mortality rate from breast cancer was second only to lung cancer (Li et al., 2023) and the mortality rate caused by breast cancer is expected to be the highest in 2040 (Sheva et al., 2024). This is due to the difficulty in identifying the molecular mechanisms responsible for cancer initiation and progression as well as the difficulty in determining the exact time of disease onset (Russo et al., 2000). Nevertheless, identifying the molecular subtypes of breast cancer plays an important role in determining the treatment and management of the tumor (Sheva et al., 2024).

While primary breast cancer is not a cause of death, distant metastases of breast cancer are the leading cause of treatment failure and death. Common sites for distant metastases of breast cancer are bone, lung, liver, and brain (Liu et al., 2022). The transformation of a primary cancer into a metastatic cancer goes through several stages and the most commonly used system for breast cancer staging is the TNM system (Pourriahi et al., 2023), which describes the anatomical extent of the cancer and determines its stage (Park et al., 2011). The TNM system refers to: (T) primary tumor features (size and relationship to the surrounding environment), (N) regional lymph node features (number and location of nodes, size of nodal involvement and presence of external extension), and (M) presence of metastasis (Cserni et al., 2018). The TNM stage classification combines these parameters and categorizes the disease into one of 5 stages (0, I, II, II, III, and IV). Breast cancers of different stages exhibit different genomic characteristics and molecular profiles (Tsang & Tse, 2020).

Molecular Classification of Breast Cancer

The breast cancer prognosis and treatment pathway are determined by its molecular classification. Research studies applying molecular techniques have determined several circulating tumor biomarkers useful for diagnosis, prognosis, therapeutic response, and monitoring minimal residual disease (Pankotai-Bod´o et al., 2024). Molecular subtypes of breast cancer are identified by measuring the expression of hormone receptors including human epidermal receptor 2 (HER2), Progesterone receptor (PR) and Estrogen receptor (ER) (Guo et al., 2024). The first prognostic marker in breast cancer recognized in the 1980s was the estrogen receptor. In the late 1990s, the HER2 receptor was discovered. In addition, a cell proliferation marker such as the Ki-67 gene was incorporated to give a greater chance of differentiating molecular subtypes (Lim & Hortobagyi, 2016).

Breast growth and development is influenced by a large number of growth factors and hormones as the breast is a hormone-responsive organ. The response of the breast to hormones is selective and consequently breast cells proliferate or differentiate, leading to irreversible changes in the structure and biological characteristics of the breast (Russo et al., 2000). In principle, the most common hormones that affect the mammary gland are hormones secreted by or modulated by the ovary (Estrogens and Progesterone) (Wang et al., 2024). The role of the ovarian sex hormones Estrogen and Progesterone (PR) in the growth and development of breast cancer was discovered more than 100 years ago when George Bateson demonstrated that oophorectomy cured a woman of breast cancer (Trabert et al., 2020). Today, more than 70% of breast cancer patients have Estrogen receptor and Progesterone receptor positive tumors (Miladinova, 2019).

Estrogen is one of the most important steroidal sex hormones in women. While estrogen is important, it also plays a role in the development of a number of cancers in females. Exposure to the estrogen hormone is a risk factor for breast cancer because the majority of breast cancers have receptors for this hormone (Russo et al., 2000). Estrogen, a form of estradiol (E2), stimulates the activation of a number of genes that increase the growth of cancer cells. Both α and β forms of the ER receptor have been discovered (Lim & Hortobagyi, 2016). In other words, Estrogen stimulates breast cancer by contributing to increased proliferation of cancer cells and reduced apoptosis. Estrogen also affects the gene expression of GATA3 and FOXA1 genes that lead to breast cancer initiation, progression and metastasis. In addition, estrogen receptors bind to G proteins on the cell membrane and this activates PI3K/AKT and Ras/MAPK signaling, which in turn stimulate the transcription of genes involved in breast cancer initiation (Wang et al., 2024). To summarize, estrogen induces breast cancer through three mechanisms: Hormonal activity mediated by the estrogen receptor which stimulates cell proliferation and increases the chances of accumulating the genetic damage that leads to breast cancer, metabolic activation through the stimulation of membrane-bound hemoproteins called cytochrome P450 which leads to toxic effects that increase mutation rates in cells and weaken the DNA repair system (Russo et al., 2000).

Progesterone is a sex steroid hormone that participates in the female menstrual cycle and pregnancy by binding to the Progesterone receptor.9 Progesterone also participates in the hormone's regulation of estrogen (Li et al., 2020). As with Estrogen, overexposure to Progesterone is a risk factor for breast cancer (Guo et al., 2024). Studies have found that women with higher levels of Progesterone are 16% more likely to develop breast cancer than other women.67 Progesterone contributes to the development of breast cancer through the following mechanisms: Progesterone receptors on the surface of mammary cells bind to the hormone Progesterone which contributes to the nourishment and proliferation of breast cancer cells. Progesterone can stimulate the proliferation of PR-positive neighboring cells, Progesterone also stimulates the proliferation of PR-negative luminal epithelial cells, Progesterone can stimulate mammary gland development by expanding the mammary stem cell population, and Progesterone can also regulate this pathway (Li et al., 2020).

HER2 (ErbB2, human epidermal growth factor receptor 2) is the second member of a family of Epidermal growth factor receptor (EGFR) trans-membrane glycoprotein receptor (Lim & Hortobagyi, 2016). The HER family consists of four receptors (HER1, HER2, HER3 and HER4). These members of the HER family of receptors participate in the regulation of many cell processes including apoptosis, migration, growth, adhesion and differentiation. This is carried out through activation of the Akt, Ras-Raf mitogen– activated protein (MAP) kinase and phosphatidylinositol 3-kinase (PI3K) pathways which lead to tumor cell proliferation, survival, adhesion and metastasis (Guo et al., 2024). HER signaling is vital for normal cell growth but dysregulated HER signaling is strongly connected to malignant transformation. Dysregulation of HER signaling can occur via a number of mechanisms: over-expression of the normal HER receptor, overexpression of the ligand or expression of the mutant HER receptor (Yarden et al., 2004). A nearly threefold increase in mortality associated with breast cancer and distant metastasis has been reported in patients with HER2 overexpression. The importance of HER2 testing has increased dramatically as it has become a strong predictive marker of response to HER2-targeted treatment (Lim & Hortobagyi, 2016).

Deregulated proliferation is a typical feature of a malignant tumor and can be evaluated by various methods, the most important of which is the expression of the Ki-67 gene. While Ki-67 is expressed in all proliferating cells, its role as a proliferation marker has attracted considerable attention (Soliman & Yussif, 2016). Ki-67 is located on the long arm of human chromosome 10 (10q25) (Ma et al., 2024). The expression rate of this gene varies according to the phases of the cell cycle, with a peak in M phase, low in G1 and early S phase, and no expression in G0 phase (Soliman & Yussif, 2016). Ki-67 has an important role in distinguishing between different molecular subtypes in breast cancers (Lim & Hortobagyi, 2016) so it is often used to distinguish between luminal A and luminal B. It is also an important marker for determining the prognosis of patients with HR+/HER2- early breast cancer. Ki-67 expression in breast cancer is associated with a higher risk of breast cancer recurrence (Ma et al., 2024). Through prognostic biomarkers such as the prevalence of estrogen receptor, progesterone receptor, HER2, and Ki-67, breast cancer can be classified into the following molecular subtypes (Li et al., 2023):

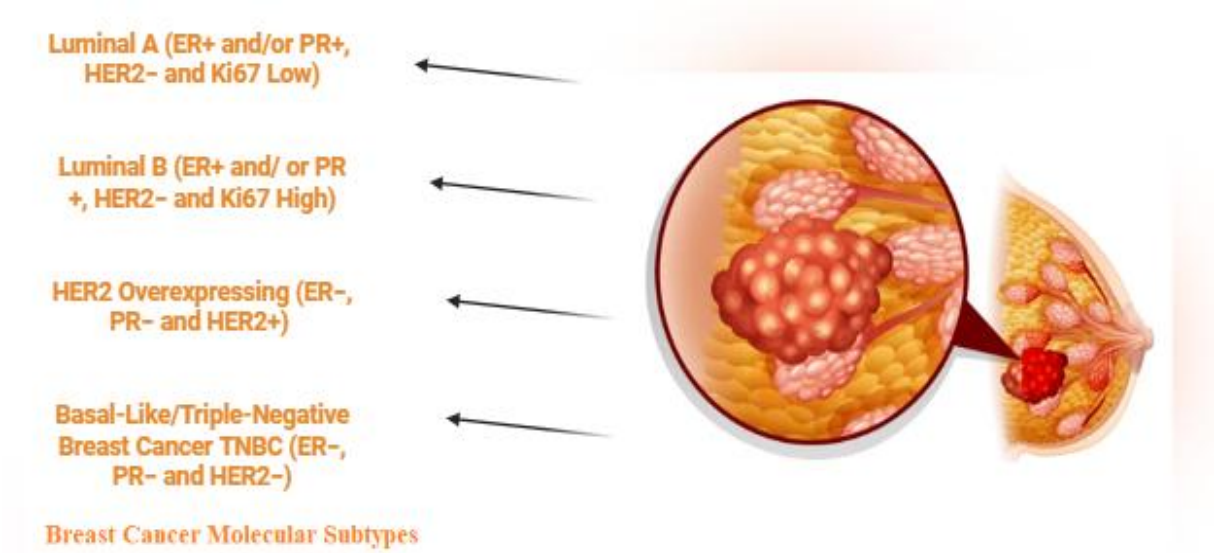

Figure 1. Breast cancer molecular subtypes

Luminal A (ER+ and/or PR+, HER2− and Ki67 Low < 15%)

Luminal A breast cancer is the most common molecular subtype, with 50-60% of all breast cancer cases falling under this type (Eroles et al., 2012). This type is typically featured by the expression of genes that are transactivated by the transcription factor ER and/or PR and that are expressed in the luminal epithelium lining the ductal mammary glands. At the same time this subtype is characterized by the absence of HER2 and low gene expression of Ki-67 which is associated with cell proliferation and division (Pankotai-Bod´o et al., 2024). Tumors classified within this subtype have a better prognosis than other subtypes because they grow slowly and have a relatively low incidence rate (27.8%) and therefore a higher survival rate (median 2.2 years) (Sheva et al., 2024). Tumors of this subtype are more likely to develop bone metastases (18.7%) and may also develop metastases to other organs such as the central nervous system, liver, and lung (less than 10%) (Eroles et al., 2012).

Luminal B (ER+ and/ or PR+, HER2− and Ki67 High ≥ 15%)

Luminal B subtype tumors account for 10%-20% of all breast cancers. This molecular subtype includes ER expression and/or PR with high Ki-67 expression and possible HER expression (Sheva et al., 2024). When comparing this subtype with luminal A subtype, tumors of this subtype are more invasive, have a higher proliferative index, a worse prognosis, and a lower survival rate (1.6 years). This is because these tumors are associated with high proliferation rates as well as potential expression of HER2. Bone is the most common site of metastasis (30%), followed by the liver (13.8%) (Pankotai-Bod´o et al., 2024).

HER2 Overexpressing (ER−, PR− and HER2+)

HER2 subtype is characterized by high levels of HER2 expression as well as being ER and PR negative. Additionally, two subgroups of HER2 can be differentiated: luminal HER2 (ER-, PR-, and HER2+, Ki-67 15%-30%) and enriched HER2 (ER-, PR-, and HER2+, Ki-67>30%) (Krishnamurti & Silverman, 2014). Tumors belonging to this subtype constitute 20-25% of all breast cancer tumors (Miladinova, 2019). Tumors of the HER2+ molecular subtype are tumors with a poor prognosis. This is because HER2 is encoded by the proto-oncogene HER2/neu or c-erbB-2, which is involved in tumor cell survival, proliferation, metastasis, angiogenesis, increased cell adhesion, and impaired apoptosis (Tsang & Tse, 2020).

Basal-Like/Triple-Negative Breast Cancer (ER−, PR− and HER2−)

The triple negative molecular subtype is characterized by the absence of estrogen, progesterone, and HER2 receptors (Sheva et al., 2024). Tumors of this subtype are characterized by the expression of genes in normal mammary basal/epithelial cells, especially basal cytokeratins (CK5 and CK17, P-cadherin, caveolin 1 and 2, nestin, CD44 and EGFR), so they are also termed basal-like tumors (Tsang & Tse, 2020). The basal-like subtype represents 10–20% of all breast carcinomas. This subtype is the most popular subtype of breast cancer among women under the age of 40 (Anothaisintawee et al., 2013). Triple-negative tumors have a high rate of p53 mutations; thus, these tumors are aggressive and have a poor prognosis (Chen et al., 2018). In addition, tumors with mutations in the BRCA1 gene fall into the same subtype. The pattern of metastatic relapse is characterized by aggressiveness with a predominance of lymph nodes and visceral organs (especially lungs and central nervous system) (Anothaisintawee et al., 2013). Relapses may occur within 5 years after diagnosis (Tsang & Tse, 2020).

Table 1. Features of molecular breast cancer subtypes

Subtype	ER/PR/HER2	Frequency	Prognosis	Significant Genes
Luminal A	ER+ and/or PR+, HER2− and Ki67 Low	50-60%	Good	PI3KCA-MAPK3K1-GATA3- CCDN1
Luminal B	ER+ and/ or PR+, HER2− and Ki67 High	10%-20%	Poor/Bad	PI3KCA-MAPK3K1-GATA3- CCDN1-TP53- RB- FOXM1
HER2 Overexpressing	ER−, PR− and HER2+	20-25%	Poor	HER2-GRB7
Basal-Like/Triple-Negative	ER−, PR− and HER2−	10%-20%	Poor	TP53- BRCA1-MYC- RB1- CK5/6

Breast Cancer Subtypes and Locations of Metastasis

Metastasis is a sequence of biological processes completed by cancer cells to exit the original tumor location to other locations where the primary tumor is transformed into a distant secondary tumor. First, the tumor cells must be able to perform invasion, which is the first step in the metastatic process. For the process of invasion, changes occur in the adhesion of cells to their neighboring cell as well as the adhesion of the cell to the extracellular matrix. Tumor cells invade the basement membrane and surrounding cells. Ultimately, cells that are able to survive leak into blood or lymphatic circulation and some cells migrate to form a tumor in a new location. The 5-year survival rate in primary breast cancer is 99%. Nevertheless, once distant metastases appear, this rate decreases to 23% (Mego et al., 2010).

Breast cancer cells metastasize preferentially to selected organs, known as "organ metastasis," which is highly regulated by breast cancer subtypes, the microenvironment of host organs, and interactions between cancer cells and organs. (Chen et al., 2018). Breast cancer metastases majorly to the lymph nodes, skeleton, lungs, liver, and brain by way of the blood circulation (Ma et al., 2015). 70% of metastatic breast cancer patients have metastases to the bone, 30% to the liver and 10-30% to the brain. Molecular subtypes of breast cancer play a critical role in the process of identifying the target organ for metastasis (Chen et al., 2018).

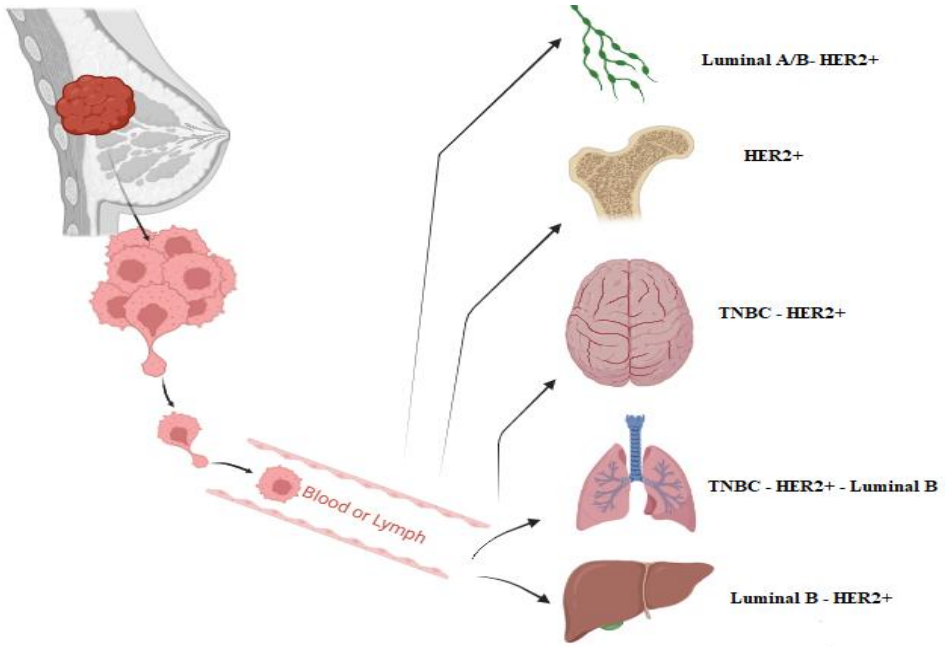

Figure 2. Breast cancer subtypes and locations of metastasis

Bone Metastases

Luminal The majority of women with advanced breast cancer have clinical evidence of bone metastases by the time of death. The most common site of metastatic breast cancer is bone and represents about 70% of metastases. Bone metastases remain asymptomatic for a long time but then pain will be common and hypercalcemia and fractures will occur. Metastatic breast cancer cells infiltrate from the capillaries into the bone matrix and mimic bone, leading to adhesion, proliferation, and survival in the bone microenvironment.76 Thus, bone loss occurs by enhancing bone degradation (Weilbaecher et al., 2011). While all subtypes are susceptible to bone metastasis, luminal A/B tumors develop bone metastases at a much higher rate (80.5%) (Jin et al., 2018) than TN tumors (41.7%) and HER2+ tumors (55.6%) (Savci-Heijink et al., 2016).

Lung Metastases

Lung metastases often begin to form within 5 years after the initial diagnosis of breast cancer. Lung metastases have a major influence on patient morbidity and mortality because it interrupts normal lung function (Medeiros & Allan, 2019). Specifically, 60-70% of metastatic breast cancer patients who die are diagnosed with lung metastasis. Life expectancy is reduced when lung metastases are diagnosed, with a median of only 22 months. Lung metastases are often developed from triple-negative primary subtype breast cancer; it occurs in about 40% of patients (Jin et al., 2018). Research has found that genes such as epidermal growth factor receptor ligand epiregulin are implicated in lung metastases by promoting tumor angiogenesis, releasing cancer cells into the circulation and penetrating lung capillaries (Chen et al., 2018). HER2+ breast cancer tends to metastasize to the lungs at about 25% while this rate is 21% for Luminal B breast cancer (Medeiros & Allan, 2019).

Liver Metastases

The third most common site of spread of metastatic tumors from breast cancer is the liver (Liu et al., 2022). Patients with metastatic breast cancer have a 15-32% incidence of liver metastases (Medeiros & Allan, 2019).

The liver is a densely vascularized organ and its endothelium has no basement membrane, which allows the transport of large molecules into the liver and also affects the interactions between tumor cells and the liver microenvironment. Liver metastases can then develop a suitable environment for their survival, replacing liver cells and internalizing blood vessels (Liu et al., 2022). Liver metastases are poorly diagnosed and if left untreated, the survival rate is only 4-8 months (Ma et al., 2015). Liver metastasis is strongly associated with ER expression and luminal subtype B is the most likely to develop liver metastases. In addition, the HER2+ subtype also has more liver metastases compared to other breast cancer subtypes (Chen et al., 2018). Triple-negative breast cancers also exhibit a high risk of liver metastasis (Liu et al., 2022).

Brain Metastases

The second most popular reason for metastatic brain disease is breast cancer (Rostami et al., 2016). About 10-30% of metastatic breast cancer patients develop brain/central nervous system metastases. Brain metastases are often a late complication of breast cancer, appearing after lung, liver and/or bone metastases. Brain metastases are associated with poor prognosis and neurological impairment affecting cognitive and sensory functions. Many risk factors for brain metastases have been identified, including young age and poorly differentiated tumors (Lanigan et al., 2007). HER2+ and triple negative breast cancer subtypes have higher probability of brain metastasis (17 and 15 %, respectively) compared to luminal A and luminal B subtype (9 and 11 %, respectively) (Rostami et al., 2016).

Lymph Node Metastases

Determining the presence of lymph node metastases is critical for prognosis, staging, and treatment guidance in breast cancer patients (Zhou et al., 2020). The presence of lymph node metastases indicates a high risk of distant metastases and the absence of lymph node metastases indicates a low risk of distant metastases. The metastases of the tumor to distant sites are well known to occur not exclusively through axillary lymph nodes but also through the circulation. Luminal A, Luminal B, and HER2+ breast cancer subtypes are associated with lymph node metastasis. High lymphovascular invasion and high Ki67 expression are independently predictive of metastasis of axillary lymph nodes (Chen et al., 2018).

Conclusion

The most prevalent malignant tumor among women all over the world is breast cancer. Breast cancer is a complex disease involving very distinct morphological and molecular structures. The heterogeneity that occurs in breast cancer cannot be explained by some characteristics such as histological grade, age, tumor size, and lymph node involvement. Today, researches are heavily focused on the molecular biology of breast cancer. Thus, there is also a need to consider some biomarkers such as estrogen receptor (ER), progesterone receptor (PR), and epidermal growth factor receptor 2 (HER2). These biomarkers are important because they are routinely used in the diagnosis and treatment of breast cancer. Despite the possibility of different classifications, in general, breast cancer can be divided into four molecular subtypes: Luminal A, Luminal B, HER2 +, and triple negative breast cancer (TNBC). Molecular subtypes of breast cancer are associated with prognosis and the occurrence of distant metastases. Metastasis is a multi-stage mechanism by which cancer cells acquire new characteristics that enable them to leave their original location and migrate to other distant locations, thus transforming the original primary tumor into a distant secondary tumor.

Metastasis is the final stage in most cancers and is the leading cause of death rather than the primary tumor in breast cancers. In both primary and secondary breast cancer, luminal A subtype shows the best survival rate, followed by luminal B subtype. With the exception of the TNBC subtype, it was observed that bone was the most common location of metastasis in all breast cancer molecular subtypes. Briefly, HER2+ subtypes show a noticeably higher rate of metastases to brain, liver, and lung than luminal A/B subtype. TN subtypes have a high rate of metastases to brain, lung, and distant lymph-node.

Scientific Ethics Declaration

* The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

Conflict of Interest

* The authors declare that they have no conflicts of interest

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