Breast Cancer Risk Factors: A Review

Authors: Aaliya Bhat[1], , Younus Ahmad Bhat[1], Shayaq ul Abeer Rasool[3], Mudasar Nabi[1], Rouf Maqbool[1], Sairish Ashraf[1] , Ganai BA[2]

Affliations: 1. Department of biochemistry, university of Kashmir
2. centre of research development, university of Kashmir
3. Department of Biotechnology, university of Kashmir
Corresponding Author: Ganai BA

Abstract: **Breast cancer continues to be a leading health problem across the globe with the number of reported cases on an ever increasing rise. It is the leading cause of cancer related deaths among women. For breast cancer early detection is best prevention. For this , woman in general and high risk group in particular should undergo regular checkups. In this review we discuss about the risk factors associated with cancer. Also it deals with the classification of breast cancer on based on different criteria.**
Key words: **breast cancer, classification, risk factors.**

1. Introduction:

Breast cancer is most frequently diagnosed and leading cancer among women world-wide. It originates in breast tissue, which is made up of glands for milk production, called lobules, and the ducts that connect the lobules to the nipple. Belonging to a heterogeneous group of diseases, breast cancer is characterized by the disordered cellular programming, where in cells loose the normal growth control regulation. Primary tumor originates in breast itself but once it switches to invasive state, breast cancer cells spread to other parts of body where they can grow into new tumors and become invasive in nature (Cady 1984, Jatoi 1997) Today, breast cancer is presenting itself as the global health burden, ranking second among most common cancers in world and first among the cancers of women population, both in the developed and less developed countries of the world. It is the leading cancer among women worldwide. A more recent study reported that 2013 saw 0.7 million cases of breast cancer with 0.5 million deaths, globally, and this number is expected to double to 3.2 million cases by year 2030 in low and middle income countries, mainly India and china (Denny et al,2016). In India, 41.3% of all cancers in females account for breast and cervical cancer with an estimated increase in breast cancer from 153,297 cases to 235,490 cases in the years between 2011-2026 (Torre et al.,2015). Similar trend is also observed in Kashmir, with 1797 cases reported between 2000-2013, accounting for the 16.83% of all the cancers among Kashmiri women (Wani et al.2014). Rise of breast cancer is so rampant in India that if we do not act now, we are in major shock for next twenty years.

For breast cancer, early detection is best prevention. Signs and symptoms of breast cancer include: Pain in the breast or armpit, hard lump in the breast, change in the position of nipple, change in the shape and size of breast and nipple , discharge or bleeding from the nipple, Skin changes, redness and, rashes over the breast and Palpable masses in axilla.

2. Classification of Breast cancer:

Different criteria have been adopted to classify breast cancer, each serving a different purpose. Most of the classifications are based on Histological type, grade, stage (TNM), presence or absence of receptors and presence or absence of genes as determined by DNA testing.

2.1. Histopathological based classification of breast cancer:

It classifies the different tumors of breast on the basis of the characteristics of biopsy specimen, as seen under light microscopy. As for as histopathology is concerned, breast cancer is classified as ductal or lobular carcinoma, which can be localized (in-situ) or invasive.

2.1.1. In-situ breast carcinoma: also referred to as non-invasive carcinoma, it is small and localized tumor. Depending, on the type of tissue from which it arises, it has been further classified as Ductal Carcinoma In –situ (DCIS), originating from the ducts of breast or Lobular carcinoma in-situ (LCIS), whose origin is the milk carrying lobules of breast. Of the two DCIS, is not life-threatening but has

high potential to develop into invasive carcinoma (Page, et al. 1982; Bellamy, et al. 1993), where as LCIS has less chances to progress to invasive type, but is multi focal, i.e. it usually , effects both the breasts (Frykberg et al. 1987;Singletary SE et al.,2002).

2.1.2. Invasive breast carcinoma: As against in-Situ carcinoma, invasive carcinoma has the potential to metastasize and spread throughout the body. For this reason it is also known as infiltrating carcinoma. Again, it is of two types: Ductal Invasive carcinoma and Lobular Invasive carcinoma. Ductal invasive carcinoma accounts for 75% of all invasive breast carcinomas (Li et al. 2003) where as Lobular invasive carcinoma, make up 5-10% of all invasive carcinomas (Borst and Ingold, 1993;Martinez and Azzopardi, 1979; Li et al. 2003).In addition to these two types, other forms of invasive breast carcinomas include tubular cancers (slow-growing, tube-shaped cancers), mucinous cancers (cancers that contain a mucous protein) and medullary cancers (cancers that look like the medulla {gray matter} of the brain),(Diab et al. 1999; Li et al. 2003) .

2.2. Classification based on grade of tumors:

This classification is based on degree of microscopic similarity between breast tumor tissue and normal breast tissue. Usually grading is done as per Scarff-Bloom-Richardson grading system (Bloom and Richardson, 1957; Achard et al. 2002) which grades breast tumors by giving scores(1 to 3 points) to the features of tissues like , nuclear pleomorphism, and mitotic count, and adding up theses scores to grade the tumor. The scores for each of these three criteria are then added together to give an overall final score and corresponding grade as Grade 1 (well differentiated) Grade 2 (moderately differentiated) and Grade 3 (poorly differentiated).Grade 3 cancers tend to grow and spread more quickly while as Grade 1 tumors have more favorable prognosis, less aggressive treatment and better rates of survival.

2.3. Classification based on Staging of breast tumors:

As recommended by American Joint committee on cancer (AJCC) and International union (UICC) against cancer, breast cancer is staged according to TNM (Tumor-node –metastasis) system, a two step procedure (Singletary SE 2002). It takes into account size of tumor (T), extent of involvement of regional lymph node (N) and presence or absence of metastasis (M) beyond regional lymph node and grouping these factors into over stage of breast tumor. Based on this system, tumors are classified from stage 0 to stage IV, in which Stage 0 refers to in situ cancer, while as stages I to IV specify invasive cancer, with stage IV indicative of metastatic tumor that has spread to distant organs.

2.4. Classification based on Receptor status:

This classification is based on presence or absence of three receptors, namely Estrogen receptor, Progesterone receptor and Her2Neu receptor, identified by immunohistochemistry.

According to this classification breast tumors are designated as estrogen positive or negative (ER+/-) tumors, Progesterone positive or negative tumors (PR +/-) and Her2Neu positive or negative tumors (Her2Neu +/-). Tumor is designated as Triple negative, if it lacks the expression of all the three receptors and has the least prognostic value among the breast tumors. This receptor status of the tumor is crucial for determining and selecting the treatment against it.

3. Risk Factors for breast cancer:

Although of such common occurrence, the exact etiology of breast cancer is still unknown. It is believed that breast cancer is a multi factorial disease arising as a result of the interaction of genetic and environmental factors (Ponder, 2001).Despite this improved knowledge, the unraveling of the complex genetic and environmental influences on this disease is still at an early stage. An even better understanding of the genetic mechanisms underlying the development and progression of breast cancer would be a major advance for improved prevention, detection and treatment strategies(Loizidou et al.2010) . To date, several risk factors have been identified that increase breast cancer risk and at the same time several protective factors have also been identified. Most of the identified risk factors for breast cancer are non-modifiable such as age, sex, family history, menopausal status while as there are many others that can be modified and controlled. Examples include: Use of menopausal hormones, alcohol consumption, breast feeding, and post menopausal obesity.

3.1. Gender and Age: Women are generally at higher risk for developing breast cancer. They are 100 times more likely to get breast cancer than men. Besides being female; age is the most important risk factor for breast cancer. Most advanced breast cancer cases are found in women over age 50. Breast cancer incidence increases with age and doubles almost every ten years until menopause, when the rate of increase slows dramatically, suggesting an important role of reproductive hormones on breast cancer etiology. The median age for developing breast cancer was 61 years during 2008-2012 (Howlader et al.2015)

3.2. Hormones and Reproductive factors: Reproductive hormones are thought to influence breast cancer risk by increasing cell proliferation, thereby increasing the likelihood of DNA damage, as well as promotion of cancer growth. Younger age at first full-term

pregnancy (<30 years) and a greater number of pregnancies decrease the risk of breast cancer over the long term; however, there also appears to be a transient increase in breast cancer risk following a full-term pregnancy, particularly among women who have a first birth at older ages.. Breastfeeding has been shown to decrease a woman's risk of breast cancer, with greater benefit associated with longer duration.

Recent use of menopausal hormones (previously referred to as hormone replacement therapy (HRT) or menopausal hormone therapy) with combined estrogen and progestin increases the risk of developing and dying from breast cancer, with higher risk associated with longer use (6-8). Risk is also greater for women who start hormone therapy soon after the onset of menopause compared to those who begin use later (Beral et al.2011; Prentice et al. 2008). The increased risk appears to diminish within 5 years of discontinuation of hormone use (Beral et al.2011; Chlebowski et al.2010) (Calle et al. 2009). Estrogen alone can be prescribed for women without a uterus, and it is less clear if this therapy increases risk of breast cancer.

3.3. Breast density and Bone Mineral Density: High breast tissue density (a mammographic indicator of the amount of glandular tissue relative to fatty tissue in the breast) has been shown to be a strong independent risk factor for the development of breast cancer (Boyd,et al. 2002; Ursin et al. 2009). Also high bone mineral density in postmenopausal women also has been recognized as a risk factor for breast cancer in most studies (Cauley et al. 1996; Zhang et al. 1997; Zmuda, Cauley et al. 2001; Kerlikowske et al. 2005; Chen et al. 2008) , probably mediated by hormonal factors.

3.4. Benign Breast diseases: Some types of benign breast conditions are more closely linked to breast cancer risk than others (London et al. 1992; Hartmann et al. 1999; Collins, Baer et al. 2007). Benign breast conditions are generally categorized into 3 general groups, reflecting the degree of risk: non-proliferative lesions, proliferative lesions without atypia, and proliferative lesions with atypia. Non-proliferative lesions are not associated with overgrowth of breast tissue and have little to no effect on breast cancer risk. Proliferative lesions without atypia (those with excessive growth of cells in the ducts or lobules of the breast tissue) are associated with a small increase in the risk of breast cancer (1.5 to 2 times normal)(Hartmann et al. 2005; Tamimi, Byrne et al. 2005; Ashbeck et al. 2007).Proliferative lesions with atypia (those with excessive growth of abnormal cells in the ducts or lobules of the breast tissue) are associated with the greatest breast cancer risk – 4 to 5 times that of average-risk women)(Hartmannet al. 2005; Tamimi et al. 2005; Ashbeck et al. 2007) .They include atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH).

3.5. Obesity: Obesity is another known risk factor for breast cancer. Obese women have an increased risk for postmenopausal but not premenopausal breast cancer. The association between obesity and breast cancer risk has been proposed to be largely due to increased estrogenic activity in overweight women. Breast, which are estrogen sensitive tissues, are therefore exposed to more estrogen stimulation in obese women, leading to increased risk for breast cancer. A second possible mechanism is that obesity, which is associated with metabolic syndrome increases the level of circulating insulin and insulin like growth factor (*IGF1*)(Lorincz and Sukumar, 2006). Insulin and IGF-1 have been implicated in breast tumorogenesis because of their ability to stimulate mitogenesis, and their key role in mammary gland cell proliferation and survival (Imagawa et al. 2002; Deming et al. 2007).

3.6. Environmental agents and life style factors: Environmental carcinogens like PCB's, arsenals, substances in plastics and certain cosmetics have been linked to increasing risk of breast cancer(Engel et al. 2005; Cohn et al. 2007;Romieu et al. 2000; Steck, Gaudet et al. 2007) link between radiation exposure and breast cancer has been demonstrated in studies of atomic bomb survivors and women who have received high-dose radiation therapy to the chest, particularly those who were first exposed at younger ages(Preston et al. 2002; Land et al. 2003).

Numerous epidemiological studies have investigated the relationship between lifestyle factors such as diet, alcohol consumption, smoking and breast cancer risk. A recent meta-analysis suggests that soy food intake in the amount in the Asian population may have protective effect against breast cancer (Wu, et al. 2008). In addition high diet seems to be weakly associated with breast cancer risk, where as a diet rich in fruits and vegetables that are good a source of natural antioxidants seems to protect women from breast cancer (DeBruin and Josephy, 2002). High risk of breast cancer has been associated with alcohol consumption and tobacco smoke (Palmer and Rosenberg. 1993). Risk is also high among post menopausal women who lead sedentary life style(Bernstein, et al. 1994; Friedenreich, 2001; Hamajima, et al. 2002).Exercise has been reported to lower women's exposure to endogenous estrogen levels, and the women who do regular exercise have low risk of developing breast cancer, indirectly(Bray, et al. 2002) .

3.7. Family history of breast cancer and genetic predisposition: Women with a family history of breast cancer, especially in a first-degree relative are at increased risk of developing breast cancer and the risk is higher if more than one first-degree relative developed breast cancer. Compared to women without a family history, risk of breast cancer is 1.8 times higher for women with one first-degree female relative who has been diagnosed, nearly 3 times higher for women with two relatives, and nearly 4 times higher for women with three or more relatives (Collaborative Group on Hormonal Factors in Breast 1997).

Estimated that 5%-10% of breast cancer cases result from inherited mutations, including those in the breast cancer susceptibility genes BRCA1 and BRCA2 (Schwartz, et al. 2008). These mutations are present in far less than 1% of the general population, but occur more often in certain ethnic groups such as those of Ashkenazi (Eastern European) Jewish descent (Schwartz et al. 2008). Women with BRCA1 mutations are estimated to have a 44-78% risk for developing breast cancer by 70 years of age; the corresponding risk for BRCA2 mutations is 31-56%.While a family history of breast cancer suggests an inherited influence on disease risk, BRCA1 or BRCA2

mutations account for only about 15-20% of familial breast cancers(Turnbull and Rahman, 2008). Breast cancer can also result from the inheritance of other less common genetic syndromes (e.g., Li-Fraumeni and Cowden syndromes). A number of more common genetic mutations have also been identified that are less strongly associated with breast cancer risk(Turnbull and Rahman, 2008). Any of these mutations can be inherited from either parents , and they may be inherited by offsprings. It is believed that much of the occurrence of breast cancer in families results from the interaction between lifestyle factors and low-risk variations in genetic factors that may be shared by women within a family (Lichtenstein, et al. 2000).

It is suggested that the effect of low penetrance cancer susceptibility genes modulated by environmental exposure and lifestyle factors are likely to account for most of sporadic breast carcinoma cases (Rothman et al. 2001). In the latter's, the proportion of breast carcinoma attributable to such genetic traits, in combination with environmental exposure, is likely to be much higher than the hereditary proportion and accounts for 90 to 95% of all breast carcinoma cases(Rothman et al. 2001). Candidate genes of low-penetrance breast carcinoma susceptibility include those encoding for Xenobiotic Metabolizing Enzymes (XMEs) involved in carcinogen metabolism and detoxification .Polymorphisms in both phase I and phase II enzyme genes may result in alteration of their expression, function and activity. Several studies have attempted to tackle the genetic polymorphisms of different XMEs alone or in combinations with altered risks of breast carcinoma (Han et al. 2004; Chacko et al. 2005) Moreover, because of the great number of carcinogen-activating and detoxifying enzymes, the complexity of exposures to environmental carcinogens and gene-gene interactions, evaluating a single polymorphic enzyme may not be sufficient to assess their role in carcinogenesis. However, accumulating series of alleles "at risk" considerably increase the cancer risk.

References:

- Achard, J.-L., I. van Praagh,(2002). "Scarff-Bloom-Richardson (SBR) grading: a pleiotropic marker of chemosensitivity in invasive ductal breast carcinomas treated by neoadjuvant chemotherapy." International journal of oncology **20**(4): 791-796.
- Ashbeck, E. L., R. D. Rosenberg, et al. "Benign breast biopsy diagnosis and subsequent risk of breast cancer." Cancer Epidemiology and Prevention Biomarkers **16**(3): 467-472.
- Bellamy, C. O. and D. J. Harrison (1994). "Evaluation of glutathione S-transferase Pi in non-invasive ductal carcinoma of breast." British journal of cancer **69**(1): 183.
- Beral, V., G. Reeves "Breast cancer risk in relation to the interval between menopause and starting hormone therapy." Journal of the National Cancer Institute.
- Bernstein, L., B. E. Henderson, (1994). "Physical exercise and reduced risk of breast cancer in young women." Journal of the National Cancer Institute **86**(18): 1403-1408.
- Bloom, H. J. G. and W. W. Richardson (1957). "Histological grading and prognosis in breast cancer: a study of 1409 cases of which 359 have been followed for 15 years." British journal of cancer **11**(3): 359
- Borst, M. J. and J. A. Ingold (1993). "Metastatic patterns of invasive lobular versus invasive ductal carcinoma of the breast." Surgery **114**(4): 637-41; discussion 641-2.
- Boyd, N. F., G. S. Dite(2002). "Heritability of mammographic density, a risk factor for breast cancer." New England journal of medicine **347**(12): 886-894
- Bray, F., R. Sankila,(2002). "Estimates of cancer incidence and mortality in Europe in 1995." European Journal of Cancer **38**(1): 99-166.
- Calle, E. E., H. S. Feigelson, (2009). "Postmenopausal hormone use and breast cancer associations differ by hormone regimen and histologic subtype." Cancer **115**(5): 936-945.
- Cauley, J. A., F. L. Lucas, (1996). "Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures." Jama **276**(17): 1404-1408.
- Chacko, P., T. Joseph, (2005). "Role of xenobiotic metabolizing gene polymorphisms in breast cancer susceptibility and treatment outcome." Mutation Research/Genetic Toxicology and Environmental Mutagenesis **581**(1): 153-163.
- Chen, Z., L. Arendell,(2008). "Hip bone density predicts breast cancer risk independently of Gail score." Cancer **113**(5): 907-915.
- Chlebowski, R. T., G. L. Anderson(2010). "Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women." Jama **304**(15): 1684-1692.
- Cohn, B. A., M. S. Wolff(2007). "DDT and breast cancer in young women: new data on the significance of age at exposure." Environmental health perspectives: 1406-1414.

- Collins, L. C., H. J. Baer(2007). "Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia." Cancer **109**(2): 180-187.
- DeBruin, L. S. and P. D. Josephy (2002). "Perspectives on the chemical etiology of breast cancer." Environmental health perspectives **110**(Suppl 1): 119.
  demographic profiles: National Cancer Registry 2000-2012." Indian journal of cancer **51**(2): 133
- Denny, L., S. de Sanjose(2016). "Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries." The Lancet.
- Diab, S. G., G. M. Clark, (1999). "Tumor characteristics and clinical outcome of tubular and mucinous breast carcinomas." Journal of clinical oncology **17**(5): 1442-1442.
- Engel, L. S., D. A. Hill, et al. (2005). "Pesticide use and breast cancer risk among farmersâ€™ wives in the agricultural health study." American journal of epidemiology **161**(2): 121-135.
  epidemiologic study of environmental carcinogens." Biochimica et Biophysica Acta (BBA)- Reviews on Cancer **1471**(2): C1-C10. cancer **98**(1): 9-14.
- Friedenreich, C. M. (2001). "Review of anthropometric factors and breast cancer risk." European Journal of Cancer Prevention **10**(1): 15-32.
- Frykberg, E. R., F. Santiago,(1987). "Lobular carcinoma in situ of the breast." Surgery, gynecology & obstetrics **164**(3): 285-301.
- Hamajima, N., K. Hirose, (2002). "Alcohol, tobacco and breast cancer--collaborative reanalysis of
- Han, W., D. Kang, (2004). "Associations between breast cancer susceptibility gene polymorphisms and clinicopathological features." Clinical Cancer Research **10**(1): 124-130.
- Hartmann, L. C., T. A. Sellers,(2005). "Benign breast disease and the risk of breast cancer." New England journal of medicine **353**(3): 229-237.
- Howlader, N., A. M. Noone, (2015). "SEER cancer statistics review, 1975â€“2010. 2013." Bethesda, MD: National Cancer Institute.
- Imagawa, W., V. K. Pedchenko, (2002). "Hormone/growth factor interactions mediating epithelial/stromal communication in mammary gland development and carcinogenesis." The Journal of steroid biochemistry and molecular biology **80**(2): 213-230.
  individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease."
- Kerlikowske, K., J. Shepherd, (2005). "Are breast density and bone mineral density independent risk factors for breast cancer?" Journal of the National Cancer Institute **97**(5): 368-374.
- Land, C. E., M. Tokunaga,(2003). "Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950â€“1990." Radiation research **160**(6): 707-717
- Li, C. I., J. R. Daling, (2003). "Incidence of invasive breast cancer by hormone receptor status from 1992 to 1998." Journal of clinical oncology **21**(1): 28-34.
- Lichtenstein, P., N. V. Holm, et al. (2000). "Environmental and heritable factors in the causation of cancerâ€"analyses of cohorts of twins from Sweden, Denmark, and Finland." New England journal of medicine **343**(2): 78-85.
- Loizidou, M. A., M. A. Cariolou, (2010). "Genetic variation in genes interacting with BRCA1/2 and risk of breast cancer in the Cypriot population." Breast cancer research and treatment **121**(1): 147-156.
- London, S. J., J. L. Connolly, (1992). "A prospective study of benign breast disease and the risk of breast cancer." Jama **267**(7): 941-944.
- Lorincz, A. M. and S. Sukumar (2006). "Molecular links between obesity and breast cancer." Endocrine- related cancer **13**(2): 279-292.
- Martinez, V. and J. G. Azzopardi (1979). "Invasive lobular carcinoma of the breast: incidence and
- Page, D. L., W. D. Dupont, (1982). "Intraductal carcinoma of the breast: Followâ€up after biopsy only." Cancer **49**(4): 751-758.
- Ponder, B. A. (2001). "Cancer genetics." Nature.(411: 336-341).
- Prentice, R. L., R. T. Chlebowski, (2008). "Estrogen plus progestin therapy and breast cancer in recently postmenopausal women." American journal of epidemiology **167**(10): 1207-1216.

- Preston, D. L., A. Mattsson, (2002). "Radiation effects on breast cancer risk: a pooled analysis of eight cohorts." Radiation research **158**(2): 220-235
- Romieu, I., M. Hernandez-Avila, (2000). "Breast cancer, lactation history, and serum organochlorines." American journal of epidemiology **152**(4): 363-370.
- Rothman, N., S. Wacholder, (2001). "The use of common genetic polymorphisms to enhance the
- Schwartz, G. F., K. S. Hughes, (2008). "Proceedings of the international consensus conference on breast cancer risk, genetics, & risk management, April, 2007." Cancer **113**(10): 2627-2637
- Singletary SE, A. C., Ashley P, et al: . (2002). "Revision of the American Joint Committee on Cancer staging system for breast cancer." J Clin Oncol **20:** : 3628-3636.
- Steck, S. E., M. M. Gaudet, et al. (2007). "Cooked meat and risk of breast cancerâ€"lifetime versus recent dietary intake." Epidemiology **18**(3): 373-382.
- Tamimi, R. M., C. Byrne, (2005). "Benign breast disease, recent alcohol consumption, and risk of breast cancer: a nested caseâ€"control study." Breast cancer research **7**(4): R555.
- Turnbull, C. and N. Rahman (2008). "Genetic predisposition to breast cancer: past, present, and future." Annu. Rev. Genomics Hum. Genet. **9**: 321-345.
- Ursin, G., E. O. Lillie, (2009). "The relative importance of genetics and environment on mammographic density." Cancer Epidemiology and Prevention Biomarkers **18**(1): 102-112.
variants." Histopathology **3**(6): 467-488.
- Wani, M. A., F. A. Jan, (2014). "Cancer trends in Kashmir; common types, site incidence and
- Zhang, Y., D. P. Kiel, (1997). "Bone mass and the risk of breast cancer among postmenopausal women." New England journal of medicine 336(9): 611-617.
- Zmuda, J. M., J. A. Cauley, (2001). "Bone mass and breast cancer risk in older women: differences by stage at diagnosis." Journal of the National Cancer Institute 93(12): 930-936.