MINI-REVIEW

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

Hafiz Muhammad Asif1*, Sabira Sultana2, Naveed Akhtar2, Jalil Ur Rehman2, Riaz Ur Rehman3

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
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 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 (Gotsche, 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., 2004).

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
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).

Bhurghi 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 (Bhurghi 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...
Hafiz Muhammad Asif et al

Asian Pacific Journal of Cancer Prevention, Vol 15, 2014

Subjects. Breast cancer patients and control subjects did study including 150 breast cancer patients and 300 control October, 2008 and April, 2009. It was a case-control the study was done in Mayo Hospital Lahore between parity, age at first live birth and lactation with breast cancer (Butt et al., 2012).

The study showed that Majority of risk factors for breast cancer for both pre and post-menopausal women. 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.

References

Adrian Lee, Carlos Arteaga (2009). “32nd Annual CTRC-AACR San Antonio Breast Cancer Symposium”. Sunday Morning Year-End Review.

American Society of Clinical Oncology (2012). “Five Things Physicians and Patients Should Question”, Choosing Wisely: an initiative of the ABIM Foundation (American Society of Clinical Oncology), retrieved 14 August 2012.

Aziz I, Muhammad UR, Faisal S, Abdul RS (2013). Frequency of pro allele on codon 72 of TP53 in female breast cancer patients of Pakistan. Pak J Zool, 45, 1437-46.

Badar F, Faruqui ZS, Uddin N, et al (2011). Management of breast lesions by breast physicians in a heavily populated south asian developing country. Asian J Cancer Prev, 12, 827-32.

Bhurgri Y (2004). Karachi Cancer Registry Data implications for the National Cancer Control Program of Pakistan. Asian Pac J Cancer Prev, 5, 77-82.

Bhurgri Y, Bhurgri A, Perez S, et al (2005). Cancer profile of Hyderabad, Pakistan 1998-2002. Asian Pac J Cancer Prev, 6, 474-80.

Bhurgri Y, Kayani N, Faridi N, et al (2007). Patho-epidemiology of breast cancer in Karachi, 1995-1997. Asian Pac J Cancer Prev, 8, 215-20.

Bhurgri Y, Bhurgri A, Hasan, SH, et al (2000). Cancer incidence in Karachi, Pakistan: First results from Karachi cancer registry. Int J Cancer, 85, 325-29.

Boffetta P, Hashibe M, La Vecchia C, Zatonski W, Rehm J (2006). The burden of cancer attributable to alcohol drinking. Int J Cancer, 119, 884-7.
Memon ZA, Shaikh AN, Rizwan S, Sardar MB (2013). Reasons
McPherson K, Steel C M, Dixon J M, (2000). Breast cancer;
Mahmood S, Rana TF, Ahmad M (2006). Common determinants
Lai FM, Chen P, Ku HC, et al (1996), A case-control study
Kaiser J (2013). Cancer; Cholesterol forges link between obesity
Jamal S, Mamoon N, Mushtaq S, Luqman M (2006). Carcinoma
Hanif M, Zaidi P, Kamal S, Hameed A (2009). Institution-based
Gilani GM, Shahid S, Gilani AM (2006). Risk factors for breast cancer in women for Punjab, Pakistan: Results from a case-control study. Pak J Stat Oper Res, 105, 444-51.
Gilani GM, Shahid S, Gilani AM (2006). Risk factors for breast cancer in women for Punjab, Pakistan: Results from a case-control study. Pak J Stat Oper Res, 2, 17-26.
Gatzke-Pearson L, Naseem M (2011). Screening for breast cancer with mammography. Cochrane Database Syst Rev, 1, 1877
Hameed B, Jameela S, Shakeela D, et al (2012). Various aspects, patterns and risk factors in breast cancer patients of Balochistan. Asian Pac J Cancer Prev, 13, 324-33.
Hanjebz M (2008). Adjuntant trastuzumab therapy for HER2-positive breast cancer. Clin Breast Cancer, 8, 324-33.
Jamal S, Mamoon N, Mushqat S, Luqman M (2006). Carcinoma of the male breast: a study of 141 cases from Northern Pakistan. Asian Pac J Cancer Prev, 7, 119-21.
Jemal A, Bray F, Center MM, et al (2011). Global Cancer statistics. CA Cancer J Clin, 61, 69-90.
Kaiser J (2013). Cancer; Cholesterol forges link between obesity and breast cancer’. Science, 342, 1028.
Khalil S, Hameed A, Khalil T, et al (2000). P53 mutations, polymorphisms and haplotypes in Pakistani ethnic groups and breast cancer patients. Genet Test, 4, 23-29.
Khoker S, Muhammad UQ, Masooma R, Naseem A, Afaf S (2012). Clinicopathologic profile of breast cancer patients in Pakistan: ten years data of a local cancer hospital. Asian Pac J Cancer Prev, 13, 693-8.
Lai FM, Chen P, Ku HC, et al (1996). A case-control study of Parity, Age at first full term pregnancy, breast-feeding and breast cancer in Taiwanese women. Proc Natl Science Council, ROC, part B: Life Sciences, 20, 71-7.
Mahmood S, Rana TF, Ahmad M (2006). Common determinants of Ca Breast-a case control study in Lahore. Ann King Edward Med Coll, 12, 227-8.
McPherson K, Steel C M, Dixon J M, (2000). Breast cancer; epidemiology, risk factors and genetics. Br Med J, 321, 624-8.
Memon ZA, Shahik AN, Rizwan S, Sardar MB (2013). Reasons for patient’s delay in diagnosis of breast carcinoma in Pakistan. Asian Pac J Cancer Prev, 14, 7409-14
Moore MA, Ariyaratne Y, Badar F, et al (2009). Cancer epidemiology in South Asia past, present and future. Asian Pac J Cancer Prev, 10, 49-67.
Naeem M, Khan N, Aman Z, et al (2008). Breast cancer: experience at lady reading hospital, Peshawar. J Ayub Med Coll, 20, 22-5.
Petit T, Dufour P, Tannock I (2011). “A critical evaluation of the role of aromatase inhibitors as adjuvant therapy for postmenopausal women with breast cancer”. Endocr Relat Cancer, 18, 79-89.
Rahim T, Sadia H, Murriam ZB, Fatima A (2013). Molecular stress or geography risk factors leading to high prevalence of Breast Cancer. J App Pharm, 4, 706-12.
Rashid UM, Zaidi A, Torres D, et al (2006). Prevalence of BRCA1 and BRCA2 mutations in Pakistani breast and ovarian cancer patients. Int J Cancer, 119, 2832-9.
Reeder, JG; Vogel, VG (2008). “Breast cancer prevention” Cancer treatment and research, 141, 149-64.
Sariego J (2010). “Breast cancer in the young patient”. The Amer surgeon, 76, 1397-401.
Saslow D, Hannan J, Osuch J, et al (2004). “Clinical breast examination: practical recommendations for optimizing performance and reporting”. CA: A Cancer J Clin, 54, 327-44.
Scavalleri E, Chakravarti D, Gutenplan J, et al. (2006). “Catechol estrogen quinones as initiators of breast and other human cancers: implications for biomarkers of susceptibility and cancer prevention”. Biochimica et Biophysica Acta, 1766, 63-78.
Shamsi U, Khan S, Usman S, Soomro S, Azam I (2013). A Multicenter Matched Case Control Study of Breast Cancer Risk Factors among Women in Karachi, Pakistan. Asian Pac J Cancer Prev, 14, 183-8.
Sohail S, Alam SN (2007). Breast cancer in Pakistan-awareness and early detection. J Coll Phys Surg Pak, 17, 711-2.
Talamini R, Franceschi S, La Vecchia C, et al (1996). The role of reproductive and menstrual factors in cancer of the breast before and after menopause, Europ J Cancer, 32, 303-10.
Watson M (2008). “Assessment of suspected cancer”. InnoATI, 1, 94-107.
World Cancer Report (2008). International agency for research on Cancer. http://www.iarc.fr/en/publications/pdfs-online/wcr/2008/wcr_2008.pdf. Retrieved 2011-02-26.
Yager JD (2006). Estrogen carcinogenesis in breast cancer. New Engl J Med, 354, 270-82.
Yousuf F and Jaffery NA (1985). On the incidence of malignant tumors of breast among females, Pakistan, Pak J Med Res, 24, 123-7.
Yu YH, Liang C, Yuan XZ (2010). Diagnostic value of vacuum-assisted breast biopsy for breast carcinoma: a meta-analysis and systematic review. Breast Cancer Res Treat, 120, 469-79.
Zahra F, Humayoun F, Yousaf T, Khan NA (2013).Evaluation of risk factors for carcinoma breast in Pakistani women. J Fatima Jinnah Med Assoc, 1, 34-8
Zhu K, Caulfield J, Hunter S, et al (2005). Body mass index and breast cancer risk in African American women. Ann Epidemiol, 15, 123-8.

Hafiz Muhammad Asif et al
Brody JG, Rudel RA, Michels KB, et al (2007). Environmental pollutants, diet, physical activity, body size, and breast cancer: where do we stand in research to identify opportunities for prevention? Cancer, 109, 2627-34.
Butt Z, Haider SF, Arif S, et al (2012). Breast cancer risk factors: A comparison between pre-menopausal and post-menopausal women. J Pak Med Assoc, 62, 120-4.
Butt Z, Naseem M, U, Naseem T, et al (2009). Reproductive risk factors for female breast cancer: a case-control study. Annals, 15, 205-10.
Choi NW, Howe GR, Miller AB, et al (1978). An epidemiologic study of the breast cancer. Am J Epidemiol, 107, 510-21.
Faheem M, Muhammad K, Imran AJ, et al (2007). Risk factors for breast cancer in patients treated at NORI Hospital, Islamabad. J Pak Med Assoc, 57, 242-5.
Farooq A, Naveed AK, Azeem Z, Ahmad T (2011). Breast and ovarian cancer risk due to prevalence of BRCA1 and BRCA2 variants in Pakistani population: a Pakistani database report. J Oncol, 1-8.
Ferro, Roberto (2012). Pesticides and breast cancer. Adv Breast Cancer Res, 1, 30-35.
Gage M, Wattendorf D, Henry LR (2012). “Translational advances regarding hereditary breast cancer syndromes”. J Surg Oncol, 105, 444-51.