Breast cancer biomarkers / An Article Review

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ABSTRACT

Background: Cancer is without a doubt a major global issue, because it is the second most common reason of mortality universal. Due to greater exposure to danger factors and longer life expectancies, the prevalence of many malignancies has grown in both industrialized and developing nations. Among all cancers, the breast malignant tumor is one of the most prevalent.

Objective: The aim of the article is to study the most important and necessary biomarkers to diagnose infected women with breast cancer or to predict before the occurrence of injury through genetic study.

Methods: According to the preferred reporting items for systematic reviews and meta-analyses, this meta-analysis was carried out.

Results: Cancer patients' bodies or tumors produce biological molecules known as cancer biomarkers. The identification of tumor alterations is aided by biomarker testing. Biomarkers could be metabolomic profiles, tumor-specific DNA, RNA, or proteins. Examples of testing include DNA or RNA checks to check for gene fusions, tests to measure RNA or protein levels, and genomic testing, which looks at the DNA sequence.
Finding tumor markers is a helpful clinical management for cancer patients, aiding in diagnosis, staging, assessing therapy response, spotting repetition and metastasis, and creating innovative approaches to treatment. This review seeks to address the primary tumor indicators in breast carcinogenesis in this setting. Breast cancer patients frequently display the tumor markers (CA 15.3), (CA 27.29) , (CEA), p53 proteins, and Cyclin D1, they are essential for diagnosis, assessing the effectiveness of therapy, in addition, the most well-known hereditary breast cancer genes as well as hormone receptors, the HER-2 oncogene, the Ki-67 will be discussed.

Conclusions: we conclude from this article that the most helpful blood tumor indicators in patients with breast cancer are CEA and Cancer Antigen (CA 15.3), (CA 27.29).

Keywords:

Introduction

An abnormal growth that has grown from breast cells is described to as "breast cancer." Breast cancer typically begins in the cells of the milk-producing lobules or the ducts, the passageways that carry milk from the lobules to the nipple. Less frequently, Breast cancer can develop from stromal tissues, which comprise the fatty and fibrous connective tissues of the breast. [4, 54]

The most prevalent kind of cancer among women worldwide is breast cancer. It influence more than one and a half million people each year and 450,000 fatalities annually in the globe and is the fundamental reason of death for cancer-stricken female . [55]

A significant part of breast cancer is also played by genetic and familial factors. A genetic component is present in more than 10% of breast cancer patients in developed nations. Overweight, inadequate exercise, and excessive alcohol consumption , ionizing radiation,are all risk factors for malignant breast tumors, also hormone treatment during menopause, starting menstruation early in life, delaying or not having children, getting older, and having breast cancer in the past or in the family. [32, 54]

Currently, There are unique four subtypes of breast cancer.: basal-like, luminal A, and luminal B. human epidermal growth factor receptor 2 (HER2) enriched subtypes have also been identified. As a result, several treatment plans have been used, and the prognosis has been projected. [4, 14]

Types of Breast cancer biomarkers

In reaction to cancer or some benign illnesses, tumors or other cells in the body create chemicals known as tumor markers. Despite the fact that both healthy cells and cancer cells generate the majority of these markers, malignant situations result in substantially greater levels of production. These indicators are used to gauge how well a patient is responding to therapy. [1]

The two primary categories of cancer biomarkers—circulating tumor markers and tumor tissue markers—have various applications. Cancer patients may have circulating tumor markers discovered in their blood, feces, urine, or other bodily fluids, whereas tumor tissue markers are found in the tumors themselves, generally in a sample of the tumor taken during a biopsy. However, there are a variety of breast cancer biomarkers accessible, and they all operate in the body differently and respond to various forms of treatment in different ways. [11]

1. A tumor Markers

A tumor marker is a biomarker that can be increased by the existence of one type or different types of cancers and is detectable in the blood, urine, or bodily tissues. It develops as a result of a tumor or a host's response to a tumor, depending on which is more prevalent. [22]

The ideal tumor marker should be able to detect tiny cancers with sufficient specificity and sensitivity to aid in early diagnosis or screening. Not many indicators are unique to a particular tumor. The majority of markers are generated by various cancers that originate from the same tissue type. Compared to the blood of healthy persons, they are more prevalent in cancer tissue or cancer patients' blood. After first chemotherapy and radiation, The main use of tumor markers is for diagnosing disease severity and monitoring the effectiveness of proposed treatments. [3]

Serum tumor markers have evolved into an effective tool for tracking of patients in various malignant tumor species because of its benefits of straightforward medical accessibility, surveillance, and economical testing. [56]

Cancer antigen (CA 15.3), (CA 27.29), and (CEA) are circulating tumor markers that may be helpful for monitoring metastatic breast cancer and clinical assessment to evaluate therapy response , with diagnostic imaging, a patient's medical history, and a somatic screening, consecutive analyses with using the same markers are necessary. Increased levels of these markers can indicate tumor development, but they can also occur when a disease is responding. [52]

1.1. Carcinoembrvonic Antigen (CEA)

The tumor-specific antigen known as carcinoembryonic antigen (CEA) was initially discovered in tumor tissue extracts. In clinical practice, the tumor marker that is most frequently employed is (CEA), It relates to a group of comparable cell surface glycoproteins. It serves as a tumor marker for breast, lung, gastro-intestinal, and colorectal cancer. Is used to determine stages, prognosis, monitor treatment and repeating of the breast tumor. Blood sample is analyzed and the reference

range is ≤ 2.5 ng/mL in nonsmoker adult while in a smoker is ≤ 5 ng/mL [40, 56]

The 29 genes that make up the human (CEA) family are organized on chromosome 19 q l3.2, These genes are divided into two main subfamilies, the pregnancy specific glycoprotein subdivisions and the CEA cellular adhesion molecule . [16] CEA is a glycoprotein with a carbohydrate content of between 45 and 50 percent. It is a 641 amino acid long polypeptide chain. [15]

Elevated CEA is linked to metastatic illness in breast cancer. It has been demonstrated that preoperative CEA values correlate with pathological stage, tumor size, and depend on stage. The size of the main and metastatic tumors strongly influences the amount of CEA in the blood of breast tumor patients. [56]

1.2. Cancer Antigen (CA 15.3)

is used to track therapy response and disease recurrence in patients with breast tumor, it has been illustrated that the severity of the illness and the size of the malignant tumor tend to correlate with the blood concentration of this marker and the percentage of patients with increased values. and the serum reference range (CA 15.3) is ≤ 30U/mL. [9]

This marker's name comes from a combination of its molecular makeup and the tests created to identify it. In immunoassays for these antigens, the antibodies are designated by the numerals 15-3. The protein antigen known as mucin, or CA 15.3, contains carbohydrates (MUC). As stated by their genetic and biomolecular properties, mucins are big trans-membrane glycoproteins with extracellular domains composed of a variable number of extremely conserved twenty amino acid repeat sequences that are strongly O-linked glycosylated protein cores, are divided into seven families, referred to as MUC1 to MUC7. [26]

The Cancer Antigen 15.3 gene product can be used as a tumor marker for the breast malignant tumor since the MUC1 gene is over-expressed in breast tumor. Blood CA 15.3 levels can be utilized for screening for a variety of cancers, consisting the colon ,pancreatic, ovarian, liver and lung cancers, As well as breast cancer. However, it was also mentioned that benign liver and benign breast illnesses had increased levels (False positive results). [9]

1.3. Cancer Antigen (CA 27.29)

Breast cancer tumor markers include the protein antigen CA 27.29, which contains carbohydrates. Breast carcinoma-associated antigen is another name for it. The MUC-1 gene generates it. Given that 80 percent of breast cancer patients had ascended (CA 27.29) levels, Cancer Antigen 27.29 is strongly linked to the disease. [18] is used to predict early disease recurrence in women who have had breast cancer treated, as well as to find metastases, The average range for serum (CA 27.29) is ≤ 38 U/mL. [9]

In individuals with breast cancer, Physical examination exists for (CA 27.29) comparable to (CA 15.3). There was some suggestion that Cancer Antigen 27.29 would be better sensitive but fewer focused marker than (CA 15.3), however this has not been illustrated with certainty., and it is widely believed that they are almost similar for the majority of medical uses. [24]

However, people with ovarian cysts, other cancers, benign tumors of the breast, kidney,or liver, or even those with benign tumors in other parts of body can also test positive for CA 27.29. So, there is no organ-specificity to the elevation of this marker [12]

2. Tumor Protein 53 (p53)

is a nuclear protein that is essential for controlling the cell cycle and consequently acts as a tumor suppressor in the fight against cancer. Its function in preserving stability by avoiding genome mutation has led to the description "the guardian of the genome" being applied to it. [20]

also are functions in the control of the cell cycle through tumor suppression. This has helped prevent cancer. [21]

The Tp53 gene, which is found on chromosome (17pl3.1). encodes the protein p53 in humans , It contains seven domains, 393 amino acids, and is complicated. Normal cells have relatively little amounts of it. However, it is highly expressed in a number of transformed cell lines and is thought to play a role in cellular transformation and malignancy. [38]

The most frequent gene mutation seen in human malignancies is P53. P53-mutated breast cancer is more invasive and has a worse generally survival rate. In almost 22% of fatal breast cancers, the mutation first manifests early in the course of the disease. [21]

The most typical genetic alteration found in human malignancies is still the p53 mutation. Numerous human malignancies have been linked to p53 tumor suppressor gene mutations . A p53 mutation in breast cancer is linked to a more aggressive form of the illness and a poorer prognosis. Nevertheless, p53 mutations are less common in breast tumor than in other persistent tumors. P53 mutations are found in roughly 22% of malignant breast tumors, and they seem to arise early in the disease's development. [25]

3. Hormone receptors

3.1. Progesterone receptors (PR)

Nuclear hormone receptor PR is encoded as a single gene on chromosome 1q22. It is divided into (PR-A and PR-B), and the functions of each group varies.[18] Some of the proteins produced by PR target genes are associated with breast cancer or mammary gland development and play a role in cell proliferation, transcription, apoptosis, lipid metabolism and steroid [21]

One tumor marker for breast cancer that successfully predicts the hormone response is PR. It belongs to the group of nuclear hormone receptors and has a particular affinity for progesterone. [39] A single gene, PGR, situated on chromosome 1q22, encodes PR. Two isoforms of the human PR protein, designated PR-A and PR-B, are produced from a single gene under the regulation of different promoters. [18]

According to most current recommendations from researchers and scientists the breast cancer tumors are considered estrogen and progesterone receptor positive if 1% of the tumor cell nuclei demonstrate immunoreactivity. [2]

In patients with ER-positive malignant breast tumors, PR is employed as a prognostic indicator. Studies demonstrate that patients receiving estrogen receptor treatment have a higher survival rate when PR is expressed in an ER-positive manner. [46]

3.2. Estrogen Receptors (ER)

ER serves as a transcription regulator, it is a nuclear steroid receptor and the estrogen hormone 17p-estradiol is in charge of controlling it. Cellular growth, differentiation, and proliferation are all impacted by it. Additionally, it is playing a vital part in the pathophysiology of malignant breast tumors. ER is well known for playing a crucial part in the lactational differentiation of the lobules and the puberty elongation of mammary ducts. ER is the most important indication of therapy response based on the following. [21]

One effective tumor marker for breast cancer is ER. The most significant physiologic measure of therapy response in malignant breast tumors, in addition to its prognostic usefulness, [23,37]

It is possible to expect the likelihood of hormonally resistant malignant breast tumors by measuring the levels of ER in breast tumor tissue. Every invasive breast cancer should have its ER level checked, along with any a metastatic tumor, if the results would have an impact on the course of therapy. [34]

4. Gene mutations : BRCA1 and BRCA2

Different forms of cancer are predisposed by mutations in the tumor suppressor genes that called Breast Cancer Susceptibility Genes (BRCA 1) and (BRCA 2). Over 20 years ago, it was initially shown that the (BRCA 1) and (BRCA 2) genes are relevant to ovarian and breast tumors susceptibility. [53] Since then, particular germline mutations in the BRCA 1 and BRCA 2 genes have been linked with an elevated danger of a number of new kinds of human cancers, including pancreatic, prostate , stomach, and colorectal cancers. [7, 29]

Detect mutations in these genes , that are linked mainly with hereditary breast tumor also to decide if a certain targeted therapy is beneficial for a patient's treatment or not .Gene BRCA1 has located on chromosome 17q21, from base pairs 43,044,294 to 43,125,482 . made up protein consists (24) exons and (1863) amino acids . It is made up of a number of domains that are necessary for it to perform

all of its many tasks, helps with DNA repair, transcriptional reactions to DNA damage, and cell cycle checkpoints, all of which are necessary for the regulation of cell proliferation. [19,27,41]

A big protein of 3418 amino acids is known as BRCA2 (situated on chromosome 13 q12.3 ,from base pairs 32,315,479 to 32,399,671. It encompasses around (84.2) kb of genomic DNA and has (27) exons. [13,45]

DNA damage repair is one of the cell's crucial functions. 5382 insertion C, 185 deletion AG, 4153 deletion A, and 3819 deletion 5 are the most frequent mutations in BRCA1, and frameshift mutation (5802 deletion 4-AATT) and 4075 deletion GT are the most frequent mutations in BRCA2. An elevated lifetime risk for numerous malignant tumors, including breast and ovarian cancer, is linked to the mutation in these two genes. [58]

Data from 10,180 patients from 16 trials were combined by Templeton et al., who came to the conclusion that BRCA mutations were not associated with a lower overall survival [48]. It is debatably linked that BRCA mutations have a bad prognosis. According to a research, patients with or without the BRCA1 mutation have a same 10-year survival rate [17]

According to a different study, those with BRCA2 mutations in their breast cancer have a worse chance of surviving than people without it. Nevertheless, the predictions are strictly restricted to carriers the gene with diploidy inheritance, slowly expanding tumors. [51]

5. Human epidermal growth factor receptor (HER)

A transmembrane tyrosine kinase receptor known as HER-2, which is produced by the ERBB2/HER2 oncogene on chromosome 17q21, is a member of the family of epidermal growth factor receptors that have structural similarities with the EGFR . This oncogene, whose amplification is linked with an invasive phenotype of cancer cells, resistance to cytotoxic, anti-hormonal therapy, and decrease generally survival rates, is thought to be a poor prognostic marker because it is increased (20 - 30%) of the breast malignant tumors. [6]

Levels of the circulating HER2 protein are used to forecast the development and existence of HER2 positive cells similar to ER and PR expression or tumor size, The amount of protein in the tumor is employed as a prognostic indicator that forecasts survival. [23]

It was discovered that a considerable drop in the patient's chance of survival is correlated with the overexpression of the HER2 receptor protein. Additionally, it said that HER2 protein presence is helpful in recurrence early identification and prediction of what would occur to breast cancer metastases. [37]

Thirty percent of breast cancer patients have HER2 expression levels above normal, and gene intensification is the primary factor causing this overexpression. Of these cases, 60% of patients have ductal carcinomas in situ, while 20% to 30% of patients have infiltrating breast carcinomas. In patients with the breast malignant tumor who have alar lymph nodes, overexpression of HER2 is associated with a low disease-free survival (DFS) rate. When HER2 is overexpressed, patients have a much lower overall survival rate and a death rate that is twice as high. High nuclear grade cancers have higher levels of HER2 than low nuclear grade tumors do, by a margin of 29% to 14%. [46]

6. Ki 67

Among other malignant breast tumor traits, the biologic Ki 67 is presently used to assess progression and aggressiveness to gauge the level of tumor growth. [42]

Due to its dubious analytical validity, Ki67 immunohistochemistry (IHC), a proliferation marker frequently employed in breast tumor, provides little relevance for treatment choices. The current substantiation for Ki 67 analytical validity and medical value in the breast tumor was evaluated at the International Ki67 in malignant breast tumor Working Group (IKWG) gathering, which was conducted in October – year 2019. [5,50]

nuclear protein that is encoded by the (MK I67) gene. It only arises during the cell proliferative phases of the cycle except the G_0 phase. Ki 67 is crucial for cell proliferation since, in the

absence of it, cell growth would be inhibited. [33,35] Although it has been difficult to determine Ki67's function, evidence suggests that DNA plays an organizing role. It also suggests that Ki 67 participates in the production of ribosomes during cell division.[46]

Ki67 is a prognostic indicator frequently utilized for breast cancer in its early stages. Age, the rate of mitosis, and nuclear grade all have an important effect on the percentage of Ki67 positive cells. [30]

7. Cyclin D1

cyclin D1, a protooncogene that positively regulates the development of cancer . Early cell proliferation is accompanied by increased cyclin D1 expression, which is induced by growth factors or other mitogens. The Ki-67 proliferation index and Cyclin D1 have both been utilized in the past as biomarkers for cell growth and prognosis in different types of malignant tumors . [31,47]

Cyclin D1 is one of the most important main controllers in the cell cycle. It is a member of the D-type cyclin family, which controls the activity of cyclin - dependent kinases to control the progression of the cell cycle from the Gap 1 to the S phase (CDKs). [49]

Recent research has identified other functions for cyclin D1 in driving cell cycle progression via CDK-independent processes, including as interaction and control of transcription factors activities. [10]

Up to 50% of human breast tumors have been reported to overexpress Cyclin D1, however its prognostic significance is still debatable. The maturation and differentiation of tumor cells may be caused directly or indirectly by cyclin D1. [57]

An essential regulator protein for Gap1 phase advancement is cyclin D1 . It is produced in response to growth stimuli, reaching its maximum level in the middle of the Gap1 phase of the cell cycle. Cyclin D1 is produced and released by the (CCND1) gene, which is situated on chromosome 11q13. Numerous incidences of cyclin D1 gene amplification in breast cancer have been found. [46]

Ki67 expression and Cyclin D1 have been reported to have both positive and negative correlations. If both of these markers are increased in breast tumors, exploratory investigation is necessary to forecast the clinical outcome. According to several research, there is a substantial correlation between the size of T1, T2 tumors and Cyclin D1 expression, Her2 positivity or negativity. Proliferative biomarkers' cell activity has been clinically linked to breast cancer survival and prognosis because it significantly contributes to the growth of neoplasia and metastasis. [8, 28,43]

In contrast to basal subgroups, which are ER negative and express less cyclin D1, luminal B subgroups exhibit robust ER positivity and high levels of cyclin D1 protein, while basal subgroups exhibit weak ER positivity and small levels of cyclin D1 expression. Nearly 70% of the breast malignant tumors groups are luminal tumors, the most common type. It is no longer important in basal tumors. [36,44]

Conclusion

Clinically significant tumor biomarkers for breast cancer patients. To ensure that patients with breast cancer receive the best care possible, we advise its clinical use. It either displays markers for a positive prognosis, such as ER and PR, or a poor prognosis, such as P 53, HER 2, BRCA 1, BRCA 2, and cyclin D1, As ER, Ki 67 and P53 are crucial in the indication of recurrent tumors. In addition, the most helpful blood tumor indicators in patients with breast cancer are CEA and MUC-1 antigen. Serial measurement of these markers may be helpful in assessing treatment response and in the early diagnosis of metastasis or recurrence.

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