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Review Report

CARCINOGENIC FACTORS OF BREAST CANCER IN FEMALE OF PAKISTAN

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ABSTRACT:

Among all forms of cancers, Breast cancer is the most common type of cancer in females worldwide. It is in fact the second leading causes of death among female population. However, incidence rate of breast cancer is higher among Pakistani females compare to other countries of Asia. The major factors that play important role in the development of breast carcinoma are the genetics and environment, the reproductive experience, the effect of endogenous and exogenous hormones in females and the change in immune status. However, in the Pakistani women hormonal factors including age of menarche, use of oral contraceptives, central obesity, family history, polycystic ovaries, nulliparity, late age at first pregnancy, smoking, alcohol consumption and lack of breast feeding are some of the most common risk factors developing breast cancer. Furthermore, the high prevalence of BRCA mutations indicates the importance of genetic counseling. Focus should be given to find out the 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.

Keywords: nulliparity, breast cancer, polycystic ovaries

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INTRODUCTION:

Among all forms of cancers, Breast cancer is the most common type of cancer in females worldwide. In fact, it is the 2nd leading cause of death among female population. The situation is more alarming in Pakistan as the incidence rate of breast cancer is higher among Pakistani females compare to other countries of Asia, i.e., it accounts for one in nine Pakistani female population. More precisely, as compared to its neighboring countries, Iran and India, the chances of breast cancer in Pakistani women are 2.5 times higher. The objectives of this mini-review were to gather literature regarding the most common risk factors attributed to breast cancer in Pakistani women, to determine disease knowledge of the population regarding breast cancer and to provide awareness about breast cancer to the general population.

RISK FACTORS ATTRIBUTING BREAST CANCER:

With the increase in frequency of diagnosis of breast cancer in Pakistani women, it is important to point out the basic etiology of breast cancer. Breast cancer etiology is a complex of genetic, environmental and lifestyle factors and there are variations in diversity of these factors among areas, therefore it highlighted the need for study of this diversification for each geographical area. Considering this, the focus is made on involvement of variety of risk factors in breast cancer etiology was explored in Pakistani population.

Physiological factors that are considered as a risk factor of breast cancer are:

Gender: Just Being a women is one of the most fundamental but unavoidable risk factor of breast cancer. It means that women are at greater risk than men. The possible reason for this might be the female sex hormones, estrogen and progesterone, which promote growth of breast cancer cells.

Age: Another unavoidable physiological risk factor for developing breast cancer is the increasing

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age. A case control study was determined to study the effect of various factors, including age, on the development of breast cancer. The risk factors investigated were age, demographic, social, menstrual, reproductive, and genetic histories. Total 115 patients were studied and interviewed from different hospitals of Karachi. It was observed that age group of 41 to 50 years were at the highest risk of developing breast cancer (Safila *et al.*, 2014).

Obesity: Being over-weight is another factor that predisposes women to breast cancer development. As mentioned earlier, the possible reason for increased risk of breast cancer in women is the presence of female sex hormones, estrogen and progesterone. Once ovaries are unable to secrete estrogen (i.e., menopause), the most prominent source of a woman's estrogen is then adipose tissues. Thus estrogen level is directly proportional to the body's fat content, and obesity, thus, increases ones chance of getting breast cancer. Different studies supported the link of breast cancer with high basal metabolic rate (BMI) (Bhurgri *et al.*, 2007, Zhu *et al.*, 2005 and Rabia *et al.*, 2013).

Social And Environmental Factors that can be the major factor for breast cancer are:

Smoking: Smoking also increases the risk of developing breast cancer. Different Studies have shown the link between smoking and breast cancer. Six months study was conducted in NORI to assess the role of smoking as breast cancer risk factor. Study population included 300 females; 150 of which were breast cancer patients and the rest were their age-matched non-cancerous women who attended the NORI. It was observed that smoking is most significantly associated with breast cancer in patients attending NORI (Faheem *et al.*, 2007). Similar results were also observed by Gillani *et al.*, 2006.

Family History: Family history is also very important risk factor. Close female relatives of patients are at greater risk of developing breast cancer. If the patient is your close relative like your sister, mother and daughter than your risk is doubled (Gillani *et al.*, 2006).

Nutritional Status: Nutritional Status is also very important. Studies have shown that fat-soluble Vitamin D is a naturally occurring anti-proliferative compound. Human genes contain vitamin D response elements that encode for proteins important in regulation of cell differentiation, proliferation and angiogenesis. Vitamin D shows its anti-cancer effect by binding to vitamin D receptor (VDR) found in various tissues and cells. Thus, lack of vitamin D intake can be considered as risk of breast cancer (Shamsi *et al.*, 2013).

Reproductive Factors: Reproductive factors are also very important to consider. Study have shown that women who started menstruating early (i.e., early menarche, before 12 years of age) and/or went through menopause later (i.e., late menopause, after 55 years of age) are at increased risk of developing breast cancer. The possible reason for this might be the increased exposure to female sex hormones, estrogen and progesterone.

Nulliparity: Nulliparity is another factor associated with breast cancer. A case control study was performed in Mayo Hospital Lahore, from October 2008 to April 2009. Menstrual and reproductive history was taken from both 150 breast cancer patients and 300 controls. Results showed that age at menarche had no association with breast cancer for both pre and postmenopausal women, but nulliparity was a risk for both pre and postmenopausal. Furthermore, it was concluded that majority of risk factors for pre and postmenopausal are also associated with postmenopausal breast cancer except less parity that is important for menopausal breast cancer only (Butt *et al.*, 2012). In another study it was found that single marital status and older age at menopause conferred an increased risk of breast cancer for women. On the other hand, increasing parity decreased the breast cancer risk (Shamsi *et al.*, 2013).

Increased age at first live birth and lack of breastfeeding: Increased age at first live birth and lack of breastfeeding have also been linked to increased breast cancer risk (Butt *et al.*, 2012). Breast feeding causes hormonal alterations, like decrease in the level of estrogen and removal of possible

carcinogens stored in the fatty breast tissue, which collectively develop the resistant to mutations in the cells that can lead to cancer.

High ratio of incomplete pregnancies also significantly increases breast cancer risk (Rabia *et al.*, 2013). As discussed, the possible reason might be the increased exposure to female sex hormones.

GENETIC ETIOLOGY OF BREAST CANCER:

Body cells are continuously dividing into new cells, and even die. There are several genes that control the growth of cells. Among these are the oncogenes that promote cell division, and tumor suppressor genes that slow down the cell division, or cause the cell to die at right time. Mutation/changes in the nucleic acids that either activates oncogenes or inhibits tumor suppressor genes can cause normal breast cells to become cancerous .

Breast cancer susceptibility is largely 'polygenic", which means breast cancer is 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. Polymorphisms of a single nucleotide in many genes have also been associated with high morbidity and susceptibility to breast cancer.

Little work has been done only in Chinese population among Asians, and scarcely on women of Pakistan, to determine the association of genetic factors with breast cancer. 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. To estimate the contribution of genetic factors, a case-control study was conducted in 2002 on 341 breast cancer patients and 200 female control subjects. Data analysis concluded that mutation in BRCA2 genes was observed in 6.7% patients and mutations of the BRCA1 gene were observed in 65% of patients. It was also observed that five mutations of BRCA1, i.e., 2080insA, 3889delAG, 4184del4, 4284delAG, and IVS14-1A->G, and one mutation of BRCA2, i.e., 3337C->T, were recurrent in case subjects and represented candidate founder mutations (Foulkes *et al.*, 2002). Interestingly, majority of detected mutations were unique to Pakistani population. Prevalence of BARCA1 and BARCA2 mutations in Pakistani females was also studied by Rashid *et al.*, 2006 and somewhat similar results were obtained (Rashid *et al.*, 2006).

Along with BARCA1 and BARCA2 genes, recent research showed presence of other genes that lead to breast cancer, as shown by the results of Farooq *et al.*, 2011. They formulated the database report on BARCA1 and BARCA2 variants in Pakistani population, aiming to check the contribution of genetic modification in prevailing breast and ovarian cancer. Percentage involvement of BARCA1 and BARCA2 gene was estimated. Nine percent of these cancers showed alterations in BRCA1 gene while 3% have shown BRCA2 variants while the remaining 88% of breast and ovarian cancers can be due to the involvement of other genes (Farooq *et al.*, 2011).

Positive family history reflects inherited mutated genes that may be due to intra-family marriages. Studies conducted in Pakistan showed high risk of breast cancer due to consanguineous marriages (Gillani *et al.*, 2006 and Shamsi *et al.*, 2013).

To study the role of estrogen-metabolizing pathway and estrogen receptor pathway in the development of breast cancer, a case control study was conducted on 100 breast cancer female patients and 100 control samples aged 15-65 years. It was observed that Polymorphism of genes involving estrogen-metabolizing pathway and estrogen receptor pathway also play an important role (Ali *et al.*, 2011).

PROSPECTS FOR THE FUTURE:

Incidence and prevalence of breast cancer is higher among Pakistani females compare to other countries of Asia. There are many factors that play important role in the development of breast

carcinoma; however, the focus should be given to find out the genetic factors causing breast cancer in Pakistani population in order to prevent and decrease its incidence. Furthermore, to prevent breast cancer hazards, there is a need for early diagnosis of cases. The development of effective screening program at the government level will be helpful in not only prevention and treatment of breast cancer, and subsequently it will also improve prognosis in these patients. Education of public is highly important to boost cancer awareness for prevention, early diagnosis and treatment. Female awareness should be increased. Training should be given to younger age group in the colleges and schools for breast self-examination (BSE). Media should play their role to provide awareness among general population. Breast care clinics and screening programmes should be started in all hospitals. Last, but not the least, 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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