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CANCER: A CHALLENGE

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Abstract: Cancer is a major cause of death in humans. Cancer is a term used for a group of diseases that cause cells in the body to change and grow out of control. Cells in the body of an individual grow and divide continuously to maintain the organism. These divisions are controlled by a complex system- The cell cycle control system. However, when this cell-cycle regulation is lost, the resulting uncontrolled growth leads to the formation of primary tumor. Cancer cells can detach from the primary tumor and circulate through the blood and the lymphatic system and invade other parts of the body to form a new tumor. In this review literature we are focusing on the breast cancer and its socio impact in the population.

Key Words: Breast cancer, p53, BRC gene.

Introduction:

Breast cancer is the third largest public health problem worldwide. According to Global Cancer Statistics 2011 [Jemal et al., 2011], the breast cancer incidence rate in India is around (17.2%) of all the cancers, and stands second in the number of cancer cases overall. Breast cancer is a complex and heterogeneous disease, with distinct biological features and clinical behavior. It is commonly used to define cancer of the female though it occurs in men too, accounting less than 1% of all the cases of cancer in men [Sharon et al., 2004].

Classification of breast tumors

Breast cancer is a broad term encompassing distinct tumor phenotypes with different gene expressions and outcomes. Generally the breast cancer patients can be grouped into two subtypes:

1. The luminal (A or B)
2. The non-luminal subtype.

The luminal subtype includes those which express estrogen receptors. The non-luminal subtype includes the ones not expressing them.

The non-luminal subtypes can be further sub classified into two groups, those expressing human epithelial growth factor receptor 2(HER-2) and those not expressing either ER or HER-2. This latter group is also called the basal subtype [Pepper corn et al., 2008]. Based on the gene expression microarray data, five subtypes of breast tumors are defined: basal-like, HER2-enriched, luminal A, luminal B, and normal-like tumors [Perou et al., 2000]. The molecular subtypes are believed to partly reflect the cell-type from which the tumor originates and to follow different tumor progression pathways. Indeed, it has been shown that

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the subtypes are associated with different prognosis, steroid receptor status, proliferation rates, hereditary backgrounds, CNAs, and sites for metastases [Pusztai et al., 2006].

The World Health Organization (WHO) has classified the breast cancer into two types based on the histological appearance: **Noninvasive and Invasive breast cancers**.

Non-invasive breast cancers

There are two main types of noninvasive breast cancers: the ductal carcinoma in situ (DCIS) and the lobular neoplasia (also called lobular carcinoma in situ, LCIS). The cancer cells of these forms are either located inside the ducts (DCIS) or inside the lobules (LCIS). Both types are so-called "in-situ" because they do not invade the surrounding fat tissue, nor spread through other organs in the body [Sharon et al., 2004].

Invasive breast cancers

Most of the invasive breast cancers (about 80%) are infiltrating (or invasive) ductal carcinomas (IDCs). These tumors start in the duct of the breast, break through the wall of the duct and invade the surrounding fat tissue, from where they can spread through the lymphatic system or bloodstream. The other main type of invasive breast cancers (about10-15%) is the infiltrating (or invasive) lobular carcinoma (ILC). These cancers begin in the lobules of the breast and then act similarly to the IDCs. [Sieber et al., 2003]

RISK FACTORS

Several factors have been shown to increase the risk of developing breast cancer. These include both hereditary and non-hereditary factors [Stewart and Wild, 2014]

Reproductive Factors

Menstrual history:

Studies have shown that higher lifetime exposure to estrogen and progesterone may lead to breast cancer. [Harold et al., 2000]

Environmental and Life Style Factors

Environmental pollutants:

Some plastics, pesticides like DDT and polychlorinated biphenyls seem to be linked with high risk of breast cancer. [Cohn et al., 2007].

Alcohol Use and smoking:

Increased alcohol consumption and smoking is linked to high risk of breast cancer. [Wells, 1998]

Dietary fat:

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Many findings suggest that breast cancer rates are minimal in countries where the standard diet is low in fat [Albert et al., 2008].

Radiation Exposure:

Women who received high-dose radiation for medical purposes during childhood or young age are at high risk [Preston et al., 2002].

GENETIC FACTORS

Gender:

Breast Cancer is about 100 times more common among women than men [Lupulescu,1993]. This is because of the fact that cells are constantly exposed to growth-promoting effects of the female hormones estrogen and progesterone. Simply being a woman is the main risk factor for developing breast cancer [Jennifer et al., 2000].

Age:

The chance of getting breast cancer goes up as a woman gets older [Jennifer et al., 2000]. About 1 out of 8 invasive breast cancers are found in women younger than 45, while about 2 out of 3 invasive breast cancers are found in women at an age 55 or older.

Breast cancer:

A previous case of breast cancer increases the risk of another occurrence by about 3 to 4 times. [Hartmann et al., 2005].

GENES IMPLICATED IN BREAST CANCER

Several genes have been co-related with the cause of breast cancer. These are as follows-

BRCA1 and BRCA2:

These genes are recognized as tumor suppressor genes. They follow autosomal dominant pattern of inheritance. Loss of heterozygosity at relevant gene locus is seen in several cases [Wooster et al., 1995]. Most common mutation associated with these genes is truncating mutation. In some cases mis-sense mutation is also seen. Although loss of heterozygosity is frequently at the *BRCA1* or*BRCA2* locus, it has been reported that the retained allele is almost wild-type in case of sporadic breast cancer [Lancaster et al., 1998].Cancer risk in *BRCA* gene mutation carriers may be increased modestly in other organs, but, highly penetrate, early-onset, site specific cancer is restricted to the breast and ovary.

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p53:

Except for the case of Li- Fraumeni syndrome, p53 mutations are rare in case of breast cancer. The presence of germline p53 mutations in approximately half of the families with classic Li-Fraumeni syndrome was reported [Malkin et al., 1990]. Those women with germline p53 mutations who survive childhood cancers, it is estimated that 50% will have developed breast cancer by the age of 50 [Easton et al., 1993].

STK11/LKB1:

STK11/LKB1is a serine-threonine kinase located on chromosome 19q13.3 [Antonioul and Easton, 2006]. Peutz-Jeghers syndrome is caused by germline mutations in STK11/LKB1 and is characterized by polyps in the small bowel and pigmented macules of the buccal mucosa, lips, fingers and toes. Patients with this syndrome have displayed early-onset breast cancer.

MSH2/MLH1:

Muir-Torre syndrome is defined by the presence of sebaceous gland tumours and visceral malignancy. It is inherited in an autosomal dominant fashion [Schwartz and Torre, 1995]. Breast cancer occurs in approximately 25% of women carriers.

THE UBIQUITINATION PATHWAY

Ubiquitination is the process of targeting the proteins for assembly into complexes, transport and many essential processes (Freemont, 2000]. In this process action of three enzymes cause covalent attachment of a polypeptide chain called ubiquitin to protein substrates. These enzymes are named – Ubiquitin-activating enzyme (E1), Ubiquitin-conjugating enzyme (E2) and Ubiquitin-protein ligase (E3).

Mechanism-

1.The E1 enzyme activates ubiquitin in an ATP-dependent manner and forms a high-energy thioester linkage with the carboxyl group of ubiquitin.

2.The activated ubiquitin is then transferred to the E2 enzyme.

3.Ubiquitin is conjugated to the ε-amino group of an internal lysine residue in the substrate protein with the help of an E3 ligase enzyme [Jentsch and Pyrowolakis, 2000].

THE DEUBIQUITINATION PATHWAY

Regulation of the abundance or functional activity of target proteins is maintained by the deubiquitinating enzymes (DUBs). These enzymes catalyze the cleavage of covalently attached mono- or polyubiquitin

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chains from the substrate protein [Massoumi, 2010]. The deubiquitination process is also involved in numerous cellular functions, such as cell cycle regulation, proteasome- and lysosome-dependent protein degradation, gene expression, DNA repair and kinase activation [Sowa et al., 2009]. The human genome encodes approximately 95 DUBs, which have been divided into five major classes: ubiquitin-specific proteases (USP), ubiquitin C-terminal hydrolases (UCH), ovarian tumour proteases (OTU), Josephins, and the Jab1/MPN/MOV34 metalloenzymes (JAMM, also known as MPN1) [Aressy et al., 2010]. Dysregulation of components involved in the ubiqutin or deubiquitin pathway have been associated with many different human diseases, including cancer [Hussain et al., 2009].

MECHANISMS OF BRCA-MEDIATED BREAST CANCER FORMATION

In 1990, the first breast cancer susceptibility gene BRCA1 was identified on chromosome 17q12-21 by linkage analysis of multiple families affected by early onset breast and ovarian cancer. BRCA1 is large spread over 80 kb genomic DNA composed of 24 exons, 22 codings and 2 non-coding exons that are transcribed into a 7.8 kb mRNA encodes a protein containing 1863 amino acids [Wooster et al., 1994]. The approximate molecular mass of the BRCA1 protein is 220 kDa [Gudmundsson et al., 1995]. The BRCA1 gene bears no homology with other genes, with the exception of a RING finger motif at the amino-terminal end. In other proteins such a motif has been shown to interact with nucleic acids and to form protein complexes, suggesting a role of BRCA1 in transcription. Nuclear localization sequence in exon 11, and a conserved acidic carboxy terminus, the BRCT (BRCA1 carboxyl terminal) domain. Till date, more than 800 different mutations mostly frame shift mutations in the BRCA1 gene have been reported. BRCA1 gene contains N-terminal RING finger domain and two C-terminal BRCT (BRCA1-C-Terminal) domain, both involved in protein-protein interactions. Exon 11 of BRCA1 gene contains over 60% of protein and encodes two putative localization signals, also contain a domain that interacts with RAD51, a homology of *E. coli* rec. a involved in DNA damage repair. BRCA1 was associated and co-purified with RNA polymerase complex, and interacts with RNA helicase in a transcription [Futreal et al., 1994]. Germline mutation in BRCA1 has been detected in approximately 80-90% of familial breast/ovarian cancer and about 45-50% of familial breast cancer alone [Futreal et al., 1994]. BRCA2 was the second gene identified as breast and/ovarian cancer susceptibility gene to be discovered [Knudson, 1971]. BRCA2 contains eight repeats of the ~40 residue BRC motifs. Six of the eight motifs in human BRCA2 can bind directly to RAD51 when expressed in vitr*o*. BRCA2 plays an important role in the error-free repair of DNA double strand breaks as well as transcriptional regulation [Beger et al., 2001]. In normal cells, BRCA2 ensures the stability of the DNA and helps to prevent uncontrolled cell growth. BRCA2 mutations have been characterized in different populations worldwide, with significant variation

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of the relative contribution of these genes to hereditary cancer between populations.[Beger et al., 2001]. Various population-based studies have shown population specific BRCA2 founder mutations and also variable number of novel mutations in different populations, and thus have defined high and low risk subsets for developing breast cancer based on ethnic origin [Esteller et al., 2000].

Discussion:

Breast cancer is the most dangerous disease in the world particularly in developing country. Although having regular screening tests of breast cancer is important aspect to avoid this disease. It is also suggested that to be aware of changes in the breasts should also be noticed. According to the American cancer society's breast cancer is the second leading cause of death in females. It was estimated that in India from 2013 to 2017 the death rate is about 1 in 38. So in this concern, our review will help the people to aware about the breast cancer and its mechanism.

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