Genetic Basis and Risk Factors Associated with Breast Cancer

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Abstract- Most common cancer among the women is breast cancer, it contributes about 30% all the cancer patients. Amazingly it very rare in men, it effects only 1% of all cancers in men. About 10% of breast cancers are genetically inherited, due to inherited germ-line mutations in high penetrance moderate penetrance and low penetrance breast cancer susceptibility genes. The remaining 90% of breast cancers are due to acquired somatic genetic and epigenetic alterations. There are many genes that are responsible for the breast cancer. For analyzing whether common variants linked to differential allelic expression, a list of genes are established on the basis of their involvement in cancer related pathways and mechanisms. A heterogeneous set of somatic alterations, involving mutations and gene amplification, are documented to be including in the etiology of breast cancer. Elucidation of the inherited and acquired genetic and epigenetic changes included in breast cancer may not only clarify molecular pathways involved in the development and progression of breast cancer itself, but may also have an important clinical and therapeutic impact on improving the management of patients with the disease.

Index Terms- Breast cancer, Gene amplification, Somatic Mutations, BRACA1, BRACA2

I. Introduction

In USA, breast cancer is one of the leading reasons of mortality among women dying due to cancer. In 2016, the breast cancer positive patients were 231840 while 40450 patients died due to breast cancer in that year [1]. Every year, about one million new cases are reported worldwide. Hereditary breast cancer makes up 5-10% of all breast cancer and is defined with autosomal dominant and recessive inheritance pattern. Every year, 14000 deaths occur worldwide due to this cancer and this mortality rate is increasing in the women of ages ranging 60-64, as most of the time breast cancer is diagnosed in women in this age group [2].

The prevalence of this disease is reported to be 2%. According to a report of WHO, 20% increase in breast cancer patients has been documented all over the world and it has become one of the most common death causes in females causing about 522000 reported deaths since 2008. According to USA's National Cancer Institute, there are about 40,000 deaths each year from the resulting cases of breast cancer of 232000 in USA. Breast cancer is not gender specific as mutation and deregulation in some genes including PIKC3A, BRCA1, BRCA2 and HER2 play significant roles in breast cancer [3].

Early onset of breast tumors has been often linked with BRCA1 and BRCA2 genes. Breast cancer development is also influenced by inherited mutations in some other genes. Excessive rate of breast cancer is also linked to CHEK2 mutation. After diagnosis to find the causal mutation, cancer can be stopped by performing prophylactic mastectomy. Deregulation or mutation of the genes TP53, RB, MDM2 also play important roles in therapeutic responses to breast cancer. There reasons have made breast cancer one of the major public health problems. Increased prevalence in breast cancer is expected in the upcoming 20 years, despite the current efforts to fight and prevent it [4] and the efforts made to eradicate it the last decade.

The susceptibility genes linked to breast cancer are classified into three classes, which have different levels of risk in the population [5].

TABLE 1: TYPES OF GENES AND THEIR CHROMOSOMAL LOCATION

GENE TYPE	LOCATION		TYPE OF MUTATION	EFFECTS
BARD 1	Chromosome	2	Missense mutation	Lethal
	Start(bps)	214,725,646		
	End(bps)	214,809,711		
BRCA 1	Chromosome	17	Missense mutation Frameshift mutation Silent mutation	Harmful
	Start(bps)	43,044,295		
	End(bps)			
BRCA 2	Chromosome	13	Missense mutation Frameshift mutation	Harmful
	Start(bps)	32,315,474		
	End(bps)	32,400,266		

			Silent mutation	
PALB 2	Chromosome	16	Frameshift mutation Non sense mutation	Harmful
	Start(bps)	23,603,160		
	End(bps)	23,641,310		
TP53	Chromosome	17	Point mutation	Lethal
	Start(bps)	7,661,779		
	End(bps)	7,687,550		
GATA 3	Chromosome	10	Frameshift mutation	Lethal
	Start(bps)	8,045,378		
	End(bps)	8,075,203		

II. INHERITED SUSCEPTIBILITY TO BREAST CANCER

About 5%of breast cancer cases are caused by germline mutations in high penetrate genes within families out of which 10-15% cases are due to the germline mutations in BRCA1 and BRCA2 genes only. The few other genes in which mutations contribute to the development of breast cancer are PTEN, CDH1, TP53 and STK11 but compared to BRCA1/2, TP53 mutations are fewer. For the identification of the high penetrance genes BRCA1/2 of breast cancer susceptibility, successful implementation of linkage study followed by positional cloning has been done as they are considered the major genes related to breast cancer although other genes are also found to be significant. Like NF1, which is also a high penetrant gene that causes Neuroectodermal disorder, which is characterized by autosomal dominant inheritance pattern [6].

- ***Role of BRCA1 and BRCA2***

BRCA1/2 play very significant role in tumor development because they respond to DNA damage and have a functional role in homologous recombination. BRCA1 is a large sequenced gene on the 17th chromosome containing 24 exons out of which 22 are codons for proteins while 2 are non-coding. BRCA2 is larger than BRCA1 as it has 70,000 bases and it contains 27 exons. Frameshift or nonsense mutations causes premature cutting or truncations of the BRCA1/2 which is the predominant genomic anomaly underlying susceptibility. The BRCA1 gene has a large number of Alu repeating units which causes structural variations in BRCA1 as compared to BRCA2 gene. The mapping of BRCA1 gene showed that genetic variations in BRCA1 on chromosome 17q21 leads to development of inherited breast cancer. The mutated areas of BRCA1/2 genes and the danger from these modified genes recommend that in the most astonishing hazard type, the BRCA1 variation carriers may have 81% or more possibility of causing breast cancer and a 63% or more risk of ovarian disease by the age of 80. While BRCA2 mutation carriers at the most serious hazard might have an 83% possibility of breast cancer by the age of 80 [7].

- ***BRCA1 and BRCA2 mutation in women***

By the age of 70, germline mutations in BRCA1/2 in women poses a higher risk of developing breast cancer. initial examinations of some case families showed that chances of breast cancer in females due to mutations in BRCA1 and BRCA2 are 85% and 84% respectively [6], while in males the mutations are more common in BRCA2; 60-70% of all breast cancer in males in high risk families is due to germline mutation in BRCA2 while mutation frequency in BRCA1 is from 10 to 16% [8].

- ***Role of TP53 in Breast Cancer***

Tp53 mutations are less than BRCA1/2. However, in cases with a strong family history, if testing for BRCA1/2 mutation identification does not reveal anything, is not determining or negative, TP53 testing is recommended. TP53 gene encodes for the tumor suppressor protein, p.TP53. Mutations in TP53 increases the risk of breast cancer in patients. Genomic alterations in TP53 also cause a multi-cancer predisposing syndrome called Li-Fraumeni syndrome(LFS). Studies about the predictive and prognostic role of TP53 alterations in breast cancer have given conflicting results. Two methods have been employed to evaluate TP53 alterations; DNA sequencing and IHC (Immune Histochemistry). Most mutations in Tp53 are point mutations that lead to the synthesis of a protein that is stable, non-degradable, malfunctional and accumulates in tumor cells, thus, become detectable by IHC. The correlation of TP53 accumulation detection by IHC and mutation in TP53 detection by sequencing is less than 75% in breast cancers. Patients that are at a young age seems to have a higher recurrence of mutations in TP53 in the tumor cells. TP53 plays significant role in many cellular activities that directly affect tumor suppression such as cell-cycle control and DNA repair as well as other activities like glycolysis and mitochondrial respiration [9].

- ***Role of CDH1 in Breast Cancer***

Germline mutations in CDH1 causes hereditary diffuse gastric cancer but there have been reports that germline mutations in CDH1 have also been assessed in patients of breast cancer. CDH1 is located on chromosome 16q22.1, a region often associated with loss of heterozygosity in breast cancer and encodes for a transmembrane glycoprotein, E-cadherin, important in maintaining hemophilic cell-to-cell adhesion in epithelial cells. In breast cancer, E-cadherin gene (CDH) loses heterozygosity, which is associated with the loss of function in this tumor suppressor gene and also co-relates with decreased disease free survival, poor prognosis, metastasis and loss of gene expression as a result of CpG island methylation in the promotor region of CDH1 gene. This leads to the loss of tissue integrity, which is essentially leads to development of tumor. Reduced expression of CDH1 leads to dysfunction of cell-to-cell adhesion, which has key importance in cancer invasion and metastasis [11].

- ***Role of STK11 in Breast Cancer***

STK11 acts as an important regulator of cell proliferation and apoptosis by multiple signaling pathways. It is also a tumor suppressor gene. STK11 regulates mammalian target of rapamycin (mTOR) which is a major downstream pathway. The first mTOR substrat is the ribosomal protein S6 kinase 1 (S6K1) and it is the most studied effector of mTOR complex 1 (mTORC1). mTORC1 mediated phophorylation activates S6K1 whose activity improves toward S6 substrate. Signlas from this

activation of S6K1 are involoved in various cellular activities like protein translation, angiogenesis, cell growth and metabolism. Mutations in STK11 inactivates itd endogenous activity that negatively regulates mTORC1 signaling that ultimately results in phosphorylation and activation of downstream targets. This relieve inhibition on protein synthesis, promoting cell growth and tumorigenesis [13].

III. MODERATE PENETRATE GENES

Overall, less than 10% of breast cancer are because of mutations in breast cancer susceptibility genes BRCA1/2. Mutations found in this class of genes pose lesser of a risk of breast cancer than BRCA1/2 mutations, and because of their rarity are not easily detectable in a population. Mutations in moderate penetrate genes pose less than 3% of a risk if familial breast cancer. Moderate penetrate genes include CHEK2, BRIPI, ATM, PALB2 and RAD50 but these genes confer far less than 5% risk of genetic breast cancer [14].

- ***Role of CHEK2***

The first moderate risk allele of breast cancer identified was CHEK1100delC which was associated with a fivefold risk of breast cancer in familial cases and twofold risk in cases unselected for family history. Mutations in CHEK2 gene pose a tenfold risk of breast cancer in males with negative BRCA1/2 mutations and account for 9% of high-risk familial breast cancer cases in males. The contribution of CHEK2 mutation to breast cancer development varies by ethnic group and from country to country. A reduced recurrence in CHEK2 mutation in both males and females is observed in North to South orientation in Europe [15].

Mutational screening of the whole CHEK2 gene sequence is done to identify CHEK2 1100delC mutation as a breast cancer associated allele although only a small number of very rare missense variants and truncating mutations have been reported in CHEK2 in breast cancer cases [16].

- ***Role of ATM***

Epidemiological studies that reported an increased breast cancer risk in an ataxia telangiectasia patient's relatives first proposed ATM to be a breast cancer susceptibility gene. Ataxia telangiectasia is a recessive syndrome caused by mutation in ATM gene but the evidencing molecular data was provided 20 years later. However. There is no data concerning the role of ATM mutation in males at risk of breast cancer [17].

- ***Role of PALB2***

PALB2 is a localizer and partner of the BRCA2 gene but it was initially identified as a BRCA2-interacting protein, which is crucial for BRCA2 genome caretaker function. Germline mutations that cause loss of function in PALB2 gives to predisposition to breast cancer. The truncating mutations in PALB2 causes a 2-3 fold increase in risk of breast cancer. Familial breast cancer with PALB2 mutations has been identified in many countries with frequencies from 0.6% to 2.7%. PALB2 mutations have been found in families with both male and female breast cancer cases suggesting that mutation in this gene may confer to the risk of breast cancer in males. To this day, five studies have given evidence of PALB2 mutations in breast cancer risk in males and it seems to have a role as moderate penetrate gene in breast cancer in males to a comparable extent than females. Reports show that PALB2 mutation carrier heterozygotes are 4 times more likely to have a male relative with breast cancer [18].

- ***Role of BRIP1 in Breast Cancer***

Deleterious mutations 1 are initially estimated to pose a twofold increased breast cancer risk and they account for 1% BRCA1/2 negative familial or early-onset breast cancer cases but recent studies showed that the contribution of BRIP1 to breast cancer risk is more limited than initially thought [19]. Only about eight BRIP1 truncating mutations in 11 negative BRCA1/2 mutation cases of breast cancer have been identified all over the world from three independent studies [20].

- ***Role of RAD51C in Breast Cancer***

Recently, mutations in another gene called RAD51C are reported to be a breast cancer susceptibility allele. This gene is associated with Fanconi anemia and the its mutation accounts for 1.3% of all breast cancer cases in females from families with at least one breast cancer and ovarian cancer case [21]. There is no evidence of contribution of RAD51C mutation in male breast cancer predisposition [22]. The identification of susceptibility genes of breast cancer especially BRCA1/2 has changed the ways of managing breast cancer patients with a family history. Several models for assessing pre-test probability of BRCA1/2 germline mutation identification have been designed for testing in individuals with high risk of hereditary breast and ovarian cancer. Further study of the breast cancer susceptibility genes, particularly BRCA1/2 will allow the elucidation and pathogenesis of this disease [23].

IV. CONCLUSION

Although great advances has been made in determining the etiology of this disease, but more investigation and study is necessary. Animal models should be used for this purpose. Recently, more attention has been focused on the use of whole-genome linkage disequilibrium studies for mapping out common disease genes, which use single nucleotide polymorphisms for detection of associations between a marker or gene and a particular disease condition. These single nucleotide polymorphisms are an abundant form of genetic variants and are distinguished form the rare variants in the way that the least abundant variant should have a frequency of 1% or more (166). The use of single nucleotide polymorphism in combination with other studies including animal model and genetic epidemiologic methodology will help in genetic analysis of complex diseases like breast cancer and has the capacity to yield a vast array of knowledge. These studies are crucial to evaluate the importance of new genes involved in breast cancer etiology, so that scientists can develop better therapies and prevention methods.

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