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Genetic And Hormonal Influence; Unraveling Breast Cancer Complexity

Debrah Asiimwe and Emmanuel Ifeanyi Obeagu
Department of Medical Laboratory Science, Kampala International University, Uganda

Abstract
Breast cancer is a disease in which abnormal breast cells grow out of control and form tumors which when not treated tumors spread throughout the body and become fatal. Breast cancer has been the most frequent disease in women worldwide, represents a significant public health concern on a global scale. Advanced breast cancer with distant organ metastases is considered incurable with current therapies. The incidence of breast cancer continues to rise in every part of the world despite advances in its identification and treatment, which have resulted in lower mortality rates, it appears vital to seek out new therapeutic approaches, predictive and prognostic indicators. Breast cancer has been the most frequent disease in women worldwide, represents a significant public health concern on a global scale. Advanced breast cancer with distant organ metastases is considered incurable with current therapies. Studies have been showing how breast cancer has succumbed many global lives for over decades and even with the available measures to combat its progress, breast cancer has remained a burden to the entire population. Therefore, more interventions need to be put in place mainly on understanding the genetic /molecular basis of breast cancer.
Keywords*: Breast Cancer, Genetic Influences, Hormonal Factors, BRCA1, BRCA2, Personalized Medicine*

Introduction

Breast cancer is a disease in which abnormal breast cells grow out of control and form tumors which when not treated tumors spread throughout the body and become fatal. Carcinogenesis is a multifactorial process that is stimulated by both genetic predispositions and environmental causes.[1-6] Breast cancer develops in the mammary glands during mammalian adulthood as the female mammary glands continue to develop after birth thereby undergoing various modifications during pregnancy, lactation and involution under the regulation of hormones and transcription factors, including those encoded by the HOX clusters (A, B, C, and D).[7]

HOX genes emerge as candidates to influence MG and BC development, encoding transcription factors that act as memory carriers of cell-specific processes.[8] Several of them are functionally required during the linear and cyclical phases of MG development and appear deregulated in BC, with an impact that reflects the great complexity of their developmental and cellular functions. Out of 39 human HOX genes, 35 have been associated with BC and expression level comparisons considering 25 of them allowed the identification of differences in 14 genes, comparing non-malignant and malignant BC tissues: HOX gene deregulation is often associated to breast cancer development. Within the HOXB cluster, 8 out of the 10 genes present altered expression levels in breast cancer with an impact in its aggressiveness and resistance to hormone therapy.[8]

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Genetic mutations are highly reported to be associated with an increased risk of breast cancer. This involves two major genes; BRCA1 (located on chromosome 17) and BRCA2 (located on chromosome. They are primarily linked to the increased risk of breast carcinogenesis S. The mutations within the above-mentioned genes are mainly inherited in an autosomal dominant manner.[9] Hormonal influence; Breast cancer is a complex disease with various risk factors and underlying mechanisms contributing to its development and progression.[10] Among these factors, hormonal imbalance has significantly affected breast cancer pathogenesis. Hormonal imbalance involving estrogen and progesterone has been extensively studied in breast cancer. Estrogen and progesterone both produced mainly in the ovaries play crucial roles in the growth and development of breast tissue and regulates the menstrual cycle and breast development respectively. Disruptions in the delicate balance of these hormones have been implicated in the initiation and progression of breast cancer.

Long-term use of hormone replacement therapy (HRT), particularly combined estrogen-progestin therapy, has been proved to be associated with an increased risk of breast cancer in women.[11] Furthermore, hormonal imbalances can also influence the microenvironment of the breast tissue Estrogen, for example, promotes the growth of blood vessels and stimulates the production of growth factors that facilitate tumor angiogenesis and metastasis.

Breast Cancer

Breast cancer is a dangerous disease that threatens thousands of lives every year. Breast cancer (oncology) is a disease caused by the transformation of normal breast cells into cancer cells.[1] Breast cancer is the second most common type of cancer after lung cancer and is the most common cancer among women. About 10% of women aged 13-90 are affected by this disease. This disease is less common in men (1%). Every year, more than 55 thousand women are diagnosed with this terrible disease(Society, 2006). In 2018, more than 2 million new cases were registered. Breast cancer, which is common among women, remains one of the most pressing problems among oncological diseases of the world.[3] More than 55 thousand women hear this terrible diagnosis every year and according to statistics, every tenth woman worldwide is diagnosed with breast cancer.[12] More than 1.5 million women die from this disease. Statistics have proven that the origin of breast cancer is associated with a change in hormonal and genetic status among older female adults. Studies conducted between 2008 and 2010 found that the incidence of breast cancer among women aged 65 years and above was an average of 45% of total cases.

Mechanism of breast cancer progression

Angiogenesis; this process involves vasodilation and an increase in vascular permeability. Numerous players referred to as angiogenic factors; work in tandem to facilitate the outgrowth of endothelial cells (EC) and the consequent vascularity. Conversely, angiogenic factors could also feature in pathological conditions such as breast cancer development. Angiogenesis is a critical factor in the development of tumors and metastases in numerous cancers.[13] An increased level of angiogenesis is associated with decreased survival in breast cancer patients. Disrupting the initiation and progression of this process by targeting angiogenic factors such as vascular endothelial growth factor (Vegf) or by targeting transcription factors, such as Hypoxia-Inducible Factors (HIFs) that act as angiogenic regulators, have been considered potential treatment options for several types of cancers including breast cancer.

Angiogenesis, the rapid increase in the formation of blood vessels, is required for supply of sufficient oxygen and nutrition for breast tumor growth. Breast cancer cells, need constant nourishment and oxygen supply through the vascular network of capillaries in the system. These capillaries usually do not proliferate because the cells that line the interior surface of blood vessels, endothelial cells (ECs), do not multiply. Low levels of O_2 (hypoxia) triggers numerous transcriptional responses, mediated by transcription factors, referred to as hypoxia-inducible factors (HIFs) which are transcription factors that regulate the expression of multiple genes responsible for stimulating specific physiological responses, such as metabolism, angiogenesis, and cell division. [13]

Risk factors related to breast cancer progression

Hormonal influence

Hormonal imbalance involving estrogen and progesterone has been studied in breast cancer. Estrogen, a hormone predominantly produced in the ovaries, plays a crucial role in the growth and development of breast tissue. Similarly, progesterone, another hormone primarily produced in the ovaries regulates the menstrual cycle and breast development. Disruptions in the delicate balance of these hormones have been implicated in the initiation and progression of breast cancer.[2] Hormonal imbalance is an abnormality or disruption in the body's optimal levels or ratios of hormones. One mechanism by which hormonal imbalance contributes to breast cancer is activating estrogen receptors (ERs) and progesterone receptors (PRs) in breast cells. Upon binding of estrogen to ER or progesterone to PR, a complex series of intracellular signaling events is initiated, which can contribute to cell proliferation regulation and cell death inhibition. In excess estrogen or impaired progesterone signaling, these pathways can become dysregulated, resulting in uncontrolled cell growth and the formation of tumors.[7] Furthermore, hormonal imbalances can also influence the microenvironment of the breast tissue Estrogen, for example, promotes the growth of blood vessels and stimulates the production of growth factors that facilitate tumor angiogenesis and metastasis. It can also impact the immune response within the breast, potentially modulating tumor immune surveillance and promoting tumor evasion of the immune system. Hormone Replacement Therapy. Studies have indicated that long-term use of hormone replacement therapy (HRT), particularly combined estrogen-progestin therapy has been associated with an increased risk of breast cancer. [8]

Genetic influence

Genetic factors play a significant role in breast cancer development. Specific gene mutations, such as mutations in the BRCA1 and BRCA2 genes, significantly increase the risk of developing breast cancer.[14] These mutations are inherited and can be passed down from generation to generation. Individuals carrying BRCA1 or BRCA2 mutations have a higher lifetime risk of developing breast cancer. In addition to BRCA1 and BRCA2, other genetic mutations, such as TP53, PTEN, and PALB2, are associated with breast cancer susceptibility. Family history also plays a significant role in breast cancer risk. Research has shown that individuals with a first-degree relative, such as a mother or sister, who has been diagnosed with breast cancer, are at a higher risk of developing the disease. This information is supported by numerous studies and scientific sources, emphasizing the importance of considering familial factors in assessing an individual's susceptibility to breast cancer.

Diagnosis of breast cancer

Cancer cells are misbehaving normal cells that are beyond the paradigm of life and death. Currently, breast cancer (BC) is the second most common cancer worldwide, after lung cancer and the leading oncological cancer in women. It's found out that survival rate of patients with early-stage breast cancer is significantly higher than those with middle- and late-stage breast cancer. Different diagnostic techniques have been developed mainly based on imaging and molecular biotechnology examination. Early detection and treatment are critical to curing breast cancer because it tends to metastasize in the middle and last stage. Therefore, finding BC is vital in early stage, which can greatly improve the survival rate of patients.[15]

Imaging techniques shows clearly the morphology and location of tumor tissues. However, imaging techniques may cause harm to patients when using contrast agents and high energy rays. Therefore, it's very important to choose the most appropriate diagnostic method for BC patients. These imaging techniques mainly include mammography (MG), ultrasonography (US), magnetic resonance imaging (MRI), positron emission computed tomography (PET), computed tomography (CT) and single-photon emission computed tomography (SPECT). Mammography (MG) is preferred strategy for screening and diagnosing BC and helps doctors obtain clinic information on BC patients. The diagnostic result of MG is only positive criteria for 4%-10% of BC patients (e.g., patients who exhibited only slight calcification). Ultrasonography (US) is applied in observing morphology and variation condition of tumor tissues and it can accurately locate the location of lesions. US is not harmful to humans and is suitable for every breast cancer patient.[15] Magnetic resonance imaging (MRI) allows early detection of familial BC regardless of patients' age, breast density or risk state.

Molecular biotechnology examinations can diagnose BC earlier than imaging techniques. It involves the analyzing of specific biomarkers such as nucleic acid, proteins, cells and tissues of patients thus it gives clinical information at the molecular level. Techniques include; nucleic acid hybridization system, real-time fluorescence quantitative PCR system, protein hybridization system, flow cytometer, needle biopsy and immunohistochemistry (IHC).[15]

Conclusion

The intricate interplay of genetic and hormonal factors in the development of breast cancer highlights the complexity of this disease. Extensive research has unraveled a myriad of genetic mutations and hormonal imbalances that contribute to the initiation and progression of breast cancer. The identification of specific genes, such as BRCA1 and BRCA2, has allowed for targeted screening and preventive measures in high-risk individuals, showcasing the potential for personalized medicine in managing genetic predispositions. Moreover, the influence of hormones, particularly estrogen and progesterone, on breast cancer development underscores the importance of understanding hormonal pathways and developing targeted therapies. Hormone receptor-positive breast cancers, for example, can be treated with endocrine therapies that aim to modulate hormonal signaling and disrupt cancer cell growth. This approach has significantly improved the prognosis and treatment outcomes for a subset of breast cancer patients.

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