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Epidemiology of Genetic Alterations in Progression of Breast Cancer

Naga Anusha P*

Department of Biotechnology, Sri Y.N. College, Andhra University, Narsapur, India

Abstract

Breast cancer is the most frequent cancer in women responsible for almost 20% of all cancer deaths. Certain aberrations in the genes results higher risk in the development of breast cancer. The present review aims to consolidate a comprehensive role of different genes involved in the development of breast cancer. This helps to know the intracellular molecular changes in tumorigenic pathways within the mammary gland.

Keywords: Breast Cancer; Alleles; Mutations; Tumor; Genes; Chromosomes

Abbreviations: BRCA1: Breast Cancer type 1 susceptibility protein; BRCA2: Breast Cancer type 2 susceptibility protein; CDH1: cadherin 1, type 1, E-cadherin (epithelial); PPAR: Peroxisome Proliferator-Activated Receptors; PTEN: Phosphatase and Tensin homolog; p53: Tumor Suppressor Protein 53; AR: Androgen Receptor; ATM: Ataxia Telangiectasia Mutated; BARD1: BRCA1-associated RING Domain 1; BRIP1: BRCA1 interacting protein C-terminal helicase 1; CHEK2: Check point Kinase 2; DIRAS3: DIRAS family, GTP-binding RAS-like 3; ERBB2: v-erb-b2 erythroblastic leukemia viral oncogene homolog 2; NBN: Nibrin; PALLB2: Partner and Localizer of BRCA2"

Introduction

Breast cancer is the most frequent cancer in women and represents the second leading cause of cancer death among women [1,2]. Breast cancer is a disease in which certain cells in the breast become abnormal and multiply without control or order to form a tumor [3]. The most common form of breast cancer begins in cells lining the ducts that carry milk to the nipple. Other forms of breast cancer begin in the glands that produce milk or in other parts of the breast. As the cancer progresses, signs and symptoms can include a lump or thickening in or near the breast; a change in the size or shape of the breast; nipple discharge, tenderness, or retraction and skin irritation, dimpling, or scaliness [4].

Breast cancer spreads when breast cancer cells move to other parts of the body through the blood vessels and lymph vessels [5-7]. This is called metastasis [8,9]. Breast cancer most commonly spreads to the regional lymph nodes. The lymph nodes can be axillary, cervical, or supraclavicular. When it spreads further through the body, it most commonly spreads to the bones, lungs, and liver. Less commonly, breast cancer may spread to the brain. The cancer can also recur locally in the skin, in the same breast, other tissues of the chest, or elsewhere in the body [10-12].

Genes Related to Breast Cancer

Cancers occur when a buildup of genetic mutations [13,14] in critical genes, those that control cell growth and division or the repair of damaged DNA, allow cells to grow and divide uncontrollably to form a tumor. Many cancers begin when one or more genes in a cell are mutated (changed), creating an abnormal protein or no protein at all. The information provided by an abnormal protein is different from that of a normal protein, which can cause cells to multiply uncontrollably and become cancerous [15,16]. A person may either be born with a genetic mutation in all of their cells or acquire a genetic mutation in a single cell during his or her lifetime [17]. An acquired mutation is passed on to all cells that develop from that single cell. Most of the breast cancers were considered as sporadic, only 5 -10% cancers are inherited [18,19]. Most inherited cases of breast cancer are associated with two abnormal genes: BRCA1 (BReast CAncer gene one) and BRCA2 (BReast CAncer gene two) [20].

Genes Developing the Risk of Breast Cancer

The most susceptible cause for breast cancer is due to small number of highly penetrated mutations such as BRCA1 and BRCA2 and much larger number of lower penetrates [21]. Some inherited mutations also increase the breast cancer risk. Deleterious mutations in the cell cycle regulator protein CHEK2 are associated with a 2-fold increase in breast cancer [22,23]. Inherited mutations of p53 and PTEN are very rare but when they occur they associate with high risks in onset of breast cancer [24].

BRCA1

The BRCA1 gene is located in the q arm of 17th chromosome at position 21. It belongs to class of Tumor suppressor genes; it is involved in repairing damaged DNA. Mutations in the BRCA1 and BRCA2 genes lead to an increased susceptibility to breast, ovarian, colon [25,26] and other cancers. It is estimated that 3%-8% of all women with breast cancer will be found to carry a mutation in 1 of these genes [27]. Germline mutation in Breast cancer susceptibility gene (BRCA1) leads to susceptibility for hereditary breast and ovarian cancer with a genotype and phenotype correlation [28]. Till now 127 mutations were discovered in BRCA1 gene that leads to breast cancer [29]. The mutations include an 11-base pair deletion, a 1-base pair insertion, a stop codon, a missense substitution, and an inferred regulatory mutation. The BRCA1 gene is expressed in numerous tissues, including breast and ovary, and encodes a predicted protein of 1863 amino acids. This protein contains a zinc finger domain in its amino-terminal region, but is otherwise unrelated to described proteins [30].

BRCA1 has been implicated in DNA damage repair. The repair

***Corresponding author:** Naga Anusha Puvvada, Department of Biotechnology, Sri Y.N. College, Narsapur, India E-mail: anushanpuvvada@gmail.com

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function may be carried out by the BRCA1 11–containing isoforms, since BRCA1 interacts with RAD51 through a domain encoded by exon 11. If the deletion of this exon results in an accumulation of unrepaired DNA damage, it leads to chromosomal aberrations. The pathological BRCA allelic variants may cause alteration of protein function, transcriptional activity and DNA repair; accumulation of the defects leads to widespread chromosome instability that may be directly responsible for cancer formation. The functional inactivation of both copies of this gene in sporadic tumor cells does not follow the traditional mode: the loss of function in BRCA1 is not accompanied by underlying mutation of the gene in tumor cells with loss of heterozygosity for the BRCA1 gene [31]. The genetic instability in BRCA1 is due to combination of defects in DNA damage repairs, loss of G2-M checkpoint and centrosome amplification [32].

BRCA2

The BRCA2 gene is located on the long (q) arm of chromosome 13 at position 12.3. Mutations in the *BRCA2* gene are one of the two major causes of hereditary breast cancer. mRNA of BRCA2 gene encodes a polypeptide of 3814 amino acids with no sequence similarity with any other known protein. Protein-truncating mutations of BRCA2 are usually deleterious and increase the risk of breast cancer up to 80% over a lifetime. A few missense mutations in *BRCA2* are believed to have a similarly high penetrance, apart from more common neutral polymorphisms [33]. BRCA2 mutations have also been associated with a range of other malignancies, including cancer of the ovary, prostate [34], pancreas, melanoma, gallbladder and stomach. Inherited mutations in the recently discovered BRCA2 gene are believed to be responsible for a significant fraction of early-onset hereditary breast cancers. Unlike BRCA1, however, which confers a high risk to both breast and ovarian cancer, the incidence of ovarian cancer appears to be much lower In BRCA2-linked families, causing uncertainty as to the relevance of BRCA2 to hereditary ovarian cancer [35].

CDHI

The official name of this gene is "cadherin 1, type 1, E-cadherin (epithelial)". The CDH1 gene is located on the long (q) arm of chromosome 16 at position 22.1. The CDH1 gene provides instructions for making a protein called epithelial cadherin or E-cadherin. Cadherins are a group of proteins on the surface of cells that help neighboring cells stick to one another (cell adhesion). These proteins bind cells together to form organized tissues. Inherited mutations in the CDH1 gene increase a woman's risk of developing a form of breast cancer that begins in the milk-producing glands (lobular breast cancer) [36]. In many cases, this increased risk occurs as part of a cancer syndrome called hereditary diffuse gastric cancer (HDGC) [37]. This condition is characterized by a very high risk of developing cancer of the stomach lining as well as an increased risk of lobular breast cancer. Lobular carcinoma of the breast accounts for 10-15% of breast cancer cases and has a distinctive histology characterized by a diffuse growth pattern that is due to loss of cell cohesiveness. E-cadherin-mediated adhesion is essential for maintaining normal epithelium, since its dysfunction is intimately related to malignancy. CDH1 is considered as tumor suppressor and its loss demonstrated invasion of tumors. There are several mechanisms for CDH1 expression in breast cancer. Allelic loss at 16q22.1 is one of the cytogenetic aberration and most frequent in breast cancer, but somatic E-CD mutations are only frequent in the lobular histotype [38]. Transcriptional repression of E-CD by promoter hypermethylation has also been reported in breast tumors and cell lines. Moreover, the presence of a single nucleotide polymorphism (SNP) located at the -160 site of *CDH1* promoter has been recently described as affecting E-CD transcription in vitro.

PTEN

The PTEN/MMAC1/TEP tumor suppressor gene at 10q23.3 is mutated in multiple types of sporadic tumors including breast cancers. The PTEN gene encodes a multifunctional protein phosphatase capable of dephosphorylating the same sites in membrane phosphatidylinositals phosphorylated by phosphatidylinositol 3'-kinase (PI3K). Loss of PTEN function leads to increase in phosphorylation of P13K signaling cascade which leads to breast cancer [39]. Activation of PPARγ- ligand associated transcription factor, through agonists increases functional PTEN protein levels that subsequently induces apoptosis and inhibits cellular growth, which suggests that PPARγ is a tumor suppressor as it regulates function of PTEN [40,41].

p53

The p53 gene is located on the seventeenth chromosome (17p13.1), also known as TP53- "Tumor Protein 53", which regulates the cell cycle and hence functions as a tumor suppressor protein. Defective p53 allows abnormal cells to proliferate resulting in cancer. 50% of all tumors contain p53 mutants. If p53 is damaged, tumor suppression is severely reduced [42]. Over expression of the nuclear phosphoprotein p53 is one of the most common abnormalities in primary human cancer and appears to be due to point mutation within a highly conserved region of the p53 gene which then encodes for a mutant, more stable protein [43]. Some experiments indicated that p53 inhibits expression of an inhibitory apoptosis protein survivin. Mutation in p53 leads to over expression of survivin which inhibits apoptosis and leads to tumors [44]. Various strategies have been proposed to restore p53 function in tumor cells [45].

Genes Associated with Breast Cancer

Apart from the above discussed genes there were some genes which are associated with breast cancer [46,47]. The activity of these genes could have effect on tumor suppressor proteins [48,49]. These genes play important role as biomarkers in diagnosing cancer [50-52].

AR

AR gene also known as "Androgen Receptor" gene is located on q arm of X chromosome at position 12. AR gene provides instructions for making a protein called Androgen Receptor. These receptors allow the body to respond appropriately to male sexual hormones that are important for normal male sexual development before birth and during puberty. In AR gene, a DNA segment known as CAG is repeated multiple times. Researchers have considered a possible relation between the lengths of CAG repeated region in an AR gene and a chance of developing breast cancer [53]. Testosterone binds to the androgen receptor in target tissue to mediate its effects. Variations in testosterone levels and androgen receptor activity may play a role in the etiology of breast cancer [54]. Mutations in the androgen receptor (AR) gene have been suggested to predispose to male breast cancer (MBC) [55]. Little is known regarding AR in human breast cancer.

ATM

ATM known as "Ataxia Telangiectasia Mutated" is located on long q arm of chromosome 11 between the positions 22 and 23. It instructs for making proteins inside the nucleus where it helps to control the

growth and division of cells. It recognizes the damaged DNA and repairs it by activating enzymes that fix on DNA strands [56]. People who have one copy of ATM gene are associated with an increased risk in developing breast cancer [57]. Cells that are missing one copy of the ATM gene produce half the normal amount of ATM protein. A shortage of this protein prevents efficient repair of DNA damage, leading to the accumulation of mutations in other genes [58]. This buildup of mutations is likely to allow cancerous tumors to develop. Many studies have tried to clarify the role of ATM in breast cancer susceptibility, but have produced inconclusive and/or inconsistent results.

BARD1

BARD1 known as "BRCA1-associated RING Domain 1" is located on long q arm of chromosome 2 positioned between 34 and 35. It helps in growth and function of cell.BRAC1 which is normally regulated by protein turnover is stabilized by BARD1 which recruits BRCA1 to nucleus to form ubiquitin E3 ligase complex which is involved in DNA repair. BARD1 regulates BRCA1 depended apoptosis by a mechanism involving nuclear sequestration [59,60]. Regulation of apoptosis by BARD1 was reduced by BRCA1 cancer mutations that disrupt Ub ligase function [61]. BRCA1-BARD1 preferentially utilizes ubiquitin [62] with a single Lys residue at Lys-6 or Lys-29 to mediate autoubiquitination of BRCA1. Transfection of BRCA1 N-terminal peptides that disrupted the cellular BRCA1-BARD1 interaction caused a loss of nuclear BRCA1 that correlated with increased apoptosis. Reducing the BARD1 levels by SiRNA caused small increase in apoptosis [63-65].

BRIP1

BRIP1 known as "BRCA1 interacting protein C-terminal helicase 1" is located on long q arm of chromosome 17 at position 22.2. Mutations occur in one copy of the gene in each cell and lead to the production of an abnormally short, nonfunctional version of the BRIP1 protein [66,67]. If this protein is defective or missing, it is unable to interact with the BRCA1 protein to repair damaged DNA effectively. As defects accumulate in DNA, they can trigger cells to grow and divide uncontrollably and form a tumor. Inactivating and truncating mutations of the nuclear BRCA1-interacting protein 1 (BRIP1) have been shown to be the major cause of Fanconi anaemia and, due to subsequent alterations of BRCA1 function, predispose to breast cancer. The newly identified BRIP1 c.2992-2995delAAGA mutation is associated with instability and functional impairment of the encoded protein; provide further evidence of a breast cancer-related role for BRIP1 [68,69].

CHEK2

CHEK2 known as "Check point Kinase 2" is located on long q arm of chromosome 22 at position 11. It translates a protein called tumor suppressor which regulates cell division by keeping cells from growing too rapidly and uncontrollably. Single nucleotide mutation at 1100 in CHEK 2 gene leads to the production of abnormally short, non functional CHEK2 protein [70]. This is unable to regulate cell division properly as a result DNA damage accumulates and cells division is not tightly controlled which leads to cancer development. CHEK2 phosphorylates p53 and BRCA1 in response to DNA damage. A protein-truncating mutation, 1100delC in exon 10, which abolishes the kinase function of CHEK2, has been found in families with Li-Fraumeni syndrome (LFS) and in those with a cancer phenotype that is suggestive of LFS, including breast cancer.

DIRAS3

DIRAS3 known as "DIRAS family, GTP-binding RAS-like 3" is located on short p arm of chromosome 1 at position 31. It is a member of large family of genes known as RAS genes which control cell growth and maturation [71]. The DIRAS3 protein differs from other proteins in the RAS family in that it suppresses the growth of cells, whereas other RAS family proteins encourage cell growth. DIRAS3 is drastically down regulated in breast cancer and sometimes cells may have only one working copy of DIRAS3. Without enough expression of this protein cells divide uncontrollably which leads to progression of tumors. DIRAS3 is down regulated by transcriptional mechanisms that involve E2F1 and E2F4, as well as by the loss of RNA binding proteins that decrease the half-life of ARHI mRNA. Treatment with CpG demethylating agents and/or HDAC inhibitors reactivated both the silenced and the imprinted *DIRAS3* alleles, and activation correlated with a concomitant increase in H3-K9/18 acetylation and a decrease in H3-K9 methylation.

ERBB2

ERBB2 known as "v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog" is located on long q arm of chromosome 17 at position 11.2 and 12. Errors in the replication process can result in multiple copies of a gene on a chromosome. The presence of multiple gene copies, known as gene amplification, can underlie the formation and growth of tumor cells depending on which gene is amplified [72]. Amplification of the ERBB2 gene is found in about 25 percent of breast cancers. Extra copies of this gene cause too much of the ErbB2 receptor protein to be made in the cell (over expression). Excess ErbB2 protein signals cells to grow and divide continuously, which can contribute to the growth of cancerous tumors [73,74]. Over expression of ErbB2 is associated with aggressive breast tumors that are more likely to spread to other tissues.

NBN

NBN known as "Nibrin" is located on long q arm of chromosome 8 at position 21. It is involved in critical cellular functions and plays role in DNA repair. It interacts with proteins named as MRE11A and RAD50 to form large protein complex. The MRE11A/RAD50/NBN complex interacts with the protein produced from ATM gene which plays important role in recognizing broken strands of DNA [75]. By repairing damaged DNA and regulating cell division. As these are critical for preventing tumors NBN is described as Tumor Suppressor gene. Studies suggested that deleterious mutation in may confer an increased risk of breast cancer by 2-3fold [76]. *NBN* sequence variations indicated that potential *NBN* alterations are present, albeit at a low frequency, of high-risk breast cancer cases.

PALB2

PALB2 known as "partner and localizer of BRCA2" is located on p arm of chromosome 16 at position 12.2. It translates a protein called partner and localizer of BRCA2 which interacts with a protein produced from BRCA2 gene. About 10 mutations in the PALB2 gene have been identified in people with familial forms of breast cancer. Monoallelic PALB2 truncating mutations were shown to confer higher risk of breast cancer [77]. These mutations occur in one copy of the gene in each cell and result in the production of an abnormally short version of the PALB2 protein. This cannot interact with protein produced by BRCA2 and cannot repair damaged DNA. This defect triggers the cells to grow and divide uncontrollably with 2-fold increase in breast cancer.

RAD50

RAD50 known as "RAD50 homolog (*S. cerevisiae*)" is located on chromosome 5 at position 31. This protein together binding with MRE11A and NBN involves in repairing of damaged DNA and helps to maintain genetic information. RAD50 mutations can lead to the production of an abnormally small, nonfunctional version of the RAD50 protein which leads to tumors.

RAD51

RAD 51 known as "RAD51 homolog (*S. cerevisiae*)" is located on chromosome 15 at position 15.1. RAD51 protein interacts with many other proteins, including BRCA1 and BRCA2, to fix damaged DNA. The BRCA2 protein regulates the activity of the RAD51 protein by transporting it to sites of DNA damage in the nucleus [78,79]. Several alterations in the RAD51 gene have been associated with an increased risk of developing breast cancer [80]. Some of these genetic changes appear to modify breast cancer risk in women who also carry a mutation in the BRCA1 or BRCA2 gene.

Conclusion

Elucidation of the factors contributing to the incidence of breast cancer is of crucial importance for the development of therapeutic or preventative strategies targeting the disease. This review displays the complexity of tumor suppressor gene function and expression in breast cancer cells. Tumor suppressor genes are involved in a diversity of cellular processes such as cell cycle control, replication, recombination, signal transduction, repair, differentiation and aging. The identification and characterization of abnormalities of gene products in breast cancer might eventually lead to the design of treatment strategies that specifically target cell cycle checkpoints and apoptosis in cancer cells, without affecting normal cells, thereby leading to decreased death rate from cancer.

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