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 lifestyle 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

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 (Bhurgri 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-
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 Khaman Memorial Cancer Hospital (SKMCH). The data set comprised of 1166 breast cancer patients and 2506 controls from three villages (Shah De KhilUi, 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 threethimes 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 1, 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, 4284del1AG, and 1VS14-1A->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 women with breast cancer was 6.7% whereas mutations of BRCA1 or BRCA2 were found in 10% of all female cancer patients of nine major ethnic groups of Pakistan (Khalid et al., 2000). Differences in allele frequencies for all three polymorphisms were observed among breast cancer patients of different ethnicities. 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.

Khalid 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 (Khalid 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, 3337C>T and 1VS14-1A->G were recurrent in case subjects and represented candidate founder mutations. 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 were 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. These 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.

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 therefore 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 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.
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.

References


