Review Article
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Genetic Mutations Associated with Breast Cancer in Pakistan

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ABSTRACT

Breast cancer is the most common malignancy in women worldwide. Various environmental and genetic factors are involved in breast carcinogenesis. Mutations in autosomal dominant genes account for 5-10% of breast cancer cases. It is also the most common female malignancy in Pakistan and account for 35.6% of all cancers in women. BRCA1 and BRCA2 are the key genes associated with familial and early-onset breast cancer in Pakistan. However, mutation in TP53, RAD51 and CHEK2 genes play the marginal role. In this review, the spectrums of genetic mutations associated with breast cancer in Pakistan are discussed in detail.

Key words: Breast Cancer, Genetic Mutation, Cell Cycle Regulation

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INTRODUCTION

Breast cancer is the most prevalent female malignancy worldwide with standardize incidence rate of 38.9, and accounting for a quarter of all cancer cases worldwide (Pimhanam et al., 2014). Once considered as the cause of mortality in economically developed countries, now breast cancer is frequently diagnosing in developing countries with higher incidence rate (Thun et al., 2009).With the emerging population age structure, rising life standard, control of epidemic diseases and population control has enhanced life expectancy the associated cancer susceptibility also enhanced (Bhurgri 2004).

Various environmental and genetic factors are involved in breast carcinogenesis (Moran 2011). However, environmental factors are more readily controlled than genetic and racial factors (Bhurgri 2004). The most common risk factors are excessive estrogen stimuli (Cheung 2007), higher birth weight (Silva et al., 2008), obesity (Zaman et al., 2012), over expression of leptin in adipose tissue (Wafa et al., 2014), and family history of breast and ovarian cancer (Hankinson 2008). However, 5-10% of all breast malignancy is due to genetic predisposition caused by mutation in autosomal dominant genes. Two types of genetic variation are involved in breast cancer, One is gain of function mutation in proto-oncogene, and second is loss of function mutation in tumor suppresser gene, this result in uncontrolled cell division and growth, failure of DNA repair mechanism, and disturbance of cell cycle check point. Women with inherited loss-of-function mutation have 70% risk of developing breast cancer before the age of 70 years (Loman et al., 1998).

The most prevalent cause of breast cancer is mutation in tumor suppressor genes BRCA1 and BRCA2 (Sheikh et al., 2015). Germ line mutation in BRCA 1 & 2 account for 16% of all hereditary breast malignancy (Van der Groep et al., 2011). Limited data is available on tumor protein (TP53), checkpoint kinase 2 (CHEK2), and Estrogen Receptor (ESR) mutations involvement in the development of breast cancer (Amir et al., 2010).

The incidence rate of breast cancer is lower in Asian countries as compared to Europe and America, but it showed increasing trend in current years (Afsharfard et al., 2013). Mutation studies of high penetrance genes are mostly based on Caucasians population; however, their allelic frequency may be higher in Asian population than in

Caucasians (Toh et al., 2007). Among Asian breast cancer patients, the prevalence of BRCA1 mutation is similar to that of BRCA2 or higher, with the exception of Pakistani and Indian breast cancer patients (Kim & Choi, 2013).

In Pakistan, Breast cancer is the most common female malignancy and account for 34.6% of all cancers in women (Bhurgri 2004). Research showed US-residing Pakistani and Indian women diagnosed with breast cancer before age 40 compared to Caucasians women (Kakarala 2010; Moran et al., 2011). For the control of any malignancy, it is indispensible to determine its genetic Predisposition. So understandings such genes, which are involved in tumor genesis and in its pathway is necessary for therapeutic targets to fight breast cancer. The literature regarding the spectrum of genetic mutation associated with breast cancer in Pakistan was reviewed. Each gene mutation was discussed individually and also how it leads the disease and its prevalence status among breast cancer patients in Pakistan.

BRCA1

Hereditary mutation in BRCA1 gene is associated with high risk of breast cancer in women of different age and ethnic group. This high penetrance gene shows loss-of-function germ line mutation in hereditary cases. In sporadic tumors, it shows decrease expression (McCoy etal., 2003). Hall et al., in 1990 showed the association of this gene with breast cancer during a pedigree study of early-onset breast cancer patients.

BRCA1 gene is positioned on the long arm of chromosome 17q and includes 22 exons (Hall et al., 1990; Miki et al., 1994). The protein molecule of this gene consists of 1863 aminoacid moieties(Miki et al., 1994). In human, this gene has four domains, one RING zinc finger domain, Two BRCT domains and one serine domain (Shuen & Foulkes, 2011). A RING zinc finger domain at the amino terminal of protein interacts with another RING domain containing protein called BARD. This interaction forms aBRCA1/BARD1 complex that carries E3 ligase activity and is responsible for ubiquitination (Chen et al., 2002).

Two BRCT repeats present at the carboxyl terminal, regulate transcriptional activation of reporter gene when attached to GAL 4 DNA binding domain(Chapman & Verma, 1996).In addition to binding with phospho-peptide which participate in DNA repair and cell cycle check points, the two BRCT repeats also interact with other protein such as RAP80, CCDC9, CtIP8 and BACH1 (Rodriguez and Songyang, 2008). Phosphorylation sites on the serine domain are phosphorylated by ATM kinases that become activated in case of DNA damage. So the BRCA1point out the DNA damage site (Clark, Rodriguez, Snyder, Hankins, & Boehning, 2012). Besides this, BRCA1 also interact with RAD51 and become phosphorylated, this interaction suggests the possible involvement of BRCA1 protein in recognition and recombination of double strand breaks (Van der Groep et al., 2011) (Figure).

Total 1639 mutations and polymorphisms have been identified in BRCA1 gene. The mutation in BRCA1 results in short protein unable to function (Van der Groep et al., 2011).

Four studies investigated the frequency of BRCA1/2 gene mutations in Pakistani patients. Liede et al. carried out a study at the National Cancer Institute, Karachi and Jinnah Hospital, Lahore in 2002. According to their study, out of the total 341 breast cancer patients investigated for genetic mutation, 4.4% (15 cases) showed mutation in BRCA1 gene (Liede et al., 2002). Rashid et al., 2006 carried out their study at Shoukat Khanum Memorial Hospital Lahore, described that 13% (23 cases) out of 176 breast cancer patients showed germ line mutation in BRCA 1 gene (Rashidet al., 2006). Malik et al., 2008 in COMSATS Institute of Information Technology Islamabad carried out a study on mutational analysis of BRCA1 gene. According to their findings, out of 150 sporadic breast cancer patents 0.67% showed BRCA1 mutation (Malik et al., 2008).Moatter et al., 2011 in Agha Khan University Karachi conducted a study on "BRCA1 status in Pakistani breast cancer patients with moderate family history", according to their result, 3(5.66%) out of 53 patients showed BRCA1 mutation (Moatter et al., 2011)(Table).

BRCA2

BRCA2 gene is positioned on long arm of chromosome 13q and consist 26 coding exons. It encode a large protein molecule comprise of 3418 amino acid moieties(Wooster et al., 1995). A 30-80 amino acid repeat BCC domain is present in the protein part encoded by exon 11 of the BRCA2 gene, and is the most outstanding characteristic of the BRCA2 protein (Warner et al., 2011). This BRC domain is the binding site for Rad51 protein (Walsh et al., 2010). The carboxyl terminal region of BRCA2 protein called TR2 is another binding site for Rad51 (Mizuta et al., 1997). This component of protein is believed to be associated with recombination repair (Davies & Pellegrini, 2007). PALB2 interact with amino acid terminus of BRCA2 protein in nuclear structures that increase the stability of BRCA2 (Xia et al., 2006). This helps in DNA repair at the S check point (Zhang et al., 2009). By interaction with Rad51 and DMC1 protein BRCA2 undertake homologues recombination at meiosis (Van der Groep et al., 2011). In 80% Breast cancer cases there is a link between loss of heterozygosity of the wild type of allele and breast cancer(Collins et al., 2000) (figure).

In one study, 7(3.9%) patients out of 176 breast cancer patients showed BRCA2 mutation (Rashid et al., 2006). Liede et al., (2002) sowed 8(2.3%) out of 341 patients diagnosed with BRCA2 mutation (Liede et al., 2002) (Table).

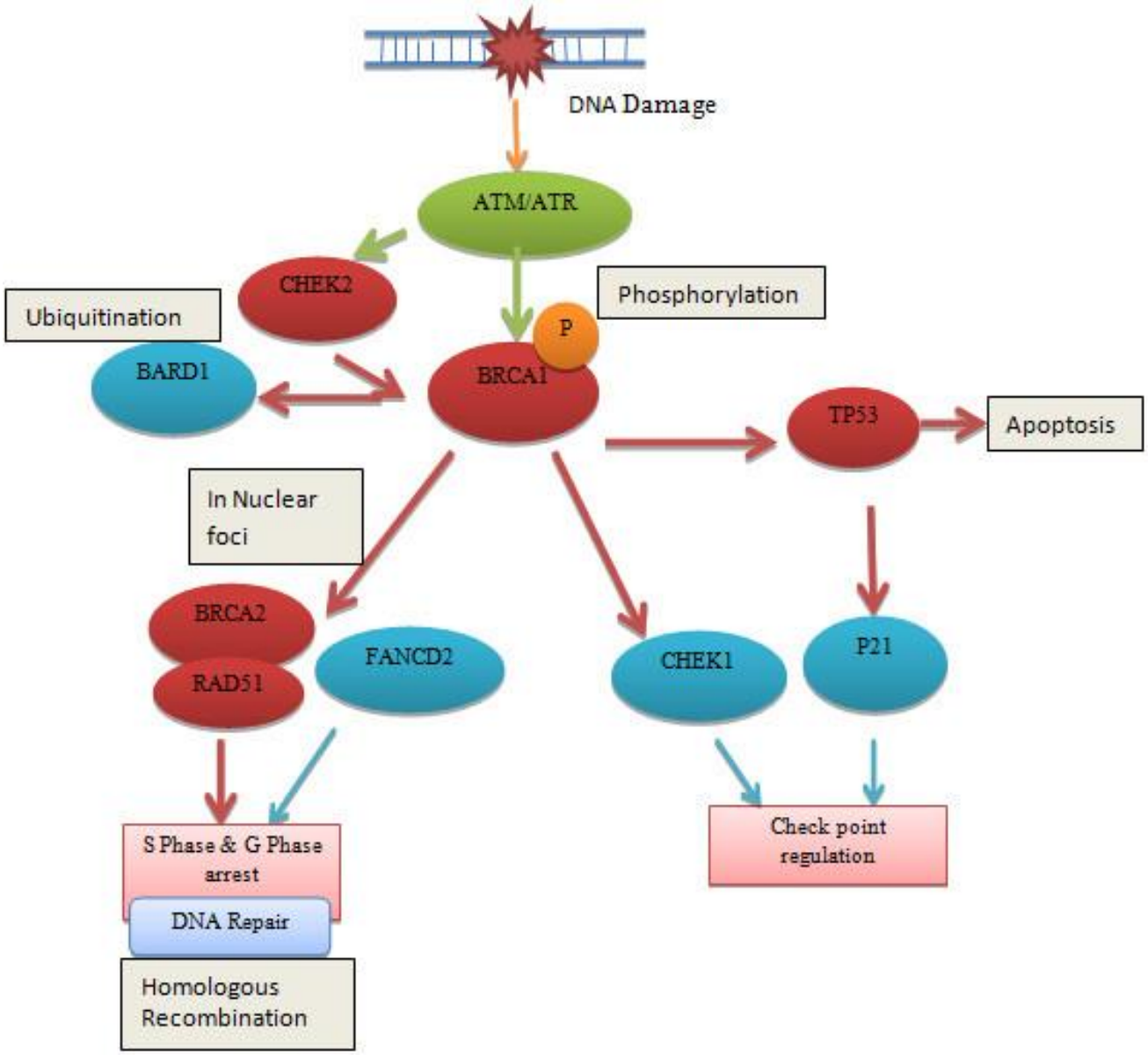

Figure: Interaction of BRCA1, BRCA2, TP53, RAD51 and CHECK1 proteins in cell cycle regulation

Table: Frequencies of various gene mutations in Pakistani breast cancer patients

Gene Name		Number of patients studied	Number of mutation cases determined (%)	Method used	Year of publication	References
BRCA1	1)	176	23(13%)	DHPLC, SSCP, PTT	2006	Rashid et al.
	2)	150	1(0.67%)	SSCP	2008	Malik et al.
	3)	341	15(4.4%)	PTT, DS	2002	Liede et al.
	4)	53	3(5.66%)	PTT, SSCP	2011	Moather et al.
BRCA2	1)	176	7(3.9%)	DHPLC, SSCP, PTT	2006	Rashid et al.
	2)	341	8(2.3%)	DS, PTT	2002	Liede et al.
TP53		105*	1(1%)	DHPLC, DS	2012	Rashid et al
RAD51C		348*	6(17%)	DHPLC, DS	2014	Rashid et al.
CHEK2		145*	2(1.38)	DHPLC, DS	2013	Rashid et al.

DHPLC = denaturing high-performance liquid chromatography; SSCP = single-strand conformation polymorphism; PTT = protein truncation test; DS = direct sequencing. * (star) indicates the number of breast cancer cases negative for BRCA1/2 germ line mutation.

TP53

TP53 tumor suppressor gene is located on the short arm of chromosome 17p13. Germline mutation in TP53 predispose to various malignancy including early onset breast cancer with the almost equal ratio of that caused by mutation in BRCA1 gene (Kern et al., 1991).Germ line mutation in TP53 tumor suppressor gene is also associated with autosomal dominant Li-Fraumeni Syndrome, bone and soft tissue tumors, adreno-cortical carcinomas and some other malignancies (Varley, 2003). About 20-40% of all breast cancers are due to mutation in TP53 gene. It encodes various transcription factors that are involved in DNA repairing, cell cycle check points and apoptosis. Its mutation cause stromal type of breast cancer and is also linked with various sporadic breast cancers (Manié et al., 2009). Missense mutation at exon 10 converts CGC to CAC at codon 337, this replace amino acid arginine by histidine (R337H) and is linked with early onset of breast cancer (Silwal-Pandit et al., 2014).

In Pakistan, a single study is conducted by Rashid et al., 2012 on "Prevalence of Tp53 mutation in young Pakistani breast cancer patients". They identified one rare deleterious (Frame shift) mutation in exon 5 of TP53 gene in 105 early onset breast cancer patients. They conclude that germ line mutation in TP53 gene contributed minimal for early onset breast cancer in Pakistan, (Rashid et al., 2012) (Table).

RAD51C

RAD51C is located on long arm of chromosome number 15 (15q15.1) (Conway et al., 2004). The main function of RAD51C protein is homologous recombination and DNA repair by interacting with some other protein like BRCA1, BRCA2 and BLB2 (Buisson et al., 2014). A bi allelic mutation of RAD51C gene was found in two patient of Pakistani origin with Fanconi anemia (Vaz et al., 2010). The role of RAD51C in breast and ovarian cancer predisposition were determined by Meindl et al., 2010. They determined six mono allelic deleterious RAD51 mutations in 480 germen families of breast and ovarian cancer, but not in a single family of breast cancer only (Meindl et al., 2010).After that, many studies conducted in Caucasian population showed controversial results (Rashid et al., 2014). In Asia, the single study conducted on chines population indicated RAD51C germline mutation with increase genetic predisposition for breast and ovarian cancer families. But no any deleterious mutations were identified in 273 patients of breast and/or ovarian cancer patients (Pang et al., 2011).

In Pakistan, Rashid et al. indicated that 6 (1.7%) out of 341 breast and ovarian cancer showed germ line mutation in RAD51C gene. According to them RAD51C play a minimal role in breast and ovarian cancer genetic predisposition (Rashid et al., 2014) (Table).

CHEK2

CHEK2 (checkpoint kinase 2) gene is cytogenetically located on long arm of chromosome number 22 (22q12.1) (Chaturvedi et al., 1999). The protein encoded by CHEK2 gene called cell cycle check point kinase 2, is a G2 check point serine/threonine kinase. In case of DNA double-strand break, CHEK2 kinase functions as tumor suppressor protein by interacting with several other proteins including TP53, BRCA1, CDC25Aand CDC25C, promoting cell cycle arrests. After repairing DNA, the cell cycle is resumed or cell undergoes apoptosis (Chehab etal., 2000; Falck et al., 2001; Lee et al., 2000). Some studies identified CHCK2 as moderately effective cancer susceptibility gene. Its mutation predisposes an individual to breast and ovarian cancers (Cybulski et al., 2002; Vahteristo et al., 2002). Until now five deleterious recurrent mutations were identified in CHEK2 gene. Some of them are associated with early-onset and familial breast cancer (Weischer et al., 2008).

In Asia, various studies investigated CHEK 2 mutation disposition in BRCA1/2 negative breast cancer patients (Zhang et al., 2008). One study identified a novel missense mutation, p.H371Y with a frequency of 4.2%, 1.8% and 0.7%, in Familial, unselected BC cases and in control respectively. This result suggests the possible contribution of CHECK2 gene to breast cancer susceptibility in chines population (Liu et al., 2011).

In Pakistan Rashid etal. 2013, pointed out one novel deleterious mutation (not been shown in any other population before) in 145 early onset and familial breast/ovarian cancer patients. They concluded that there is no significant contribution of CHEK2 mutation to breast and ovarian cancer in Pakistani women (Rashid et al., 2013) (Table).

CONCLUSION

The study conducted on genetic mutations associated with breast cancer in Pakistan indicated that BRCA1/2 are the two key genes associated with familial and early onset breast cancers of different ethnic groups. Mutation in TP53, RAD51 and CHEK2 play the marginal role in Pakistan breast cancer prevalence. To know the prevalence of these genes mutation in the country, studies of large sample size within different ethnic groups of the country are needed.

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