

MINI-REVIEW

Epidemiology, Major Risk Factors and Genetic Predisposition for Breast Cancer in the Pakistani Population

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Abstract

Occurrence of breast cancer is related to genetic as well as cultural, environmental and life-style factors. Variations in diversity of these factors among different ethnic groups and geographical areas emphasize the immense need for studies in all racial-ethnic populations. The incidence of breast cancer in Pakistan is highest in Asians after Jews in Israel and 2.5 times higher than that in neighboring countries like Iran and India, accounting for 34.6% of female cancers. The Pakistani population is deficient in information regarding breast cancer etiology and epidemiology, but efforts done so far had suggested consanguinity as a major risk factor for frequent mutations leading to breast cancer and has also shed light on genetic origins in different ethnic groups within Pakistan. World-wide research efforts on different ethnicities have enhanced our understanding of genetic predisposition to breast cancer but despite these discoveries, 75% of the familial risk of breast cancer remains unexplained, highlighting the fact that the majority of breast cancer susceptibility genes remain unidentified. For this purpose Pakistani population provides a strong genetic pool to elucidate the genetic etiology of breast cancer because of cousin marriages. In this review, we describe the known breast cancer predisposition factors found in the local Pakistani population and the epidemiological research work done to emphasize the importance of exploring factors/variants contributing to breast cancer, in order to prevent, cure and decrease its incidence in our country.

Keywords: Breast cancer - incidence - environmental and genetic factors - Pakistan

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Breast Cancer

Breast cancer is a tumor originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules supplying ducts with milk. Breast cancer is differentiated into different types on basis of stage, genetic makeup and aggressiveness. However the exact causative agents remain unknown yet primary risk factors identified are sex, age, genetics, lack of child bearing, breast feeding, higher hormonal levels and individual lifestyle.

Epidemiology of Breast Cancer in Pakistan

Cancer incidence and mortality rates are increasing rapidly. Among women breast cancer is the fifth most common cause of cancer death worldwide, as it comprises of 10.4% of all cancer incidence thus making it the most common type of non-skin cancer in women. Worldwide 519,000 deaths were caused by breast cancer (7% of cancer deaths) in 2004 (Farea and Zhenwu, 2011).

Among Asian countries especially in Pakistani population there has been alarming increase in the incidence of breast cancer. Although in Pakistan there is scarce national breast cancer incidence, mortality, or

risk factor data available yet it was reported as the most common malignancy, accounting for 34.6% of female cancers. Its incidence in Pakistan is 2.5 times higher than neighboring countries; Iran and India, highlighting the highest incidence of breast cancer for any Asian population, after Jews in Israel (Liede et al., 2002).

The initial data was published by Karachi Cancer Registry in 2000, for population of the Karachi South district (for period of 1995-1997). The survey indicated incidence rates for all cancers as 91.8 per 100,000 and 163.2 per 100,000 for females. Furthermore the frequency of male breast cancers was determined by 10 year (July 1991 to June 2001) data collected by the Aga Khan University. Out of total 213,377 surgical specimens registered during the above mentioned period 53,012 specimens were breast cancers and only 51 (0.096%) of these were male breast cancers (Bhurgru et al., 2000).

Furthermore Jamal et al worked on 141 cases of male breast carcinoma diagnosed during a ten year period (1992-2001), belonging to northern Pakistan. In 2006 they concluded that these tumors comprised 0.7% of all cancers, 1.1% of all malignancies in males and 5.9% of all breast carcinomas in both genders. A male to female ratio of 1:16 was observed. The age group between 50-

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60 years was at higher risk while majority of the patients were below 60 years. Comparison with their previous similar data showed highly significant increase in breast carcinoma cases in both sexes and also in number of malignancies in males (Jamal et al., 2006).

To evaluate incidence of cancer in districts of Dir, medical records of 1,105 patients registered at the Institute of Radiotherapy and Nuclear Medicine in Peshawar were traced. Information regarding age, gender and affected sites were obtained. In 2008 it was reported that the incidence of cancer was alarmingly increasing, with a mean incidence of 15.04 per 100,000 in 2000-2004. Of the 1,105 patients, 62% were male and 38% were female with affected age range of 41-60 in fem 51-70 for males (Zeb et al., 2008).

Risk Factors Attributing Breast Cancer

Etiology of breast cancer involves complex combination of genetic, environmental and lifestyle factors (such as menarche, no of pregnancies, late menopause) and variation in diversity of these factors among areas highlights the need for study for each geographical area. Keeping this in view involvement of variety of risk factors in breast cancer etiology was explored in Pakistani population.

In 2002, it was reported that due to lack of public awareness and use of unconventional therapies patients in Pakistan present at an advanced stage (Malik, 2002). Furthermore a cross-sectional descriptive study was carried out from January 2004 to December 2006 at AFIP, Rawalpindi on 822 cases of female breast carcinoma belonging to northern areas of Pakistan. The results of the present data were compared with studies done over the past three decades by Malik et al. (2002) on subjects belonging to same region. The results revealed that age of presentation (average age 48 years) remains younger as compared to the West but decrease in tumor size of cancer patients was found in the local population. The results emphasized on need to launch effective screening programmes at the national level for early detection and treatment of cases (Mamoon et al., 2009).

Zeb et al. (2004), correlated occupation and cancer incidence in District Dir (NWFP) Pakistan. Data regarding occupational cancer was collected from cancer registry of Institute of Radiotherapy and Nuclear Medicine (IRNUM) Peshawar for January-2000 to December-2004 (Zeb et al., 2004). Data analysis of 1105 patients suggested that farmers accounted for 43.8% of cancers, the second most effected were housewives (33.8%) and children/students at third place with 12.8%. Cancers in laborers and other professionals like government employees, businessmen and shopkeepers were less often found.

In 2003 an epidemiological survey, involving a matched case-control study on breast cancer was carried out to determine the risk factors of breast cancer in Punjab, Pakistan (Gilani, 2003: <http://eprints.hec.gov.pk/1504/1/1385.HTM>). The data for breast cancer patients was collected from the two leading cancer hospitals in Punjab; Institute of Nuclear Medicines and Oncology Lahore (INMOL) and Shaukat Khanum Memorial Cancer

Hospital (SKMCH). The data set comprised of 1166 breast cancer patients and 2506 controls from three villages (Shah De KIU, Manga Mandi and Ghandran) and two cities (Lahore being metropolitan city and Gujranwala being an industrial city). Data analysis was based on cases with complete information on all variables. Cases with missing information for any covariate were deleted along with the corresponding matched controls. It was concluded that women with late age at menopause were at significantly higher risk of breast cancer. Furthermore there is a significant increase in risk of breast cancer in individuals with history of smoking, family marriage, family history of breast cancer, late age at first full-term pregnancy (above 25 years) and higher body mass index (greater than or equal to 28). High parity (>3 children) was a significant protective factor but no protective effect of late menarche and breastfeeding was observed. Late age at menopause was strongly associated with postmenopausal breast cancer risk. In the study ascertained here, socio economic status, higher or lower was found not to be indicator of breast cancer risk. However women from lower class with late age at first full term pregnancy were at threetimes higher risk. In addition premenopausal women socio economic status was a moderate risk factor. Although postmenopausal women of the lower class, risk of breast cancer was higher yet they were protected by higher number of full term pregnancies.

Butt et al. (2009) worked on association of reproductive factors like parity, age at first live birth and lactation with breast cancer (Butt et al., 2009). Case-control study comprised of 150 breast cancer patients (Mayo Hospital Lahore) and 300 control subjects. In 2009, they reported that nullparity and more age at first live birth was associated with increased breast cancer risk whereas breastfeeding was not protective against breast cancer.

In addition to determine the significance of various reproductive risk factors amongst Pakistani women suffering from breast carcinoma an observational study was carried out from March 2007 to February 2009 at three hospitals (Hamdard University Hospital, Kutiyana Memon Hospital and Burhani Hospital) in Karachi by Saria et al. (2010). They concluded that the frequency of breast cancer in postmenopausal women having early menarche (≤ 11 years) was higher and also more frequent among those with early first full term pregnancy (FFTP) i.e below 20 years of age compared with the pre-menopausal group.

Genetic Etiology of Breast Cancer

Epidemiological evidence highlights genetic susceptibility to breast cancer i.e. female relatives of breast cancer patients present two fold risk of developing the disease as compared to general population. Breast cancer susceptibility is largely 'polygenic', i.e. It has been found to be associated with inherited mutation of high penetrance genes (*BRCA1* and *BRCA2*) as well as large number of moderate/low penetrance genes in populations of diverse ethnicities. Single nucleotide polymorphisms in many genes have also been associated with high morbidity and susceptibility to breast cancer. Genetic variants in susceptibility genes leading to a disease

are highly polymorphic in populations of diverse races and ethnicities. However most of the studies have been carried out in Europeans, only some of their research encompasses few ethnic groups (including Asians) localized there. A few studies conducted in European or Whites and among American Asians, have discovered loci on chromosomes 1p11, 2q25, 6q22, 6q25, 3p24, 14q24 and 17q23 (Turnbull and Rahman, 2008). Among Asians some work has been done only in Chinese population and scarcely on women of Pakistan.

Among Pakistani women breast cancer has been identified as the most common malignancy, accounting for 34.6% of all female cancers and genetic factors are suggested to play a key role. Therefore efforts were initiated to carry out genetic characterization of breast cancer in our local population (Rashid et al., 2006).

In 2002, to explore the contribution of genetic factors a case-control study was conducted on 341 case subjects with breast cancer and 200 female control subjects from two major cities of Pakistan (Karachi and Lahore) (Foulkes et al., 2002). Data analysis concluded that the prevalence of *BRCA1* or *BRCA2* mutations among case subjects with breast cancer was 6.7% whereas mutations of the *BRCA1* gene accounted for 65% of mutations. Five *BRCA1* mutations (2080insA, 3889delAG, 4184del4, 4284delAG, and IVS14-1A->G) and one *BRCA2* mutation (3337C->T) were recurrent in case subjects and represented candidate founder mutations. Majority of detected mutations are unique to Pakistani population. It was established that risk of cancer to age 85 years in female first-degree relatives of *BRCA1*-mutation-positive case subjects was 48% and 37% for first-degree relatives of the *BRCA2*-mutation-positive case subjects. The effects of consanguinity were significant for case subjects with early-onset breast cancer (age <40 years) and suggested that recessively inherited genes contribute to breast cancer risk in Pakistan.

Germline mutational penetrance (of *BRCA1*) in sporadic breast cancer cases with respect to Pakistani was studied by Malik et al. (2008). One hundred fifty cases of unilateral breast cancer patients, with no prior family history of breast cancer and no other disorders with age range 35-75 years, were included in the study. These cases belonged from Punjab, Blochistan, North Western Frontier and Sindh. Mutational analysis for hot spots on Exon 2, 3 and 13 of *BRCA1* revealed five variants (missense) and one novel splice site mutation at exon 13. No germline mutation was observed on the remaining exons. The study provided a base for designing a better genetic screening tool for germline *BRCA* mutations in sporadic breast cancer patients of Pakistani population and suggested screening of entire coding region of *BRCA1* to explore the merits of genetic diagnosis and counseling in breast cancer patients.

In 2009 a retrospective study was carried out for identification of genetic and non-genetic risk factors in 27 specific mutation positive females out of 100 females diagnosed with breast cancer, representing Punjabi ethnic population (Lahore) (Malik et al., 2009). All the mutation positive breast cancers had unilateral ductal carcinoma. Furthermore, 24 of 27 patients had a positive family

history of breast cancer. Among 27% patients positive for specific *BRCA* mutations, 23% were positive for *BRCA1* mutations and 4% for *BRCA2*. *BRCA1*-IVS14, 1G>A mutation was identified in 5 Punjabi ethnic females with Rajput subethnicity, *BRCA1*-3889delAG in 10 (8 with Mughal and 2 with Khan sub-ethnicity), *BRCA1*-2080insA in 8 (Rajput sub-ethnics) and *BRCA2*-3337C>T in 4, Minhas sub-ethnic individuals. Two *BRCA1* mutations (3889delAG and 2080insA) were found to coexist in only one case, with Mughal sub-ethnicity. Out of 23 cases positive for *BRCA1* mutations, 17 were diagnosed at a relatively early age (age<40), 6 were diagnosed at late age (age≥41) whereas all cases positive for single *BRCA2* mutation under consideration were diagnosed for breast cancer at late age.

Three biallelic polymorphisms in the p53 gene (16-bp duplication in intron 3 and BstU I and Msp I restriction fragment length polymorphisms (RFLPs) in exon 4 and intron 6 respectively, leading to gene inactivation) have been linked to development of various malignancies. Prevalence of these polymorphisms was studied in breast cancer patients of nine major ethnic groups of Pakistan (Khaliq et al., 20002). Differences in allele frequencies for all three polymorphisms were observed among breast cancer cases belonging to various ethnic groups. The absence of the 16-bp duplication was common among the northern ethnic groups, being highest in the Hazara (0.90). The Msp I A1 allele frequency in the southern Makrani population was significantly higher in comparison with the other ethnic groups. 16-bp duplication absence in combination with the BstU I Pro and Msp I restriction site absence were the most frequent. Ten substitution mutations were found in the p53 gene, seven of which were reported previously for breast cancer however the remaining three mutations were found in other malignancies, but not in breast cancer.

Khaliq et al. (2001), reported p53 mutation presence in breast carcinoma in Pakistani population however no significant correlation between p53 mutation and tumour aggressiveness (being evaluated by size, nodal status and histopathology) was found (Khaliq et al., 2001).

Rashid et al. (2006), reported thirty deleterious germline mutations in 176 families, including 23 in *BRCA1* and 7 in *BRCA2*. Four mutations, 185insA, S1503X, 185delAG and R1835X, were recurrent (accounted for 52% of all identified *BRCA1* mutations). Haplotype analysis suggested founder effects for 3 of these. The prevalence of *BRCA1* or *BRCA2* mutations was 42.8% for families with familial breast cancer, and 11.9% for single cases of early-onset breast cancer (≤30 years). The data suggested that *BRCA* mutations account for a substantial proportion of hereditary as well early-onset breast cancer cases in Pakistan (Rashid et al., 2006).

Faraz et al. (2010), explored involvement of *BRCA1* gene (responsible for majority of familial breast cancer cases) in sporadic breast cancer cases, especially in Pakistani population (Malik, 2010). Five silent mutations along with one novel splice site mutation was observed on *BRCA1* however, most of the *BRCA1* portions analyzed remained conserved at genomic levels. This highlighted the involvement of other signaling cascade

molecules as well as transcriptional and translational regulatory mechanism responsible for breast cancer. In addition two metastasis suppressor genes (Kiss1 and KAI1) were screened for mutations/polymorphism in these patients because metastasis is most lethal attribute of cancer. No exon or introns deletions were identified in these genes. However significant decrease in KAI1 expression was observed in localized and invasive cancer cells as compared to normal cells as well as a significant correlation between KAI1 and TNM staging was also established ($p=0.045$). Thereby patients showing higher expression of KAI1 showed better survival rate (after median follow up of 120 months) than those showing less or almost negative expression ($p=0.0136$). Expressional correlation of KAI1 with disease progression and potential involvement of KAI1 molecule as a marker of prognostic significance was established for the first time in literature by this study. The fact was established that both genetic and epigenetic factors are mainly responsible for systematic progression and establishing a marker of prognostic significance as well as its potential role in metastatic cascade suppression can help in designing most promising gene therapy for breast tumour patients.

PTEN gene, a candidate tumor suppressor, is one of the most inactivated and extensively studied gene for cancer. Extent of involvement of this gene in breast cancer in Pakistan was studied by Baig et al. (2011). Population based case-control study was conducted in 350 breast cancer patients along 400 healthy controls. Nineteen different types of mutations in different regions of PTEN (in exon 2, 4, 5, 6, 7 and splicing sites of intron 2 and 4 and also in the 3' UTR region). These included 3 silent, 8 missense, 2 frame shift and 6 splice site variations. The three missense mutations were already reported i.e. 319G>A (Asp106Asn), 389G>A (Arg129Gln) and 482G>A (Arg160Lys) in different populations. The results suggested that a wide range of germline PTEN mutations may play a role in the pathogenesis of breast cancer and may vary in different populations.

Farooq et al. (2011) emphasized on the formulation of a BRCA1 and BRCA2 database for the Pakistani population (Farooq et al., 2011). Data of mutational screening of the these genes exons along with the results of the previous Pakistani studies for both BRCA1 and BRCA2 genes were summed up to prepare a Pakistani database. Percentage involvement of BRCA1 and BRCA2 was estimated. Nine percent of these cancers show alterations in BRCA1 gene while 3 percent have shown BRCA2 variants whereas the remaining 88 percent of breast and ovarian cancers were suggested to be attributed by other genes.

In 2011 study was aimed at evaluation of GSTM1 and GSTT1 gene deletions in 150 unrelated breast cancer patients and 150 healthy controls from Pakistani population (Nosheen et al., 2011) as Glutathione S-transferases constitute the phase II detoxification enzymes involved in the metabolism and detoxification of a wide range of potential environmental carcinogens. GSTM1 and GSTT1 are polymorphic and their deletions have been found to be associated with breast cancer risk in some of the world populations. Statistical analysis suggested that a non significant number ($p>0.05$) of individuals compared to

controls had GSTM1 and GSTT1 gene deletions. Deletion in both genes was not observed in any of the patients or controls. Thereby the case control study suggested no association of GSTM1 and GSTT1 gene deletions with sporadic form of breast cancer in Pakistani population.

Methylenetetrahydrofolate reductase (MTHFR) maintains the balance of circulating folate and methionine and blocks the formation of homocysteine, its regulation in relation to different cancers has extensively been studied in different populations therefore Akram et al. (2012) designed a study on Pakistani breast cancer patients (Akram et al., 2012). The MTHFR gene has two most common mutations which result in change of amino acids C677T to Ala222val and A1298C to Glu429Ala. 110 sporadic breast cancer patients along with 110 normal individuals were screened for mutations in exons 1 to exon 9. The p values for the 677CC, 677CT, and 677TT genotypes were 0.223, 0.006, and 0.077, respectively. Those for the 1298AA, 1298AC, and 1298CC genotypes were 0.555, 0.009, and 0.003, respectively. Overall a significant, weak inverse association between breast cancer risk and the 677TT genotype and an inverse association with the 1298C variant was observed, highlighting that MTHFR polymorphism might be population specific in sporadic breast cancer patients but many other factors (folate intake, disease heterogeneity etc) need to be excluded before making final conclusions.

The research findings mentioned above clearly depicts that Pakistani Population have varied genetic makeup and mutations/polymorphism associated with breast cancer risk in other populations may or may not be present in local women of Pakistan therefore there is still need to rule out genetic association of breast cancer among women of variety of racial-ethnic populations.

Future Prospective

In Pakistani women breast cancer incidence is increasing and age of presentation is younger than the West thereby there is immense need for launching of effective screening programmes at the national level for early detection of cases which will help in treatment and subsequently improve prognosis in these patients. Furthermore a national cancer data center registering breast cancer cases from throughout Pakistan including all sub-ethnicities/races belonging to varied socioeconomic class should be founded for future mass screening and determination of risk factors within the country. Public education is highly important to enhance cancer awareness for early diagnosis, treatment and prevention as being strongly advocated in the West.

Consanguinity is established as the major risk factor for recurrent population specific mutations. Hormonal factors including age of menarche, use of oral contraceptives, central obesity, polycystic ovaries, nulliparity, late age at first pregnancy, and lack of breast feeding population had little impact on developing breast cancer risk in Pakistani population as compared to genetic factors however studies have revealed that the Pakistani women having early menarche less than 11 years bear special risk for developing breast cancer in post-menopausal age as

well as women who had FFTP below 20 years and need monitoring for the risk of breast cancer. High parity (>3 children) is a significant protective factor whereas breast feeding is not found to be a protective factor against breast cancer, in our local population. Furthermore dietary factors (smoking) were less likely risk factors than dietary deficiency of vitamins, especially in low income group. Anxiety and exposure to traffic pollution are additional risk factors for breast cancer development.

In addition the high prevalence of BRCA mutations in certain Punjabi sub-ethnicities indicates the importance of genetic counseling. Even after accounting for all the known breast cancer loci, more than 75% of the familial risk of the disease remains unexplained, this highlights the fact that majority of breast cancer susceptibility genes still remain unidentified. The identification of novel predisposition factors as well as ongoing clarification and characterization of known genetic risk factors is also important. There is immense need to explore genetic factors/variants attributing to breast cancer in Pakistani population to elucidate the genetic causes leading to breast cancer development in order to prevent and ultimately cure and decrease its incidence. Identifying key genes involved in breast cancer development will give in-depth insight about breast cancer development and susceptibility especially in our local population and to rule out whether loci/polymorphisms associated with breast cancer in other races/populations (mostly Europeans) also prevail and associate with breast cancer etiology in population of Pakistan. The information gleaned from such studies will lead to identification of clinically relevant pathways for targeted prevention and cure of breast cancer which will ultimately decrease breast cancer incidence, especially through prenatal diagnosis and genetic counseling, worldwide.

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