

## MINI-REVIEW

# Prevalence, Risk Factors and Disease Knowledge of Breast Cancer in Pakistan

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### Abstract

Breast cancer is the most common cancer in females all over the world with approximately one million new cases each year as well as one of second leading causes of death among females. In Pakistan, the most frequently diagnosed cancer among females is also breast cancer, accounting for nearly one in nine female patients. Its incidence in Pakistan is 2.5 times higher than that in neighboring countries like Iran and India. The risk factors associated with breast cancer are age, family history, early menarche, intake of combined estrogen and progestin menopausal hormones, alcohol consumption, physical inactivity, low socioeconomic status and lack of awareness regarding the disease. This mini-review article aims to provide awareness about breast cancer as well as an updated knowledge about the prevalence, risk factors and disease knowledge of breast cancer in Pakistan.

**Keywords:** Breast cancer - incidence - prevalence - risk factors - Pakistan

*Asian Pac J Cancer Prev*, 15 (11), 4411-4416

### Introduction

Breast cancer is the malignancy of the breast tissue which is the most frequently diagnosed cancer in the women worldwide. Globally it is accounted for 23% of all cancer cases (Jemal et al., 2011). All women despite of their racial or ethnic origin or heritage are at risk of breast cancer (Naeem et al., 2008). According to WHO figures, more than 1.2 million people are diagnosed with breast cancer worldwide every year (Zahara et al., 2013). Breast cancer is very rare in males, although they can also be affected with it (McPherson et al., 2000; World Cancer Report, 2008). Breast cancer is more common in Pakistani population as compared to the Western population (Mahmood et al., 2006). One in every nine Pakistani women suffers from breast cancer which is one of the highest incidence rates in Asia (Sohail et al., 2007). Recently, incidence of breast cancer is 21.5% among all and 45.9% among female patients, reported from Shaukat Khanum Memorial Cancer hospital (Badar et al., 2011).

Breast cancers are classified in different forms according to their origin, grading, staging and receptor status. Reproductive and menstrual factors also called hormonal factors are considered the most important risk factors for breast cancer. Early menarche, nulliparity, older age at first live birth and no breastfeeding have been found to increase breast cancer risk.

Breast cancer originates from breast tissue, most

commonly from the inner lining of milk ducts (ductal carcinoma) or the lobules (lobular carcinoma) that supply the ducts with milk (Sariego et al., 2010). Worldwide in women, almost 22.9% of all cancers are the breast cancer. Breast cancer have resulted 458,503 deaths in 2008, (13.7% of cancer deaths in women) (Cancer report, 2008). Prognosis and survival rates for breast cancer depend on the cancer type, stage, treatment, and geographical location of the patient.

Normal cells divide as many times as needed and stop dividing when they are no longer needed. Normal cells turns cancerous when they lose their ability to stop dividing, to attach to other cells, to stay where they belong, and to die at the proper time. Sometimes the gene that control the protective pathways P13K/AKT and RAS/MEK/ERK (involves in apoptosis i.e cell suicide when it is no longer needed) is mutated in a way that turns them permanently "on", rendering the cell incapable of committing suicide when it is no longer needed. This is one of the steps that causes cancer in combination with other mutations (Adrian et al., 2009) Genetic mutations and damage to the DNA can lead to breast cancer have been experimentally linked to estrogen exposure (Scavaliere et al., 2006). Some individuals inherit defects in the DNA and genes like the P53, BRCA1 and BRCA2 among others. Breast cancer grading compares the appearance of the breast cancer cells to the appearance of normal breast tissue. Normal cells become differentiated, meaning that

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they take on specific shapes and forms that reflect their function as part of that organ. Cells that become cancerous lose that differentiation. Pathologists illustrate cells as well differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade) as the cells gradually lose the features seen in normal breast cells. Poorly differentiated cancers (the ones whose tissue is least like normal breast tissue) have a little prognosis.

TNM system is used for the grading of breast cancer. TNM indicates the size of the tumor (T), whether or not the tumor has spread to the lymph nodes (N) in the armpits, and whether the tumor has metastasized (M) (i.e. spread to a more distant part of the body). The main stages are: Stage 0 shows pre-cancerous or marker condition, either ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS). Stages 1-3 indicate whether within the breast or regional lymph nodes. Stage 4 show the cancer is metastatic and has a less favorable prognosis (Saslow et al., 2004).

Breast cancer cells have receptors such as estrogen receptor (ER), progesterone receptor (PR), and HER2 on their surface and in their cytoplasm and nucleus. Chemical messenger such as hormones bind to receptors, and causes the changes in the cell. Cancer cells that have estrogen receptors i.e. ER+ depend on estrogen for their growth, so they can be treated with drugs to block estrogen effects (e.g. tamoxifen), and generally have a better prognosis (Yu YH et al., 2010) HER2+ cancer cells respond to drugs such as the monoclonal antibody trastuzumab (in combination with conventional chemotherapy), and this has improved the prognosis significantly (American cancer society, 2012). Cells those do not have any of these three receptor types are called triple-negative, although they frequently do express receptors for other hormones, such as androgen receptor and prolactin receptor.

The first noticeable symptom of breast cancer is appearance of lump that feels different from the rest of the breast tissue. Signs of breast cancer beside a lump may include thickening of breast tissue, one breast becoming larger or lower, a nipple changing position or shape or becoming inverted, a rash on or around a nipple, discharge from nipple/s, constant pain in part of the breast or armpit, and swelling beneath the armpit or around the collarbone (Waston, 2008).

Female sex and older age are the primary risk factors for breast cancer (Reeder et al., 2008). Other possible risk factors for breast cancer may be genetics, lack of childbearing or lack of breast feeding, increase level of some hormones (Yager et al., 2006) change in dietary patterns, obesity, exposure to light pollution, tobacco, intake of high fat diet, alcohol intake (Boffetta et al., 2006) related to higher cholesterol levels (Kaiser et al., 2013). Many chemicals such as polychlorinated biphenyls, polycyclic aromatic hydrocarbons, organic solvents (Brody et al., 2007) and a number of pesticides (Fero, 2012). Overall, 5-10% of all cases are believed to be due to genetics (Gage et al., 2012).

Breast cancer is diagnosed by physical examination, imaging test such as mammogram, MRI, breast ultrasound, ductogram, biopsy, (Excisional biopsy, a core biopsy or

vacuum-assisted breast biopsy) and FNAC (a procedure known as fine needle aspiration, or fine needle aspiration and cytology).

The management of breast cancer depends on number of factors, including the stage of the cancer. It is generally treated with surgery, which may be followed by chemotherapy or radiation therapy, or both. Hormone receptor-positive cancers are usually treated with hormone-blocking drugs over courses of several years. Monoclonal antibodies, or other immune-modulating therapy, may be given in certain cases of metastatic and advanced stages of breast cancer (Gotzsche, 2011). Radiotherapy is given after surgery to the region of the tumor bed and regional lymph nodes to destroy microscopic tumor cells and to exert beneficial effects on tumor microenvironment (Jahanzeb et al., 2008; Petit et al., 2011).

## Prevalence of breast cancer in Pakistan

Breast carcinoma is the most common cancer in Pakistani females. Incidence of breast cancer in Pakistan is about 2.5 times that in India and Iran. Pakistan has the highest breast cancer incidence rate in Asia except that in Jews in Israel. In Pakistan every year at least 90,000 women suffer from breast cancer. The frequency of breast cancer in Karachi was 69.1 per 100,000 from 1998-2002 (Bhurgri et al., 2004). The population based cancer registry data from South Asia shows that Pakistan has the highest age standardized rate at 69 per 100,000, of breast cancer (Moore et al., 2009).

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

Jamal et al, (2006) studied 141 cases of male breast carcinoma diagnosed during a ten year period (1992-2001), belonging to northern Pakistan. 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 in the study. The incidence was higher in the age group between 50-60 years while majority of the patients were below 60 years. This report showed highly significant increase in breast cancer cases in both sexes and also in number of malignancies in males when compared with their previous similar data (Jamal et al., 2006).

Another study was conducted by Bhurgri and his colleagues with the objective of providing the cancer profile of Hyderabad, which has an urban population of 2,840,653 (52.2% M, 47.8% F) with annual growth rate 1.13. The study included incident of cancer cases in residents of Hyderabad and the cancer cases registered in the Aga Khan University Pathology-based Cancer Registry (APCR) collection points at Hyderabad and

subsequently registered at APCR during 1st January 1998 to 31st December 2002. The age-standardized rates (ASR) for cancer (all sites) 1998 to 2002 in Hyderabad were 91.6/100,000 in males and 96.0/100,000 in females. The most common malignancies among females (ASR per 100,000) were breast (22.4), oral cavity (11.5), gall bladder (4.8), esophagus (4.2), cervix (3.6), ovary (3.4), colorectum (3.4), lymphoma (3.4), uterus (3.4), and thyroid (2.4). The incidence of breast cancer in this time period was high compare to other malignancies (Bhurgri et al., 2005).

A total of 28,740 patients with diagnosis of cancer were registered at INMOL during the ten year period from 1st January 2000 to 31st December 2009. Among these 6,718 patients were diagnosed with breast cancer. The incidence of breast cancer among females in this time period was 41% (38% in the first five years and 42% in the later five years). The female to male ratio was 100:2. Majority of patients (46%) were from Lahore and a small proportion were resident in nearby cities. Only 7% of patients were from Gujranwala, 6% of Sialkot, 4% each of Sargodha and Sheikhpura and 3% were from each Kasur, Okara, Sahiwal, Faisalabad and Gujrat (Khoker et al., 2012).

Another study was carried out during January 2004 to December 2006 at Histopathology department, Armed Forces Institute of Pathology (AFIP), Rawalpindi, a tertiary care referral laboratory with samples from military hospitals and as well as civil public and private sector hospitals from upper Punjab, NWFP and adjacent Rawalpindi Islamabad region. During the study period total 822 cases of breast cancer were diagnosed (Mamoon et al., 2009).

A study was conducted by Hameed and his fellows in Balochistan University of Information Technology, Engineering and Management Sciences Quetta, and Center of Excellence for Nuclear medicines and Radiotherapy Quetta from August 2010 to February 2012. In this study, 134 patients of breast cancer were investigated, of which the invasive ductal carcinoma (IDC) was the most common type of breast cancer with a total of 128 patients (95.5%) followed by invasive lobular carcinoma (ILC) (Hameed et al., 2012).

Furthermore, a study was carried out in Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN), providing a comprehensive healthcare facility for diagnosis, treatment and research of all cancers. This was a retrospective analysis of the cancer patients of both genders of all age groups to determine frequencies of different cancers presented to this Institute from 1st January 2000 to 31 December 2008. A total of 16,351 cancer patients were diagnosed at KIRAN during the nine year period. Male cancers accounted for 48.1% and female cancers 51.8%, 558 (3.4%) were in children (0-15 years). In males the most frequent malignancies were lung (15%), gastrointestinal tract (6.9%), head and neck (32.6%), lymphoma (6.1%), and bone and soft tissue (4.9%). In females, breast cancer was the most common cancer for 38.2% followed by head and neck (15.1%), cervical (5.5%), ovarian (4.9%) and GIT cancer (4.9%) respectively. Overall cancer incidence in nine years duration showed that head and neck cancers in males and

breast cancers in females are most common at rates almost highest in Asia (Haneef et al., 2009).

#### *Risk factors of breast cancer in Pakistan*

Breast cancer is the most frequently diagnosed cancer in Pakistani females. Cancer statistics in Pakistan show that breast cancer disease involving the largest proportion of the population (Yousuf & Jafarey, 1985) compared to other Asian countries. What exactly is responsible for the cause of breast cancer is still unknown, however certain risk factors known to increase a person's chance of getting breast cancer such as dietary factors, obesity, use of oral contraceptives, old age and family history.

Early menarche, late age at menopause, late age at the first full term pregnancy and three or fewer full-term pregnancies and positive history of breast cancer in the family have a significantly increased risk of breast cancer (Lai et al., 1996; Talamini et al., 1996). Younger age at menarche, Nulliparity, older age at first live birth and no breastfeeding have been consistently found to increase breast cancer risk (Butt et al., 2012). However, for the postmenopausal women an increasing risk with earlier age at menarche was observed (Choi et al., 1978). A strong association of increasing breast cancer risk with increasing age at menopause was reported in some studies (Talamini et al., 1996). High body mass index (BMI) has also been shown to be associated with an increased risk of breast carcinoma in most of the studies (Zhu et al., 2005).

Gillani et al (2006) designed case control study to identify the risk factors for breast cancer in Pakistani parous women. The risk factors investigated in the study were; age at menarche, age at menopause, family history of breast cancer, socio-economic status, consanguineous marriage, history of smoking, age at first full term pregnancy, number of live-births and body mass index (BMI). A study was carried out at two cancer hospitals at Lahore (INMOL and SKMCH) to determine the association of breast cancer risk with age, early menarche, premenopause, postmenopause, smoking and high BMI. A total of 564 female breast cancer cases diagnosed during the time period Jan 1, 1998 to Dec 31, 1998. The study showed that women with family history of breast cancer, history of consanguineous marriage, smoking and high BMI are at increased risk of breast cancer for all three groups (Gillani et al., 2006).

Bhurgri et al. (2007) reviewed the 709 incident breast cancer cases registered at Karachi Cancer Registry during 1st January 1995 to 31st December 1997. Study showed that incidence of breast cancer in Karachi South (KS) for the period of 1995-1997 was ranked as the third highest in Asia. The majority of the risk factors were high reproductive age, a lower socio-economic class, family history of breast cancer and high BMI (Bhurgri et al., 2007).

To assess potential risk factors for breast cancer Shamsi and his fellows conducted a matched case-control study in two tertiary care hospitals of Karachi, Pakistan. The study population included 297 cases of breast cancer patients diagnosed between January 2009 and December 2010. Positive family history of breast cancer, single marital status, and older age at menopause aged below 45 years

conferred an increased risk of breast cancer for women. Increasing parity decreased the risk of breast cancer. Intake of Vitamin D supplements was protective compared to non-users of Vitamin D. Therefore, the study confirmed only few of the recognized risk factors in Pakistani women (Shamsi et al., 2013).

Zahra et al. (2013) evaluated the risk factors for breast cancer in women attending OPD Breast Clinic, Sir Ganga Ram Hospital, Lahore and compare the local with the western risk factors. The study was cross-sectional conducted at OPD Breast Clinic from January 2008 to June 2013. A total of 200 females with breast cancer were included. Age at presentation, stage and type of carcinoma breast, age at menarche, age at menopause, marital status, age at first full term pregnancy, parity, use of oral contraceptives (regular uptake for at least one year), breast feeding history (12 months at least), family history of breast cancer and other cancers (first degree relatives), smoking (20 pack years), were evaluated as risk factors for breast cancer in the study. The mean age of diagnosis was 45 years. Presentation at advanced stage was most common (61%) and Invasive Ductal carcinoma was the most common type (95%). 99% of the patients were married, 93% parous, and 96% patients had age <30 years at first full term pregnancy. 78% had a history of breast feeding for 12 months. Early menarche ( $\leq 12$  years) and late menopause ( $\geq 50$  years) were seen 20% and 3.6% of patients respectively. Only 10% of patients had used oral contraceptive pills. 90% were non smokers, and 35% were obese with BMI >30. Family history of breast cancer was +ve in 12% of patients and 13% of patients had first degree relatives affected from other types of cancer. The study therefore concluded that In Pakistan, the females presents with breast cancer at a younger age (<50 years) and with an advanced disease (mostly Stage III). Female population here manifests low levels of traditional risk factors because they generally exhibit high fertility levels, multiple births, and extended breast-feeding, early age at first pregnancy. The causative factor can be genetic susceptibility in females or environmental factors which are yet to be looked into (Zahra et al., 2013).

Another study was carried to evaluate the difference between pre and post-menopausal breast cancer regarding menstrual and reproductive risk factors. This was the case-control study conducted in Mayo Hospital Lahore from October 2008 to April 2009, including 150 cases and 300 controls. Among the breast cancer patients, pre-menopausal were 42.7% and 57.3% were post-menopausal. Age at menarche had no relationship with breast cancer for both pre and post-menopausal women. The study showed that Majority of risk factors for pre-menopausal breast cancer are also associated with post-menopausal breast cancer except less parity, which increased the risk for post-menopausal breast cancer only (Butt et al., 2012).

To find out the association of reproductive factors like parity, age at first live birth and lactation with breast cancer the study was done in Mayo Hospital Lahore between October, 2008 and April, 2009. It was a case-control study including 150 breast cancer patients and 300 control subjects. Breast cancer patients and control subjects did

not differ regarding age ( $p=0.9$ ), early menarche and late menopause. History of breast cancer in 1st degree relatives did not increase breast cancer risk. Nulliparous women had higher risk than parous women. Women with younger age at first live birth (<30 years) had less breast cancer risk as compared to women with  $\geq 30$  years of age at first live birth. Breastfeeding had no protective effect against breast cancer (Butt et al., 2009).

Another study was carried out to assess the risk factors for breast cancer in women attending Nuclear Medicine, Oncology and Radiotherapy Institute (NORI) hospital, Islamabad from January to July 2005. A total 300 females, comprises 150 cases and their age matched healthy 150 controls were included. Marital status, family history of breast cancer (first degree relatives), breast feeding history (12 months at least), smoking, parity, use of oral contraceptives (regular uptake for at least one year), and menopausal status were evaluated as risk factors for breast cancer in females. The result showed that lack of breast-feeding, less parity, and smoking are most significantly associated with breast cancer in patients attending NORI (Faheem et al., 2007).

Recently, Farooq and his colleagues put emphasized on the formulation of a BRCA1 and BRCA2 database for the Pakistani population. In this study data from diagnosed cases of both sporadic and inherited female breast and ovarian cancer cases was gathered after performing molecular genetic analysis by screening for alterations in the coding sequence of the BRCA gene. Mutational screening of the exons in the entire samples group did not showed any pathogenic mutation. Data of the Mutational screening of the exons along with the results of the previous Pakistani studies for both BRCA1 and BRCA2 genes were summed up to prepare a Pakistani database. They then estimate the Percentage involvement of these genes. Nine percent of these cancers show alterations in BRCA1 gene while 3 percent have shown BRCA2 variants while the remaining 88 percent of breast and ovarian cancers can be due to the involvement of other genes (Farooq et al., 2011).

A 6 month cross sectional study (from July 2012 to Dec 2012), was carried out in Surgical and Oncology Units of Civil Hospital, Karachi to evaluate the reasons for patients delay in the diagnoses of breast cancer as delay in the diagnosis of breast cancer is associated with poor survival. A total of 100 female diagnosed with breast cancer were included. Significant delay in approach to health care center was observed in this study due to several reasons given by women. Sufficient awareness should be given to our general population regarding breast cancer, its symptoms and favorable effects of timely diagnosis on prognosis (Memon et al., 2013).

Rabia et al. (2013) conducted a study on 100 patients in different hospitals of Lahore, aiming to evaluate risk factors leading to high prevalence of breast cancer in women. The result of their study showed that women with advanced age, having middle class family background, higher body mass index and a high ratio of incomplete pregnancies were at significantly increased risk of breast cancer. Increase body weight and the use of oral contraceptives are minor whereas family history,



employment status, physical activity and smoking don't serve as risk factors. The protective role of breastfeeding and full term pregnancies is suppressed and not very significant.

Amongst all possible risk factors, the change in the genetic information is the most frequent factor. Prevalence of BRCA1 or BRCA2 mutations in breast cancer patients of Pakistan (Rashid et al., 2006) have been found unique to Pakistan. The prevalence of polymorphisms and haplotypes of TP53 has been studied in Pakistani ethnic groups (Khaliq et al., 2000) and the pro allele has been found to be common among Pakistan people. Study was designed to investigate allele frequency and genetic or geographical value of TP53 gene codon 72 polymorphism in normal subjects, sporadic breast cancer patients and in those with genetic lineage of Pakistan. Presence of homozygous arginine allele at codon 72 considered is a risk factor for breast cancer. The objective of the study was to evaluate the frequency of codon 72 polymorphism of TP53 gene in breast cancer patients and those with genetic lineage. One hundred and fifty female patients with sporadic breast cancer were included in this study, of these, one hundred female patients were from Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore and fifty patients were from Mayo Hospital Lahore Pakistan, from January 2005 to December 2008. The median age of the patients was in the range 18-65. It was concluded that Proline allele was more dominant compared to arginine allele. RFLP analysis showed that arg/pro (53%) and pro/pro (35%) genotypes were more common in Pakistani breast cancer patients compared to arg/arg (12%) genotype. Similar type of genotypic was also found in normal control samples. The arg/pro and pro/pro alleles were also prominent in familial breast cancer patients. Compare to arg allele which is usually involved in breast cancer development in western countries, the pro allele in the study was more prominent in Pakistani sporadic breast cancer patients, normal subjects and those of genetic lineage. Frequency of pro allele codon 72 of TP53 among Pakistani female breast cancer patients may be due to some specific geographical reasons (Aziz et al., 2013).

### Prospects for the future

In Pakistan, breast cancer incidence rate is higher among females compare to other countries of Asia excluding Jews in Israel. Key factors that play role in the development of breast carcinoma are the genetics and environment, the reproductive experience, the effect of endogenous and exogenous hormones in females, the change in immune status, host vulnerability, and the biologic determinants of breast carcinoma. Studies have revealed that in the Pakistani women 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 are some of the risk factors developing breast cancer in Pakistani population. 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

first full term pregnancy below 20 years. These women need special monitoring. High parity (>3 children) is a significant protective factor while breast feeding is not found to be a protective factor against breast cancer, in our local population. Furthermore, the high prevalence of BRCA mutations in certain Punjabi sub-ethnicities indicates the importance of genetic counseling. Focus should be given in searching genetic factors causing breast cancer in Pakistani population to elucidate the genetic cause leading to breast cancer development in order to prevent and decrease its incidence. Hence there is an urgent need for establishing the effective screening program at the national level for early detection of cases which will help in treatment and subsequently improve prognosis in these patients. Furthermore Central cancer registry program/system should be introduced by Government to monitor breast cancer registry cases from throughout Pakistan including all sub-ethnicities/races belonging to varied socioeconomic class for future mass screening and determination of risk factors within the country. Public education is highly important to boost cancer awareness for early diagnosis, treatment and prevention. Female awareness regarding lumps in the breast should be increased. Training should be given to younger age group in the colleges and schools for breast self-examination (BSE). Media should play a role to provide awareness among general practitioners. Breast care clinics and screening programmed should be started in all hospitals. All concerned people like Tibb Physician (Hakeem), Homeopaths and other alternate therapists should be provided awareness for early referral of such patients to the tertiary referral hospitals.

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