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Breast Cancer Classification: A Review

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ABSTRACT

Breast cancer becomes one of the most serious health issues among women and leading cause of death among them. Breast cancer continues to be prevalent and growing malignancy among women. While since last two decades, breast cancer research has led to a remarkable progress in understanding the breast malignancies and thus resulting in treatments of less toxicity and more efficiency. Breast cancer is a diverse disease having different molecular and histological features; and different groups of breast cancer response differently to different treatment therapies. Besides stage of the disease, the rate of prognosis and survival also depends on molecular subtype. So, for the proper treatment of breast cancer, it is important to know the complete classification of breast cancer and their response to different treatment strategies. About 25% of histological type of breast cancer is invasive breast cancer. Based on morphology, behavior and clinical presentation invasive breast cancer show broad range of tumor types. Molecular classification generally based on gene expression of mRNA. Molecular subtype provide new provides for the treatment strategies for breast cancer treatment.

Key Words: breast cancer, classification, histological subtype, estrogen receptor, molecular subtype

INTRODUCTION

Carcinogenesis might occur in every cell, tissue, and organ, leading to the pathological alterations which results in a various kind of cancers. The major mechanisms that help its progression include avoidance of apoptosis, acceleration of rate of cell division, enhanced angiogenesis, resistance to anti-growth signals and induction of own growth signals; and capacity to metastasized. Carcinogenesis is a process which is stimulated by multiple factors but the primary factors are- predispositions of genetic materials and environmental causes [1].

Cancer cells are the normal cells that behaving abnormally that are beyond the paradigm of life and death. Like an organism that evolves through a process of mutation and natural selection, cancer cells also progress from normal cell through selective transformation to malignancy [2]. Breast cancer is the most common type of malignancy among women, the number one cause of mortality by cancer, and one of the leading causes of morbidity and mortality for women worldwide [3]. Breast cancer is currently one of the most frequently diagnosed cancers and 5th cause of death related to cancer which estimated a number of 2.3 million cases worldwide according to the GLOBOCAN 2020 data [4].

The current edition reports of the International Agency for Research on Cancer (IARC), an increase of 66% global number of cancer deaths since 1960. Currently, breast cancer is the second most common cancer after lung cancer worldwide. Regarding possible minimization of breast cancer incidence, several procedures such as prevention behaviors as well as screening programs are crucial and the implementation of early treatment. Currently, the Breast Health Global Initiative (BHGI) is responsible for preparation of proper guidelines and approaches to provide sufficient breast cancer control worldwide [4]. In this review

article, we aim at providing information regarding breast cancer.

1. Breast Cancer

Cancer is usually named after the body part in which it originated; thus, breast cancer refers the abnormal growth and proliferation of cells that originate in the breast tissue [5]. Generally, breast is composed of two main types of tissue: glandular tissues and stromal tissues. Glandular tissues have glands (lobules) which produce milk; while stromal tissues are fatty and fibrous connective tissues of the breast. The breast is also made up of lymphatic tissue, immune system tissue which removes cellular fluids and waste [6]. There are several types of tumors that may develop within different areas of the breast. Most of the tumors are benign i.e., non-cancerous. For example, Fibrocystic change in which cysts is develop in women; fibrosis i.e., formation of scar-like connective tissue; lumpiness, and areas of thickening, tenderness or breast pain [7]. Most of the breast cancers begin in the cells that line the ducts (i.e., ductal cancers). Some begins in the cells that line the lobules (lobular cancers) and some starts in the other tissue [8].

The main risk factor for breast cancer is age. Other significant factors are low rates of breastfeeding and low parity, which explains why breast cancer is the classical cancer of nations of high-resource and is, continues to increase in almost all countries [9]. Breast cancer is a tragedy for the individual who are affected. When detected at early stages, it is highly curable disease and an inevitably mortal disease when discovered too late. Access to high-quality care, early diagnosis, and proper surgical and medical treatment can mean the difference between life and death [10].

2. Classification of Breast Cancer

Breast Cancer is a disease which is heterogeneous in nature, having different histological features and molecular behavior [11, 12]. Earlier, breast cancer treatments were done by characterization of tumor's histological features, tumor's clinical stage and biomarker profiling. But from the last few decades, it can be now subgroup by molecular profiling, growth factor expression and hormone indicators etc. The diversity of breast cancer was known to histopathologist and divides the disease into subtypes [12, 13, 14, 15]. But the multiple molecular subtypes of breast cancer revealed after researcher published high-throughput micro-array based class discovery studies of breast cancer [16, 17, 18, 19].

Histological classification

The pattern of growth of the tumors refers to as histological subtype. The pathologist has been fascinated by adenocarcinomas in breast and they have identified distinct cytological patterns and morphological features that are associated with specific clinical outcomes or symptoms. This pattern of classification is called as histological types. The World Health Organization (WHO) recognizes about 18 distinct histological types of breast cancer [20]. WHO classified breast cancer primarily into two categories- Carcinomas and Sarcomas [21]. Breast cancer classified under carcinomas, if it originates from epithelial cell-based components i.e., terminal ducts that are responsible for milk and lobules. Then further spreads to the Mammary Stem Cells (MSC) [22, 23]. But inception of sarcoma takes place from connective tissues, which support the ducts and the lobules of the breast such as blood vessels and myofibroblast.

Breast carcinoma heterogeneity sub-divided into invasive and in-situ carcinomas. Study demonstrated that most of invasive breast cancer and their in-situ precursors originate or localized from terminal lobular-duct unit [24, 25]. If not intercepted, the invasive carcinomas could penetrate the neighboring tissues and metastasize to other body tissue and organs. Based on the morphology, invasive carcinomas are further classified into No Special Type (NST) or formal Not Otherwise Specified (NOS) type or

Morphologically Identifiable types. No special type (NST) which was formally known as Invasive Ductal Carcinoma (IDC), is the most frequently occurring type of subgroup (40-80% of all breast cancer) [26]. About 25% of invasive breast cancers are recategorised into specific subtypes such as Invasive Lobular Carcinoma (ILC), Mucinous A, Mucinous B, Neuroendocrine and Tubular as they presents some specific cytological features and growth patterns [27]. In Invasive Lobular Carcinoma (ILC), the tumor growth involves by penetration of single cells or cells segregated in sheets with some genetic and molecular aberration which differ from Invasive Ductal Carcinoma (IDC) [28].

Recently, two new entities of rare subtypes of invasive carcinomas have been identified and listed in World Health Organization (WHO) list of Breast cancer's classification 2019 :- Mucinous cystadenocarcinoma of No Special Type (NST) and Tall Cell Carcinoma with Reverse Polarity (TCCRP) [29]. They both possess same tall columnar cell morphology, but their core components are different. TCCRP shows some features similar to salivary gland-type tumor and papillary thyroid carcinoma. However, Mucinous cystadenocarcinoma of NST contains abundance of luminal mucin and they possess cytomorphology of ovarian mucinous cystadenocarcinoma and pancreatobiliary adenocarcinoma. They exhibit low malignant potential, although they are categorized to invasive carcinomas [29]. The grading system of invasive breast cancer heterogeneity analyzes the tubular structures, percentage of tumor in glands, the mitotic rate and degree of nuclear polymorphism or nodes. But the stages of breast cancer differ from its grading system. Grading system allows simplification of breast cancer staging by exhibiting breast cancer's spread; however, breast cancer staging represents the tumor's appearance. But in Nottingham Prognosis Index (NPI), which is a clinical tool determining the prognosis during breast cancer surgery, both grading and staging system incorporated [30].

Molecular Classification

Based on gene expression levels of mRNA, invasive breast cancer can also be categorized into molecular subclasses called as molecular classification. Gradually, various molecular biomarkers have been recognized which help in sub typing breast cancer based on cytogenic pathways [31], genomic instability [32], gene expression levels [16, 33] etc. Now, the high-throughput screening on biomarkers technology of modern molecular pathology provides more explanation for breast cancer heterogeneity. It delivers various biomarkers such as- Progesterone Receptors (PR), Estrogen Receptors (ER) and Human Epidermal Growth-factor Receptor 2 (HER2) that categorized breast cancer into several molecular subtypes. In 2000, Perou et al., identified 4 molecular subtypes from microarray gene expression data which was done by a experiment on a sample of 38 breast cancers, that 4 subtypes are- Luminal, HER2-enriched, Triple-negative or Basal-like and Normal Breast-like [16]. Again, further studies divide the luminal breast cancer into subgroups i.e., Luminal A and B [17, 34]. Additionally, another 5th subtype- Claudin-low breast cancer was discovered in 2007 in an experiment where the human and murine mammary tumors were analyzed together [35]. Classification of breast cancer will help in accelerating the prognosis and selection of treatment.

Luminal Breast Cancer

About 70% of all cases of breast cancers in Western populations are comprise of Luminal breast cancer which are Estrogen Receptor (ER) - positive tumors [36]. Commonly Luminal-like breast cancers falls under invasive breast cancer (IBC) of no special subgroup, but sometimes may be divided into invasive cribriform, mucinous, invasive lobular, tubular, and invasive micropapillary carcinomas [12, 37]. Luminal-like tumors are divided into-

Luminal A and Luminal B subgroups based on different clinical outcomes of two biological pathways:- Luminal-regulated pathways and proliferation related pathways.

The main characteristics features of Luminal A tumors are presence estrogen-receptor (ER) and/or progesterone-receptor (PR) and absence of HER2. In this type the expression of the luminal epithelium lining the mammary duct due to the activation of the genes by the estrogen-receptor (ER) transcription factors [11, 38] and this type also shows low expression of cell proliferating genes [39]. In contrast to Luminal A type, Luminal B tumors may be progesterone-receptor (PR) negative and HER2 positive but estrogen-receptor (ER) positive. This type shows high expression of cell-proliferation related genes, example, MK167 and AURKA [40, 41] and shows lower expression of luminal epithelium related genes or proteins such as FOXA1 [38, 42] and progesterone-receptor (PR) [38]. Generally, luminal A tumors are of low histological grade and lower proliferating rate while luminal B tumors are of higher histological grade and shows higher proliferating rates and worse prognosis than the tumors of luminal A [11, 16, 17, 43, 44].

Estrogen-receptor (ER) is the earliest and most commonly used biomarkers for breast cancer [45, 46]. Studies suggest that approximately 80% of all breast cancers are Estrogen-receptor positive (ER^+). Originally the luminal tumors of ER-positive were described as those that express patterns of growth that similar to 'normal luminal epithelial cells' of the mammary gland associated with an active pathway of ER pathway, and low molecular weight cytokeratins 8/18 [11, 16, 17, 18, 44]. According to stem-cell cancer model, from the most primitive stem cells, the ER negative breast cancer ascends, where the pattern of mutations makes it difficult to differentiate into ER-positive (ER^+) cells [47]. On approximately 500 genes' intrinsic factors, a broader gene expression profiling (GEP) differentiate ER positive breast cancer into subtypes- luminal A and B [18]. According to a study, the expression of ER^+ genes and luminal genes are high in luminal-A subtype than in luminal B subtype. Similarly, prognosis and overall survival of luminal-A is greater than luminal-B subtype. Likewise luminal-B subtype also expresses low response to endocrine therapy which corroborates with the low ER/PR-expression [48, 49, 50], but shows high expression of Ki-67 [51] and an over expression of HER2 which is unusual [52].

Progesterone-receptor (PR) is an ER-regulated gene which plays an important role for the lobuloalveolar development of mammary glands [53]. Ductal outgrowth of the mammary gland is induced by estrogen and receptors of estrogen, while progesterone and progesterone-receptor (PR) regulates morphogenesis of ducts of mammary gland [54]. The side-branching of mammary gland is stimulated by localized PR cluster by inducing Insulin-like Growth Factor 1 (IGF-1) [55]. Progesterone-receptor negative (PR^-) breast cancer is more aggressive than progesterone-receptor positive (PR^+) breast cancer as PR acts as a negative indicator of tumor aggression [56].

ER and PR receptors have four subgroups under Luminal A and B subtypes: ER^+/PR^+, ER^+/PR^-, ER^-/PR^- and ER^-/PR^+. In a study of the subgroups, it was found that double positive subgroup (ER^+/PR^+) shows more receptiveness towards the treatment of endocrine such as tamoxifen as compared to the subgroups where the expression of PR lacks in the ER^+ subset (ER^+/PR^-) [57, 58]. Double negative subgroup (ER^-/PR^-) possesses a greater relapse rate, and worst prognosis and overall survival rate. The patients with ER^-/PR^- breast cancer are appropriate for chemotherapy if unresponsive for endocrine treatment therapy [48].

HER2-Enriched Breast Cancer

About 10-15% of breast cancer groups make up HER2-enriched group. HER2 is a tyrosine kinase receptor which is a transmembrane protein present on the epithelial cells of normal mammary gland. However, the over expression of the HER2 receptor causes genetic instability and excessive proliferation, which is categorized as a HER2 positive ($HER2^+$), a breast cancer subtype [59]. The unusual over expression of HER2 also shows insensitivity to endocrine therapy and this resistance power towards endocrine therapies is contributed by intimate crosslink between HER2 and ER/PR signaling pathways [60, 57]. This crosslink excludes the deletion of expression of ER/PR through Selective ER Modulators (SERM) [61]. This subtype does not express luminal and basal gene and protein clusters; rather it expresses genes and proteins related to proliferation [41, 42] studies show evidence of mutagenesis in the HER2-enriched subtype, which is mediated by APOBEC3B. APOBEC3B is APOBEC cytidine deaminases' subclass, which is a source of mutation clusters and induces cytosine mutation biases [62]. Preclinical and clinical studies of HER2 breast cancer patient show some promising outcomes. When chemotherapy was merged with anti-HER2 monoclonal antibodies (trastuzumab and pertuzumab) [63] and inhibitor of tyrosine kinase (lapatinib and neratinib) based therapies [64].

Triple-Negative/Basal-Like Breast Cancer

About 20% of the total breast cancer's constituted Basal-like or Triple-Negative Breast Cancer (TNBC). TNBC are very heterogeneous of all breast cancer subtypes and tends to be biologically extremely aggressive [65]. The characteristics of the heterogeneous group of TNBC are, lack of three biomarkers such as HER2, progesterone-receptor (PR), and estrogen-receptor (ER), and due to these characters, this type of cancer leads to a cancer of high stage nuclear grade with extreme mitotic activity and low rate of prognosis. TNBC is usually common among American and African; and women younger than the age of 40 years [66]. Due to lack of hormones like, estrogen and progesterone, this breast cancer type shows response to endocrine and other treatment therapies. The histological features found in TNBC are: ductal carcinoma infiltrates; metaplastic cancers, which show differentiation of spindle or squamous cell; rare type of cancers such as Adenoid cystic carcinoma (AdCC); may also present medullary-like cancer which show lymphocytic infiltration [67].

Though the term basal-like and TNBC have been used to designate the same type of cancer interchangeably, but not all cancer of TNBC is basal-like type. Based on the study of gene expression profiling and ontology of 587 patients by Lehmann and colleagues, subdivided TNBC into six subtypes: basal-like (BL1 and BL2), mesenchymal stem-like (MSL), mesenchymal (M), immuno-modulatory (IM) and luminal androgen receptor (LER) [68]. But recent analysis of gene expression profiling of long non-coding RNAs (lncRNAs) and upregulated mRNAs, joined the two subsets-mesenchymal stem-like (MSL) and immunomodulatory (IM) into mesenchymal; and BL1/ BL2 into basal-like to give a classification of four subtypes [69]. In IM subtype of TNBC, generally genes and cells of immune system are associated as biomarkers, such as chemokines, cytokines signaling components and antigen-presenting cells, etc [69].

The mesenchymal-like subtype of TNBC cells shows properties of stem cell and genes expresses signature of epithelial-mesenchymal transition (EMT). Due to its high expression of motility-related genes, is associated with pathways of cell differentiation [68] and it is also known as metastatic breast cancer [68]. In mesenchymal-like TNBC, involves signaling pathways related to cell migration, example, Wnt pathways, extracellular matrix-receptor interactions pathways,

TGFβ signaling, biomarker of breast stem cell, ALDH1A1, and genes of stem cells etc [68]. The patients with mesenchymal-like TNBC may be benefited by chemotherapeutic drugs targeting epithelial-mesenchymal transition (EMT), as this type of breast cancer is connected with growth factors [70].

Basal-like Subtype of TNBC, the neoplastic cells of the tumors express the genes generally found in normal basal or myoepithelial cells mammary gland, as well as cytokeratins of high molecular weight [71]. The biomarkers express by the Basal-like breast cancer are: genes related to DNA replication and repair; and cell-cycle checkpoints [68]. Burstein and colleagues studied and reclassified TNBC subtypes. They highlight that Basal-like subtypes into two types i.e., BL-immune activated (BLIA) subtype which is upregulated by immune response gene and BL-immune suppressive (BLIS) subtype which is downregulated by immune regulating genes [72]. The ascending order of TNBC in disease-free survival recorded from the index of prognosis found- BLIA > M > LAR > BLIS [72]. The reason behind this order could be due to presence of tumor-infiltrating lymphocytes (TILs) in BLIA subtypes. In 2014, TILs are recommended as a one of the significant parameters or stratification factor to evaluate breast cancer heterogeneity by the International TILs group [73].

Normal Breast-Like

About 5-10% of all breast carcinomas, constitute normal breast-like tumors. The characteristics of this type of breast cancer are so poor and so have been classified into a subtype with normal breast sample and fibroadenomas. These kinds of breast cancers generally do not respond to neoadjuvant chemotherapy and express genes that are characteristics of genes usually an intermediate prognosis between basal-like and luminal cancers. This breast cancer subtypes does not express HER2, ER and PR. The clinical significance of this subtype is still unknown and only few studies are there about this subtype of breast cancer. Some researchers doubt the existence of this subtypes and thought that this kind of breast cancer could be technical artifact which could be form during the microarrays due to high contamination with normal tissue [74]. In fact, to support this hypothesis no cases of normal breast-like subtypes were found, when samples of a series of neoplastic cells were isolated by the process of microdissection.

Claudin-Low Breast Cancer

About 7-14% of all invasive breast cancers are Claudin-Low (CL) breast cancer tumors [75]. Claudin-low (CL) breast cancers are ER, PR and HER2 negative; and prognosis is poor [80]. The rate of survival of claudin-low tumors is almost same with other poor prognosis subtypes such as, Basal-like, Luminal B, HER2-enriched etc. other characteristics of CL subtypes are low expression genes which involve in cell-cell adhesion such as, occluding, E-cadherin and claudins 3, 4 & 7. While the tumors of this subtypes show high expression of genes including, stem-like gene patterns and epithelial-mesenchymal transition (EMT) gene; and stomal and immune cell infiltration seen in CL tumors [75]. Genomically, tumors of CL are stable due to preventive effect of a transcription factor ZEB1 and less differentiated state of tumors [76].

Traditional classification of breast cancer includes analysis of gene expression profiling (GEP), evaluation of immune histocompatibility hormone and examination of pathological features in lab check-ups. But in breast cancer numerous factors used as biomarkers. So, to acquire the knowledge on pathological features in breast cancer, analysis of data extracted from various fields such as proteomics, genomics, epigenetics, transcriptomics etc is essential to know the various pathways and biomarkers involved in tumors.

CONCLUSION

Now days, there are so many treatment approaches of breast cancer such as surgery, radiation therapy, chemotherapy, recently nanotechnology and genetherapy etc. Advances in breast cancer diagnosis, screening and treatment decreased the rate of death. But the breast cancer mortality rate is still higher in less developed countries. The incidence of breast cancer is affected by various factors, of which environmental factors, genetic factors and lifestyle are important among them. Some factors can reduce the risk of the disease such as lactation, parities and exercise etc. Since, over the past few decades, the mortality and morbidity rate of breast cancer have increased significantly, thus there is an urgent need of effective prevention strategies to provide reduced risk. The modification of risk factors might play a crucial role in reduction of breast malignancies. Manual screening such as sonography and mammography test enables early diagnosis of breast cancer. Breast cancer is preventable if detected in early stage. Taking chemoprevention and reducing risk factors are two main measures of breast cancer prevention. But we have to create public awareness about breast cancer and associated risk factors. Improvement in sequencing technology, sequencing of individual genome may be an important evaluation method for risk of breast cancer. Better curative medication with less toxic effects and reducing mortality risk need to be developed in future.

Conflict of Interest: None

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