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Breast Cancer and its treatment

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Abstract

Breast cancer is the most prevalent cancer in the world. Approximately one in every nine Pakistani women is likely to suffer from breast cancer showing an incidence rate of 50/100,000 and breast cancer is growing at an alarming rate in Pakistan. The main causative element remain unknown yet primary risk factors identified are sex, age, parity, genetics, lack of child bearing, breast feeding, higher hormonal levels individual lifestyle etc in Indian and Asian women as compared with western women. Knowledge of this factor emphasizes the need to modify the timing of modalities of detection of early carcinoma and its management Inherited mutations in the breast cancer susceptibility gene 1 (BRCA1) [MIM 113705] and breast cancer susceptibility gene 2 (BRCA2) [MIM 600185] are associated with a high risk of developing breast cancers in females of different age and ethnic group.

Keywords: Breast cancer; BRCA1; BRCA2

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Introduction

Breast cancer was first documented in Egypt around 1600BC. In 1860 in an ancient Egyptian tomb, eight cases of tumour or ulcers of the breast were described by the Edwin Smith papyrus. Breast Cancer is unlimited growth of breast cells and it is caused by genetic disorder, hormonal imbalance and environmental factors. The most common type of cancer in females is breast cancer, which accounts for 23% of all cancer types diagnosed in females. Globally 1.4 million new cases of breast cancer were diagnosed every year. Breast cancer is the most common malignancy in women with 6.6% is diagnosed in young women below 40 years. About 459000 deaths are recorded [1,2].

At the age of 30, breast cells grow independently that cause cancer. The malignant cells of the breast cells can spread to the other organs of the body. The incidence of breast cancer is high in women as compared to the men. Approximately 90000 new cases are diagnosed in Asian countries every year. The death rate is about 40000. Pakistan has the highest rate of breast cancer than any other country. In urban areas of India, breast cancer is three times higher than in rural areas. Indian Council of Medical Research estimates the number of breast cancer cases in India, rise to 106,124 in 2015 and to 123,634 in 2020 [3-5].

Vdr Polymorphism

In many cases, breast cancer's growth is due to the oestrogen receptor and vitamin D Receptor. The observed associations between VDR genotypes and breast cancer risk have varied in different ethnic groups. The VDR Taq polymorphism has major risk effect on the breast cancer development, particularly in Caucasians. Moreover, no associations between Taq polymorphism and breast cancer have been found in Swedish, Turkish, and Taiwanese. The investigations on functional effects of VDR polymorphisms, the BAt haplotype compared to baT haplotype exhibited a slightly higher tendency for increased levels of VDR mRNA expression, although contrasting results also exist. In contrast, FokI and Cdx2 polymorphisms would seem to possess functional effects on binding efficiency to transcription factors TFIIB and Cdx2, respectively. Further evidence for an association between breast cancer risk and VDR polymorphisms has been revealed in subgroup analyses stratified, e.g., by the use of HRT or metastatic breast cancer. The Genome Atlas, increase the expression of RAC1 and VASP in breast cancer. They decrease cell differentiation and inhibit cancer cell migration [6-11].

Anatomy

The breasts are specialised organs, which are located on the anterior chest wall 12- 20 types of secretion in the healthy female breast. Breast tissue consists of tissue, lobe, Ducts, areola, nipple,

lobules. The main parts of the female breast are lobules which are the milk-producing glands, ducts are the milk passages that connect the lobules and the nipple, stroma are the fatty tissue and ligaments surrounding the ducts and lobules, blood vessels, and lymphatic vessels). The breast cancer originates in lobules. Adult women have 15 to 20 lobes in each breast. The breast and armpit also contain lymph nodes and vessels carrying lymph fluid, which are part of the immune system. Sometimes breast cancer can spread to other areas of the body through this lymph system or blood vessels [12-14].

Subtypes

The molecular subtypes of breast cancer were classified according to a gene expression profile- validated immunohistochemical replacement panel as follows: luminal A (ER-positive and/or PR positive and Ki-67 < 14%), luminal B (ER-positive and/or PR positive and Ki-67 ≥ 14%), luminal/HER2 (ER-positive and/or PR positive and HER2 positive), HER2 enriched (ER-negative and PR negative and HER2 positive), and basal-like (ER-negative and PR negative and HER2 negative and EGFR positive and/or CK5/6 positive). the breast cancer cells tested negative for Oestrogen Receptors (ER-), Progesterone Receptors (PR-) and HER2 (HER2-). Testing negative for all three means the cancer is triple-negative. Triple-negative (TN) tumours that did not express EGFR or CK5/6 were considered as TN non basal in this study and were included as a separate group for the multivariable analysis [15]. Triple-negative breast cancers have a more aggressive clinical course than other forms of breast cancer. ER shows 80-90% expression in breast cancer while PR shows 70-80% expression [16].

Breast Cell Lines

Over the past few years, RNA-editing technologies employing the CRISPR technology and nuclease Cas13, adenosine deaminase acting on RNA (ADAR), and apolipoprotein B mRNA-editing enzyme, catalytic polypeptide 1 (APOBEC1) and their derived enzymes have become increasingly hot topics in gene editing, mRNA editing, and viral restriction [42](Figure 1B and 1C).

Human breast cell lines exhibits a cellular hierarchy that is characteristics of primary breast tumours, in which small population of cells such as CD44+CD24+ESA+ for initiating cells that have self- renewable property in vitro, target to these breast cell tumour lines CD24+ESA+CD44+ to identify that therapies that prevent self-renewal and force depletion tumour original breast cancer stem cell lines [17].

Genes

Breast cancer is highly identified in BRCA1, BRCA2, PTEN, and TP53; also have some other genes that are involved in DNA repairing like RAD59C, PALBL, ATM, CHEK2, ATM, BRTP1 also affiliated with modest breast cancer. Genetic mutation BRCA1 and BRCA2 are the major cause of breast cancer. There are 48 differentially expressed genes in the tumour, from which 3 differentially expressed genes IGHG3, CDK6, and RPS9 were suggested to play a novel role in breast cancer [18,19].

BRCA1 and BRCA2

Around 5-10% of breast cancer due to a mutation in the germ line. Two susceptibility breast cancer genes BRCA1 and BRCA2 have been identified on chromosome 17q and 13q. They are high prevalence genes of breast cancer [20].

P53

P53 is a transcriptional factor activated by genotoxic stress; depend upon the level of DNA damage. P53 can trigger cell cycle, apoptosis, and DNA repair. If p53 inducible proteins that stimulate repair and inhibit apoptosis are up-regulated. Tumours can become resistant to many types of treatment. Multidrug resistance leads to the treatment failure and causes the death of the patient. That patient relies exclusively on chemotherapy because they don't express hormone receptors [21].

Symptoms

Breast cancer symptoms include a lump in the breast or armpit, changes in breast shape, bloody nipple discharge, inverted nipple, orange-peel texture or dimpling of the breasts skin, breast pain or sore nipple, skin changes, swollen lymph nodes, change in the breast size and shape [22].

Risk factor

The risk factors of Breast cancer includes mutation in gene sequence, Physical activity, body mass index, breastfeeding duration less than 1.15-2 years, 1st child after the age of thirty ,diet, obesity, smoking, alcohol drinking, chemicals, carcinogenic elements that expose in environment, Hormonal imbalance, dense breast tissue increase and ROS [23].

ER and PR

Estrogen Receptor was available for 50.5% and progesterone receptor status available for 49.8% of all breast cancer cases, including in situ ductal or lobular carcinoma (n=204), invasive ductal (n=817), invasive lobular (n=50) and inflammatory breast cancer (n=16) in Asian Indian Pakistani Females (n=1087) [24,25].

Cholesterol Role

Cholesterol play role in breast cancer development high density lipoprotein cholesterol processes anti-inflammatory characteristics and inversely associated with breast cancer risk, low HDL- cholesterol associated with higher oestrogen levels and absolute mammographic density, different lipoprotein sub fractions vary by progesterone receptor, the influence of HDL-cholesterol on breast cancer prognosis may differ by breast cancer phenotype [26-29].

Spk2

F-box protein skp2 (S-phase kinase protein-2) plays an important role in breast cancer pathogenicity. Skp2 related to the system of ubiquitin-proteasome that plays important role in different

biological processes by regulating the proper turn-over of proteins. S-phase kinase-associated protein-2 is a particular determinant of SCFskp2 E3 ligase that involved in the progression of the cell cycle by deregulating its target. P27 is a substrate for skp2, its lower level caused by Skp2 overexpression which shows expression of cancer in humans. Skp2 act as a prognostic marker, an important factor in cell growth, invasion, apoptosis, and metastasis in breast cancer [30,31].

Diagnose

The physician examines the patient's breasts and the detection is by lumps, thickening, asymmetry, changes in breast and other symptoms. The patient will be asked to sit or stand with her arms in different positions, such as above her head and by her sides [32].

A biopsy

A biopsy is a sample of tissue, surgically removed for laboratory analysis. This can show whether the cells are cancerous, and, if so, which type of cancer it is, either or not the cancer is hormone-sensitive. Diagnosis also involves staging cancer, to establish: the size of a tumour, how far it has spread, whether it is invasive or non-invasive, whether it has metastasized, or spread to other parts of the body. Another method of breast cancer detection includes injecting a liquid into the breast, sucking the injected liquid and examines the sucking liquid. This method is very painful and therefore cannot be used for large-scale cancer examination [33,34].

Mammogram

Is a type of x-ray used for screening it produces images that can help in the identification of tumour or abnormalities? Mammogram sometime shows up a doubtful area that is not cancer. This can lead to unnecessary stress and sometimes interferences. An ultrasound scan can help differentiate between a solid mass and a fluid-filled cyst. Screening Whole Breast Ultrasound (SWBUS) is being more widely used as a supplemental screening tool in addition to mammography. Mammography is an imperfect test and limited by dense breast tissue. Dense tissue may have an underlying tumour, therefore, decrease mammographic sensitivity. An ultrasound performed in dense breast tissue with sensitivities of mammography and ultrasound 56% and 88%, whereas their performance in the non-dense breast was similar with mammography and ultrasound80% and 88% [35-37].

Blood Marker Tests

Blood marker tests are done before treatment, to help diagnose the breast cancer and determine whether cancer moved to other parts of the body. CA 15.3 used to find the breast. TRU- QUANT and CA 27.29 may mean that breast cancer is present. CA125 may signal ovarian cancer, ovarian cancer recurrence, and breast cancer recurrence. CEA (Carcinoembryonic Antigen) is a marker for the presence of colon, lung, and liver cancers. This marker may be used to determine if breast cancer has travelled to other areas of the body.

Urokinase plasminogen activator protein inhibitory test

The urokinase plasminogen activator and its inhibitor proteins are found on the outside of breast cancer cells that help cancer grow and spread. The levels of the urokinase plasminogen activator protein and its inhibitor protein in women diagnosed with hormone-receptor-positive, HER2- negative breast cancers that have not spread to the lymph nodes.

Margin probe

The Margin Probe System detects subtle electromagnetic differences between breast cancer cells and normal breast tissue. In 3 to 5 minutes, a surgeon can test the margins and decide if more tissue needs to be removed. Margin Probe can be used during lumpectomy for both DCIS (Ductal Carcinoma In Situ) and invasive breast cancer.

Serological proteomics method

Breast cancers protein isolation then run on SDS-PAGE and then electrophoresis, After 2-Dimensional Electrophoresis was completed, the gels were equilibrated with Tris-glycine transfer buffer containing 20% methanol for 15 min, and the proteins were electro-blotted onto a Sequi- Blot PVDF membrane (Bio-Rad) in the same buffer at 30 mA for 1.5 h. A Bio-Rad Transfer unit was used for this purpose. The membrane was then stained with 0.1% Coomassie blue R-250 for 2 min and distained with 40% methanol, 10% acetic acid for 10 min [38].

Human epidermal growth factor receptor 2

The HER2 oncogenic protein is a transmembrane glycoprotein, member of the HER family encodes by ERBB2. HER2 express at a low level in several epithelia, including the breast. HER2 overexpression occurs in approximately 15% to 20%. HER2 status can be determined in formalin-fixed, paraffin-embedded (FFPF) by assessing protein expression on the membrane of the tumour cells using IHC. In situ hybridization methods include fluorescence in situ hybridization, chromogenic in situ hybridization, dual in situ hybridization, and silver-enhanced in situ hybridization. Some assay use single probes [39-41].

Serum marker

The mamma globin protein as a secreted, 14- to 21-kDa species, which is likely post-transnationally treated based on predicted 7-kDa size. Immunostaining for mamma globin was conducted. An ELISA was developed for the detection of the mamma globin protein in serum, and levels were compared between women with and without breast cancer. A receiver operating characteristic curve was used to show sensitivity and specificity for cut points on the continuous mamma globin scale [42].

Molecular Analysis

Molecular analyses extract the DNA from blood sample. Then design primers and run PCR. PCR amplified result run on Gel Electrophoresis.

Treatment

Beta-blocker, propranolols inhibit norepinephrine-induced breast cell migration. Treatment of breast cancer depends on the type of cancer and its stages (0-4) and may involve surgery, radiation or chemotherapy. Doxorubicin and Anthracyclines are chemotherapies. Doxorubicin prevents topoisomerase activity and DNA synthesis produce free radical and cytotoxicity. Doxorubicin is more similar structure to Daunorubicin. It is more abundant, a natural product produced by wild types strains of Streptomyces [43,44].

Neupogen

Granulocyte colony stimulating factors help the body make more neutrophils; neutrophils are a type of white blood cell. Neupogen is used to reduce the risk of infection during chemotherapy treatment [45].

Aromasin

Aromatase inhibitor hormonal therapy. Aromatase inhibitors lower the amount of oestrogen in postmenopausal women. Aromasin used to treat postmenopausal women, is used to reduce the risk of early-stage, hormone-receptor-positive breast cancer coming back after surgery and other treatments [46].

Xeloda

Capecitabine is Antimetabolite chemotherapy. Antimetabolites kill cancer cells by acting as false building blocks in a cancer cell's genes, causing the cancer cell to die. Xeloda often is used in combination with other anticancer medicines. It's used to treat metastatic breast cancer that has stopped responding to Taxol, Taxotere, and Adriamycin. Xeloda is taken orally as a pill [47].

Natural Drugs Anti-Cancer Properties of Natural Drugs

Carotenoid

Substances have vigorous antioxidants that exhibit different therapeutic activities, such as protecting against oxidative damage to cells, searching of free radicals, modulation of the immune system and enzyme's activity regulation involved in cancer production and also simulates the activity of immune system [48].

Turmeric (*Curcuma longa*)

Curcumin (the active ingredient of turmeric) has a role in anti-cancerous activity due to its phenolic substances. Curcumin has inhibitory action in all phases like initiation, promotion, and propagation of tumour [49].

Garlic (*Allium sativum*)

It has Anti-cancer activity due to the presence of poly sulphides and organic sulphides. Mechanism of antitumor activity stimulates the lymphocytes and macrophages. They also interfere with cancerous cells metabolism and kill the cancerous cells [50].

Black cohosh (*Cimicifuga recemosa*)

It has synergistic effects for patients of breast cancer when used in combination with chemotherapeutic agents [51].

Green tea (*Camellia sinensis*)

Polyphenolic compounds show anti-tumour activity. Green tea also stimulates the necrosis and apoptosis of tumour cells and enhances anti mutagenic activity. All these properties are due to the antioxidant activity of phenolic compounds present in green tea [52,53].

Burdock

Burdocks (Arctium lappa) contain active ingredients that alter the oncogenes. Burdock seeds also contain Arctigenin that has an ability to inhibit tumour cells. The most important active ingredient is Tannin which is a phenolic lappa [54].

Surgery Axillary Nodes

The safety of more traditional methods for the surgery of the axilla. If sentinel lymph nodes are clear, axillary dissection can be lost. The ACOSOG trial Z0011 for patients with a clinically node-negative axilla who experienced lumpectomy and tangential whole-breast irradiation showed at an average addition of 6.3 years that axillary dissection can be absent without adversely affecting diagnosis in the presence of one or two positive sentinel nodes Axillary dissection vs. no axillary dissection in women with invasive breast cancer and watch node metastasis [55].

Radiation therapy partial breast irradiation

A randomized trial of targeted intraoperative radiotherapy generated results closely similar to conservative whole-breast irradiation. It is 14% of the targeted intraoperative radiotherapy group also received external beam radiotherapy and the average supplement in the study is 2.5 years. A single institution series of 1822 patients treated with breast-conserving surgery has recognized excellent local control with intraoperative electron beam therapy in selected patients [55,56].

PARP inhibition

In the presence of tumour defects in homologous recombination DNA repair, inhibition of the PARP enzyme system may result in 'synthetic lethality' and increased cell kill. This is seen in carriers of BRCA1 and BRCA2 mutations. In such patients, single-agent PARP inhibitors, such as olaparib, produce important tumour responses. Other cases of the triple-negative disease rarely respond to single-agent PARP inhibition. DNA disrupting cytotoxic agents is being investigated in combination with PARP inhibitors in the patient [57,58].

Overcoming resistance to endocrine therapies

A better understanding of the mechanisms of endocrine therapy resistance includes the role of growth factors, integrin's, stress

kinases, and molecular pathways including PI3K/AKT and MEK/MAPK [59].

Treatment of germ line genetic tendency

The 394 genes, which have been involved in human cancer, some 10% are transmitted in the germ line leading to increased susceptibility. Of these, the BRCA1 and BRCA2 have been best studied, but others include TP53, PTEN, and CDH1, all of which can increase the risk of breast cancer. BRCA1- and BRCA2-associated breast cancer is sensitive to cross-linking agents such as cisplatin [60].

Host factors and cancer risk

Host factors containing obesity and hyperinsulinemia are associated with increased risk of breast cancer and recurrence of breast cancer. Diabetic patients receiving metformin have a lower incidence of cancer compared with diabetic patients not receiving this agent.

Vitamins and antioxidants

Treatment with beta-carotene, vitamin A, and vitamin E may increase death. The potential role of vitamin C and selenium on mortality remains unsettled. Reduced breast cancer occurrence in young women. The relationship between vitamin D levels and breast cancer risk or prognosis is controversial [61].

Stem cells

Mammary stem cells suggest a synergistic role for progesterone and RANK ligand in tumour formation. This increases the possibility of an additional mechanism of action of clinically available RANK ligand competitors such as denosumab. Studies of mouse mammary stem cells demonstrated that they are highly reactive to steroid hormone signalling though they lack both oestrogen and progesterone receptors [62].

Immunity and autoimmunity

Tumour-infiltrating regulatory T cells stimulate mammary cancer metastases through receptor activator (RANKL-RANK) signalling. Tumour FOXP3+T reg cells are a major source of RANKL, which stimulates the metastatic development of HER2-positive RANK-expressing breast cancer cells [62-64].

Conclusion

Anti-Her2 therapy without chemotherapy

Metastatic breast cancer and in the neo adjuvant setting have demonstrated activity of trastuzumab and other anti-HER2 agents without chemotherapy although usually less than the activity seen for the combination with chemotherapy. There are no data in the adjuvant setting.it may be rational to recommend that anti-HER2 therapy, alone or with endocrine therapy if Sui, may be effective in patients who for various reasons cannot receive cytotoxic therapy.

Sunlight

Sunlight is a protective factor for breast cancer, particularly in regions with the highest levels of solar radiation in the United States.

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