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BREAST CANCER BIOMARKERS: A QUICK REVIEW

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Abstract:

Carcinoma of breast is a highly prevalent tumor in females and about 1 million cases of this cancer are reported annually worldwide. Brest cancer is responsible for second highest number of deaths globally. In addition to tests like mammography, biopsy, MRI, sonography, ELISA and RIA, measurement of progesterone receptors (PR), estrogen receptors (ER), and human epithelial growth factor receptor 2 (HEGF-2) should also be measured. Because of heterogeneity of breast cancer, new biomarkers have proven to be useful for their predictive significance. Levels of glyco-proteins, microRNA, DNA biomarkers, circulatory tumor cells (CTC) and autoantibodies should always be measured wherever the facilities are available especially in developing countries for timely and proper diagnosis and subsequent management of breast cancer.

Key Words:*Carcinoma, breast, biomarkers, tumor receptors, CEA, tumor proteins.*

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INTRODUCTION:

Breast cancer is the most prevalent malignant tumor in females globally affecting about 2.1 million females yearly, and the highest numbers of cancer-related demises among these females are associated with this disease. In 2018, about 627,000 women expired from breast cancer which is around 15% of all cancer deaths among women (WHO). Its prevalence is high in developing countries but it is also on rise in all societies [1]. American Cancer Society reported that any of the below-mentioned unfamiliar alterations in the breast can be a predictable indication of breast cancer:

Abnormal growth of either all or a portion of the breast (in excess of 80% of breast cancers patients) is revealed by a swelling in breast [2].

- Skin irritation or dimpling
- Breast pain is an undependable symptom in diagnosing the presence or absence of breast cancer.
- Pain in nipple or retracted nipple.
- Breast skin turning red or nipple gradually becoming thick.
- Discharge of secretions from nipple in place of milk.
- In later or terminal stages, other frequent symptoms of this cancer include unusual emaciation, aching pain in bone and/or joints, inexplicable jaundice and sometimes neurological manifestations [3].

Risk factors: The main risk factors for breast cancer are when patient is a female and especially if she is old. Other likely risk factors include genetic history [4] ,some nutritional patterns, and mothers without a child or absence of breast-feeding, greater than normal levels of some hormones[5] along with obesity. In one report contact to light contamination has also been associated as a probable risk factor for the breast cancer development [6]. Obese women having an unusual fat in the middle portion of their bodies have an enhanced threat as compared to those in which excess weight is present in the lower part of body. This report highlights the assumption that taking abundant food is of more important than body mass index (BMI) as a risk factor. Another report indicated that taking too much alcohol in any form enhances the risk of breast cancer, even if these drinks are taken in a comparatively little (one to three drinks per week) and modest amount [7]. Breast cancer risk is also increased if tobacco is smoked excessively and especially if smoking is started at an early age [8].

A link has also been established between use of medicines for control of birth and the development of breast cancer at premenopausal stage of age [9]. Similarly some chemical substances have also been implicated as risk factors like polycyclic aromatic polychlorinated biphenyls, hydrocarbons, and organic solvents [10]. Genetic predisposition has also been supposed to be the chief cause in breast cancer patients in 5-10% of patients. Those women whose mothers were identified as cancer patients before reaching 50 years of age have a higher risk (1.7 times), while those patients whose mothers were diagnosed of the cancer after 50 years have 1.4 times risk of developing breast cancer [11].

Pathophysiology: Like some other cancers, breast cancer develops due to an interaction between some environmental factors also called external factors and a person who is hereditarily prone to develop disease process. Normal cells divide for as numerous times as necessary and then cell division is arrested. They usually remain attached to other neighboring cells and remain bound in tissues. Cells become cancerous when either their multiplications cannot be halted, or they do not stay adherent to their adjacent tissues or attach to other cells, and eventually succumb to these abnormal conditions.

Normally cells do not commit suicide because they are protected by several protein clusters and pathways. Out of these P13K/AKT and RAS/MEKERK pathways are important. Normally just before apoptosis of a cell, a protein called PTEN protein switches off the PI3K/AKT pathway. In few cancer patients, the gene responsible for the synthesis of PTEN protein is modified in such a way that the PI3K/AKT pathway is seized in the “on”point, and so the cancer cells are unable to commit apoptosis [12]. These mutations have been linked to exposure to estrogen and one report mentioned that G-protein coupled estrogen receptors had been found to be linked with some types of malignancies of female reproductive system along with breast cancers [13]. More over in breast adipose tissues, over-expression of leptin also increases the risk of cell multiplication and eventually cancer [14].

Some mutations like BRCA mutations confers a life time breast cancer risk, whereas mutations like p53, BRCA 1 and BRCA 2 are inherited or acquired afterwards which allow further mutation resulting in uncontrolled cell division and metastasis to other organs [15]. Another factor is GATA3 which is a transcription factor and is encoded by the GATA3 gene and it controls the expression of a

wide range of biologically and clinically important genes and its damage causes loss of differentiation and spread of tumor [16].

Diagnosis: Screening depends on physical examination and mammography. If these methods are indecisive then FNAC(Fine needle aspiration and cytology), under local anesthesia is helpful in establishing a diagnosis. Physical examination, mammography and FNAC can yield an accurate diagnosis of breast cancer with fairly adequate precision. Other possible options are core biopsy or excisional biopsy, ultrasound and MRI.

TNM method is frequently used for staging of the breast cancer.

Stage 0. is pre-cancerous or marker situation which can be either lobular carcinoma in situ or duct cell carcinoma in situ.
Stage 1. Tumor size is less than 2 cm.
Stage 2. Tumor size is from 2 to 5 cm.
Stage 3. Tumor size is more than 5 cm.
Stage 4. Tumor has metastasized to other tissues outside breast.

Breast cancer cell receptors: Cells of breast cancer develop receptors either on their cell membranes, or in cytoplasm and in their nuclei. These receptors may be either estrogen receptors (ER), progesterone receptors (PR) or *h*uman *e*pithelial growth factor *r*eceptor 2 (HER2 receptors). Some breast cancers are triple negative (they do not have any of these receptors). In fact, the levels of these receptors i.e. estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor type 2 (HER2) are being used as possible markers for recognizing a high-risk class of cancer and also for the type of the most effective treatment for their management [17]. About 30-40 years back, tamoxifen was available which was used as a treatment of cancer. This anti-estrogen treatment was supposed to target the estrogen receptors.The mechanism of action of this drug is that it binds to the ligand-binding domain of estrogen receptors, and so obstructing the receptor stimulation because of estrogen.

HER-2 belongs to a group of epithelial growth factor receptors and is a trans-membrane tyrosine kinase receptor. It is encoded by an oncogene ERBB2/HER2 situated on chromosome 17q21. This oncogene is augmented in about 20 to 30% of breast cancers patients and its amplification is considered as a sign of poor prognostic status, especially if that is also associated with destructive tumor morphology, failure of cytotoxic treatment, and eventually overall survival rate of these patients falls to low levels [18]. Presently, trastuzumab, which is a humanized monoclonal antibody focused against the extracellular domains of HER-2, is valuable for the treatment of those breast cancer patients who are HER-2 positive. The effectiveness of trastuzumab has been established in numerous clinical trials. However, the exact mechanism by which trastuzumab prevents the signaling arbitrated by HER-2 receptors is still undefined. It is supposed that its effects are mediated by its ability to suppress receptor-receptor interaction, endocytosis causing decrease in receptors, blocking of receptors' extracellular domain cleavage, or stimulation of antibody-dependent cellular cytotoxicity (ADCC) [19].

Tumor protein p53: This protein is involved in apoptosis, cellular senescence and cell cycle arrest. About 30% of breast cancer patients display mutation of TP53 gene [20]. In one study, expression of this mutant p53 protein was linked with high tumor multiplying speed, initial disease reappearance, and also early death especially in patients in whom lymph node were not involved [21]. Alterations in TP53 gene cause a changed molecular structure and lengthy protein half-life causing build-up of nuclear p53 protein. The immunohistochemistry (IHC) method can also be used to detect its anomalous accumulation and it indicates TP53 gene mutation [22].

Carbohydrate 15-3 and Carcinoembryonic Antigens (CA 15-3 and CEA): The CEA is a glycoprotein which is expressed in a large number of gastric, pancreatic, colonic, rectal, lungs as well as in certain breast carcinomas [23]. Higher levels of CEA in breast cancer patients are suggestive of extent of tumor and its connection with the regional lymph nodes. Existence of abnormally high levels of CA 15-3 before surgery is related with a high risk of reappearance and eventual death [24]. Mendes et al. reported that estimation of tumor markers is a good indication that tumor has metastasized to other organs, and therefore estimation of tumor marker CA 15-3 seems to be more reliable when it is compared to levels of CEA [25]. However, in 60-80% of breast cancer patients, concurrent use of both these serum markers i.e. CA 15-3 and CEA permits the timely finding of metastasis [26].

MicroRNA: The MicroRNAs are small RNA molecules & contain 21-24-nucleotides. These non-coding molecules occur naturally although their exact origin is not completely understood so far. These are attached partly or totally to untranslated regions

3′untranslated (3′-UTRs) of protein-coding genes, which results in cleavage of targets. The microRNA may be present in plasma, serum or blood. It has been suggested that microRNAs may enter into blood when cancerous cells are vanishing or tumor cells may be secreting microRNA along with exosomes [27,28].

MicroRNA 21 is over expressed and is mostly used to diagnose breast cancer at an early stage because it is highly sensitive (87.6%) and specific (87.3%). [31].Wu et al, reported the presence of about 800 miRNAs in the blood of breast carcinoma patients [29].

DNA biomarkers: BRCA1 and BRCA2 (*br*east *ca*ncer gene) are the most commonly determined DNA biomarkers. These are tumor suppressor genes present in normal cells and regulate cell division. 21-40% of breast cancer cases are due to mutation in genes of BRCA1 and BRCA2 [30]. Estimation of biomarker BRCA2 can be effectively used for prognosis and diagnosis of breast cancer.

Circulatory tumor cells (CTC): Metastasis of cancer cells may be detected by counting the cells although it is difficult at times because of their very low count. However, CTC does indicate the invasive nature of cancer, and also anti-cancer drug response can be predicted [31].

Auto-antibodies: Tumor associated antigen (TAA) induces antibodies which can be detected usually before any clinical symptoms appear. Sometimes these anti-bodies appear in salivary secretions. This test can be useful for early diagnosis of breast cancer patients [32]. There is a direct relationship between serum level of auto-antibodies and progression of breast cancer and can be used as an early diagnostic tool in near future [33]. The only limitation is the heterogenic nature of breast cancers when accurate estimation cannot be contemplated.

CONCLUSION:

Although history, physical examination, mammography, biopsy, MRI etc. can be used as diagnostic tools in breast tumors but determination of biomarkers can offer simple, early and cost-effective methods to diagnose suspected cases. These biomarkers can also help in pre-clinical diagnosis of breast cancers especially in women who have strong familial history as well as the prognosis of the disease. Because of the heterogeneity of breast cancers further research is required in biomarkers specific for a particular type of cancer so as to reduce the mortality associated with the disease.

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