



A Review of the Clinical Implications of Breast Cancer Biology

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Abstract

Background: Histologically similar tumors may have different prognoses and responses to treatment. These differences are due to molecular differences. Hence, in this review, the biological interaction of breast cancer in several different areas is discussed. In addition, the performance and clinical application of the most widely-recognized biomarkers, metastasis, and recurrences from a biological perspective and current global advances in these areas are addressed.

Objective: This review provides the performance and clinical application of the most widely-recognized biomarkers, metastasis, and recurrences from the biological perspective and current global advances in these areas.

Methods: PubMed, Scopus, and Google Scholar were searched comprehensively with combinations of the following keywords: “breast cancer,” “biological markers,” and “clinical.” The definition of breast cancer, diagnostic methods, biological markers, and available treatment approaches were extracted from the literature.

Results: Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2), and Ki-67 are the most well-known biological markers that have important roles in prognosis and response to therapeutic methods. Some studies showed the response of ER-positive and PR-negative tumors to anti-estrogenic treatment to be lower than ER-positive and PR-positive tumors. Patients with high expression of HER-2 and Ki-67 had a poor prognosis. In addition, recent investigations indicated the roles of new biomarkers, such as VEGF, IGF, P53 and P21, which are associated with many factors, such as age, race, and histological features.

Conclusion: The objective of scientists, from establishing a relationship between cancer biology infrastructures with clinical manifestations, is to find new ways of prevention and progression inhibition and then possible introduction of less dangerous and better treatments to resolve this dilemma of human society.

Keywords: Estrogen receptor, progesterone receptor, biological markers, breast cancer, human epidermal growth factor receptor-2

1. Introduction

Breast cancer is one of the most common types of cancer, and it is the reason high annual mortality rate among men and women (1, 2). While new approaches are introduced frequently to deal with breast cancer, many people are still at risk of this disease. Perhaps more attention to micro-molecular structure and biologic basis of the disease would help us to gain further information about the development and pathogenesis of this fatal disease by obtaining more knowledge about the development of the disease at the cellular level (3). Today, the need to understand the biology of breast cancer is obvious to everyone. Since surgeons are at the forefront of the fight against this disease, further knowledge in this regard would provide deeper insight and a broader perspective so more effective steps could be

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taken for prevention, early diagnosis, and treatment of these patients. This article provides a brief and novel approach for surgeons to help them be effective for their patients. Some definitions and common processes in the field of cancer development, the biological interaction of breast cancer in several different areas (genetic, histopathological characteristics, age and race), and the performance and clinical application of the most widely-recognized biomarkers, metastasis, recurrence from biological perspective, and current global advances in these areas are discussed. Regarding the methods of this literature review, PubMed, Scopus, and Google Scholar were searched comprehensively with a combination of the following keywords: “breast cancer,” “biological markers,” and “metastasis.” The definition of breast cancer, diagnostic methods, biological markers, and available treatment approaches were extracted from the literature.

2. Discussion

2.1. Definition

Cancer is, in fact, an uncontrolled growth. Cancer cells are not good citizens anymore, and they do not perform their duties nor do they respect their neighbors. They compress normal cells, invade their limits, and use nutrients as the fuel required for their accelerated growth. The word ‘tumor’ refers to the accumulation of a group of cancer cells in the body. Indeed, not all tumors are cancer. They are divided into two categories of benign and malignant. Benign tumors are not life-threatening, except in special circumstances, such as brain tumors, which can be dangerous and fatal even if they are histologically benign. Malignant or cancerous tumors always are dangerous and a threat to a person’s life, and they are able to metastasize to other organs of the body, a phenomenon called metastasis (4, 5).

2.2. Interaction of genetics and breast cancer biology

Cancer is a genetic disorder, but this doesn't mean that cancer is a hereditary disease. Cancer is inherited in rare cases (e.g., retinoblastoma, a rare malignant tumor of children’s eyes), but this is an exception to the general rule of non-inheritance of cancer, and most cancers are not inherited. However, some cancers, such as breast cancer, may have a hereditary component for development of the disease (susceptibility). In general, all cancers, including breast cancer, have a genetic origin, i.e., they occur due to the abnormal functioning of genes (4, 6, 7). Cancer occurs when the genes of normal cells mutate. There are about 35,000 genes in each human cell. Mutation in a single gene does not cause cancer; further, it occurs when mutations occur in key genes that are categorized into three groups, i.e., 1) proto-oncogenes, 2) tumor suppressor genes, and 3) DNA repair genes (8). Growth and proliferation of the cells are controlled through the cell cycle. Indeed, the cell cycle is a freeway into which the cells enter in order to divide and produce daughter cells. (9). There are signals that control the time of entrance of cells into the cell cycle, the duration of their stay in the cycle, and the continuation of division. There also are other signals that control cells’ exit from the cell cycle. If any of these controlling signals are impaired, the cells lose control of their division. The specific genes that control the normal functioning of the cell cycle are listed below:

1) Proto-oncogenes and oncogenes:

Proto-oncogenes are normal genes that give the “move” command during the control of cell division. Changes in the genetic material of a proto-oncogene turn it to an oncogene that makes cells divide and replicate repeatedly and out of control. Oncogenes cause the cells to stay in the cell cycle and to continue repeated division. The most widely-recognized proto-oncogenes are human epidermal growth factor receptor-2 (HER-2), c-myc, and Cyclin D; they will be discussed further in the following sections of this article.

2) Tumor suppressor genes:

Other genes exist in the cells that give the “stop” command. If tumor suppressor genes undergo mutations, the cell will lose the ability to stop. Stopping is essential for cells to discover and repair any DNA damage. Otherwise, faulty DNA is duplicated, and two daughter cells are produced, and this phenomenon becomes a permanent mutation that will continue the production of new cells. P53 is a typical tumor suppressor gene, and the most common genetic variations are found in breast cancer cells (10). In a normal cell with damaged DNA, the P53 gene gives the stop command to stop proliferation and correct damage, and, if the cell cannot repair the damage, the gene gives the apoptosis command. If the P53 gene is damaged and its function is impaired, cells with damaged DNA will continue to proliferate and will produce more abnormal cells (10, 11). The P53 gene has a central role in controlling the cells’ cycles. If the cell cannot repair its DNA damage, P53 gives the suicide or apoptosis command to prevent the passage of mutated genes into the daughter cells. Mutation of P53 occurs in about 1% of sporadic breast cancers. Inherited mutant P53 causes a syndrome called Fraumeni-Li, which predisposes patients to have cancers, including breast cancer, at an early age (12, 13). Hereditary breast cancers include only 5-10% of the cases of the disease, because inheriting a mutated tumor suppressor gene is a rare event, and it does not always lead to cancer (14). A study published in 1993 introduced a gene on chromosome 17 that was associated with multiple cases of breast and ovarian cancer in some families, suggesting a genetic factor in these cancers (15). Further research in 1994 led to the

discovery of the BRCA1 gene (16), and a similar gene on chromosome 13 was discovered the next year and was named BRCA2, which increases susceptibility to breast cancer (17). MutaBRCA1 and BRCA2 mutations are found in 40 and 30% of familial breast cancer, respectively. The cumulative risks of breast cancer in carriers of BRCA1 and BRCA2 mutations are 50 and 70%, respectively (18-20). Mutations in BRCA2 occur more often than in BRCA1 in men's breast cancer. Carriers of the BRCA1 mutation will have more serious outcomes than carriers of BRCA2, even if the cancer is detected in its early stages; breast cancer in carriers of BRCA1 often is associated with axillary lymph node involvement (N+) in the early stages, as well as lack of estrogen receptor (ER-negative) and progesterone receptor (PR) (21).

2.3. Relation of histopathological features with the biology of breast cancer

Histopathological features of breast cancer, such as the size of the tumor, degree of differentiation, and the status of axillary lymph nodes reflect the biological characteristics of breast cancer and the duration of the disease. Among the histopathological characteristics, the size of the tumor and the status of the lymph nodes are affected by the duration of the disease in addition to the environmental infrastructure, but the grade of the tumor is determined only by biological properties (22, 23). Perhaps one of the purposes of classifying invasive breast cancer is to establish a relationship between the tumor's biology and its prognosis. For example, medullary carcinoma presenting with cytokeratins is more likely positive P53, ER-negative, and HER-2 positive, strongly suggesting that the person also carries mutations of the BRCA1 gene (24). Genetic differences also have been reported in the most malignant type of breast cancer, i.e., inflammatory breast cancer. It seems that the different biological behavior of this type of breast cancer arises from the over-expression of certain types of genes, resulting in more aggressive characteristics and weaker prognosis (25). A recent study showed the over-expression of a series of chemokine receptors, called CXCR4 and CCR7, which are introduced as biomarkers related to the metastasis strength of breast cancer. Of course, the same property can apply to the treatment of cancer, because inhibition of these receptors may help to improve patients' outcomes (26). One of the histological characteristics of breast cancer is the role of myoepithelial cells in the prognosis of breast cancer that can be called "natural tumor suppressors." These cells are, in fact, the regulators of the transition stage between in situ and invasive cancer. In addition, hormonal interactions between myoepithelial cells and ductal epithelial cells in the breast have an important role in the regulation of the advancement of the cell cycle and the migration and invasion of cells. Therefore, more attention should be directed to the characteristics and functions of these cells in order to pave the way for more effective measures in the treatment of breast cancer (27, 28).

2.4. Relationship between age and the biology of breast cancer

Age is the most important demographic risk factor for most human malignancies, including breast cancer. Scientists believe that the overall risk of cancer is higher in old age due to the exposure to carcinogens over a longer period of time and the decreasing power of the immune system with age (29, 30). Studies have shown that the biology of breast cancer and its clinical behavior obviously are affected by age and the time of diagnosis. Thus, breast cancer that occurred before the age of 40 is clinically more aggressive and has a higher possibility of metastasis and lower survival of older patients (31). Some biological markers indicating their genetic instability, such as nuclear differentiation, aneuploidy, P53, and those that show the rate of growth of the tumor growth, i.e., ki-67 and HER-2, have a significant negative correlation with age at the time then breast cancer was diagnosed, i.e., growth indicators in patients older than 40 years show an obvious reduction (32). Since some of these biomarkers can predict response to anti-cancer therapies, changes in these factors later in life will change anti-cancer therapies based on age (33). For example, a significant correlation exists between ER-positive and the increasing age of breast-cancer patients. For this reason, patients' responses to other anti-estrogenic therapies are the main pillars of breast cancer treatment in older age (34). According to some studies, other prognosis-determining factors are different for women under 45 and for older women, so that breast cancer manifests with larger size tumors, higher grade, more involvement of lymph nodes, and a shorter period of disease-free survival (DFS) among younger women (32, 35, 36).

2.5. The role of Race

The biology of breast cancer varies between different ethnic groups. Although the study of the etiology of ethnic differences in breast cancer is a complex task, the difference between the various races can be considered in two categories, i.e., 1) socio-economic reasons, such as access to health care, quality of care, and social support, and 2) personal reasons, such as reproductive history, use of exogenous hormones, diet, exercise, and anxiety, all of which affect the cells. Increased risk of breast cancer in some races is related to the contrast between the two sets of reasons (37). Breast cancer occurs at younger ages in African-American women than in European-American women. Breast cancer in the black race usually is associated biologically with a high differentiation grade and

negative estrogen and progesterone receptors (38, 39). However, black women in America are at lower risk for breast cancer than Caucasian women, but they have a poorer prognosis when they do have breast cancer (40).

2.6. Prognostic factors

The course and clinical outcome of breast cancer can be predicted by using prognostic factors, the most common of which are PR, ER, Ki-67, and HER-2. There also are other factors that help predict the prognosis, such as UPA, Cyclin E, Cyclin D1, and Cathepsin D, but they are not measured routinely. Predictive factors refer to the response of the tumor to anti-cancer treatments, the most widely recognized of which are ER and HER-2 (41, 42).

2.6.1. ER:

Estrogen has an important role in the development and progression of breast cancer. This effect is reflected in the three most definite risk factors of breast cancer, which are associated with changes in estrogen secretion. These risk factors include age, age at first menstruation (menarche), age at menopause, and age at first full-term pregnancy. About 60% of breast cancers are ER-positive with slower growth rate, clear differentiation and longer DFS (43). Exposure to estrogen is important in determining the risk of breast cancer. The adipose tissue is the main source of estrogen in the body, therefore, early menarche, late menopause, and especially obesity after menopause are risk factors for breast cancer (44, 45). Some studies have shown that adipokines, such as leptin and adiponectin, which are secreted from adipose tissue by activating estrogen receptors and increasing cell growth through angiogenesis, are involved in the biology of breast cancer in obese people. These factors have been considered in terms of their inhibiting application for treatment of breast cancer (46). Since estrogen stimulates cell division, the chances of error during DNA division increase, thus, the possibility of mutation is high (47, 48). In addition, estrogen forces the target cells to build ERs on their surfaces. This is performed for the estrogen's own receptors and for PRs, i.e., estrogen enhances the effects of progesterone on cells by forcing the target tissue to build PRs (49, 50). Progesterone affects the cell cycle, such as estrogen, and it inhibits PRs, both of which change the evolution of breast cancer. It should be noted that the interaction of these two hormones in breast cancer is of particular importance, so that when a tumor is ER-positive and PR-negative, only one third of anti-estrogen therapies (tamoxifen) against breast cancer will respond. Also, a reverse relationship exists between ER and growth factor receptors. In order to promote hormonal responses in some ER-negative cases, which are resistant to the responses, this relationship can be used to reconstitute the appearance of ERs on the surface of breast cancer cells by blocking the receptors of growth factors (51, 52). There are two types of ER, i.e., α and β . However, breast cancer patients with increasing β -type ER have a better outcome and a longer DFS (53). PRs also consist also of α and β types. Just like ERs, PRs are considered as a prognostic factor in breast cancer, so that, if the density of α -type PR receptors is higher than β -type receptors in a tumor, it will relapse faster and be more invasive. The ratio of PR- α to PR- β is involved in the biology of breast cancer and in the response of ER-positive tumors, meaning that the response of ER-positive and PR-negative tumors to anti-estrogenic treatment is lower than ER-positive and PR-positive tumors (54). One of the other hormones involved in breast carcinogenesis is prolactin, which induces mitosis, stimulates proliferation, and stops apoptosis in breast cancer cells. Prolactin carcinogenic effect is applied through change in the biological structure of breast tissue (55).

2.6.2. HER-2:

The proto-oncogenes HER-2 and C-erbB2 are among the most interesting and controversial biomarkers, either as a prognosis factor or a predictive factor of breast cancer. This receptor binds to the cell growth factors, induces tyrosine kinase activity, and promotes growth and proliferation of cells through the G1-S phase. If this proto-oncogene undergoes mutation and amplification for any reason, it turns to HER-2 oncogene, which results in uncontrollable growth and repeated division of cells. The over-activation of Her-2 occurs in about 20-30% of breast cancer cases. Her-2-positive is an estimator of growth rate, higher invasiveness, greater metastasis power, and as a result, shorter DFS. This means that HER-2 is a poor prognostic factor for patients with breast cancer. As antibodies against HER-2, Trastuzumab and Herceptin gradually are becoming common and effective treatments of HER-2 positive metastatic breast cancer; this shows the role of HER-2 as a predictive factor of response to treatment of breast cancer. It also interacts with other factors that change the biologic infrastructures of these patients and alter the therapeutic response to various chemotherapy drugs (56, 57).

2.6.3. Insulin-like growth factors (IGFs):

The family of IGFs, including IGF-I and IGF-II, are involved in both normal growth of the breast and the development of breast cancer. The IGF family, particularly IGF-I, has an important role in promoting cell division, metastasis, and inhibition of apoptosis in breast cancer cells (58, 59). Some studies have shown a significant relationship between IGF-I receptor (IGF-IR) with Ers, particularly ER- α . Understanding the interaction of these two factors that alter the biological behavior of breast cancer can explain the cause of some drug resistance to anti-estrogen treatment (60).

2.7. New biomarkers

Even with the many advances in the field of biotechnology, new biomarkers increasingly are being introduced. The application of some of them is controversial; here, we discuss some of the less-known indicators that have important roles.

2.7.1. Vascular endothelial growth factor (VEGF):

VEGFs have the role in angiogenesis of providing nutrients and oxygen needed for growth. Among this family, VEGF has an utmost importance, because, in addition to its role in angiogenesis, it seems that estrogen and progesterone induce their angiogenesis effects through VEGF; this relationship can be used for devising novel treatments for breast cancer, so that if VEGF and its effect on angiogenesis can be inhibited, some drug resistances to anti-estrogen treatment of breast cancer may be overcome, and even new methods of chemical prevention of breast cancer can be introduced to inhibit angiogenesis (21, 61).

2.7.2. CD24:

CD24, a cell surface protein, has a significant relationship with high grade nuclear. It is a prognostic factor and can predict higher aggressiveness of biological behavior, shorter life expectancy, and higher metastatic power for breast cancer patients (62).

2.7.3. P21:

P21 is a unique marker and the major mediator through which P53 gives the growth arrest command. In addition, the P21 gene singly can lead to apoptosis or cell death. Polymorphism in this gene causes a change in behavior of the tumor and increases its growth rate. If the results of this research are confirmed by later studies, a new perspective will be created about breast cancer, which moves quickly to recurrence (63).

2.7.4. Stanniocalcin (STC):

Stanniocalcin has is, in fact, a survival factor for cells and takes cancer into a state of dormancy, so that the protein level is higher when the breast cancer relapses after a long time of onset (late relapse) compared to cases with early relapse. If this observation is confirmed in future research, this protein can be used to postpone the progression of invasive breast cancer and to slow its rate of progression (64).

2.7.5. Ki-67:

Ki-67 is a prognostic factor in breast cancer, and its high levels indicate a poor prognosis, invasiveness of the tumor, and shorter survival of the patients. As a pharmacodynamics marker, Ki-67 indicates the efficacy of treatment after a period of anti-cancer treatment, especially before surgery, so that, if the antigen appears at high levels after two weeks of treatment, the DFS will be lower for patients. However, since Ki-67 is a marker of mitosis and shows the growth and proliferation of tumors, tumors with higher levels of Ki-67 respond better to chemotherapeutic agents that have a better effect on cells that have a high growth rate. Therefore, knowing the status of Ki-67 will have a significant impact on treatment decisions (65, 66).

2.8. Biologic relationship of breast cancer with its metastatic properties

Cancer cells are separated from the site of the tumor and reach secondary tissues. However, the cells are capable of replacement in these tissues and grow and proliferate only if they have special abilities, such as angiogenesis. The mechanism of metastasis is complex, and its sequence varies according to different target tissues (67). For example, bone is involved in up to 75% of breast cancer patients with metastatic disease. The breast cancer cells secrete many cytokines that stimulate osteoclastic activity in bone. Increased activity of osteoclasts produces a wide range of lymphokines and growth factors that secondarily affect tumor cells and stimulate their proliferation. Therefore, a network of cytokines is formed in bone that disrupts the balance between bone production and resorption, leading to the gradual expansion of the tumor in bone and increased bone resorption through stimulating osteoclasts, which results in reduced strength of the bone, fractures, and pain. Better understanding of the biology of metastasis provides a new window for better management and proper treatment of metastatic breast cancer. For instance, new approaches are available that inhibit inducing signals of osteoclasts or prevent the invasion and adhesion of tumor cells at secondary sites of metastasis (68, 69). By using some biological characteristics in breast cancer patients, it is predictable that a patient is more likely to develop metastatic disease at an earlier time from the diagnosis of breast cancer (26).

3. Conclusions

With the advancement of science, attention has been directed toward the function of organs and their functional interactions, and surgical treatment has been promoted from anatomy to physiology, resulting in a significant improvement in the treatment of patients. However, despite all of these efforts, the incidence and mortality rate of patients due to various cancers, including breast cancer, is still high, and despite the widespread use of different treatment approaches, such as chemotherapy and radiation therapy, some people still die due to cancer. In the past

two decades, we have tried to look beyond the various issues relative to cancer, i.e., the molecular biology infrastructures of this life-threatening and complex disease, and it seems that the definitive treatment of cancer is to put the frontline battle on the surfaces of the cells, not on the affected organs. Given environmental pollution and the stress that people incur today, knowing the impact of pathogens and factors that are detrimental to the health of normal cells and vital molecules in people's bodies can minimize the carcinogenic effects of these factors. Many advances have been made in this regard, all of which help prevent the development and progression of cancers, rather than treating individual incidents as they occur. The objective of scientists is to determine new, more effective ways of preventing cancer and inhibiting its progression. The approaches being used to achieve that objective include establishing the relationships between the infrastructures of cancer biology and clinical manifestations in order to inhibit the formation of cancer and possibly introduce less dangerous and better treatments to resolve this dilemma that faces all of human society.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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