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Breast Cancer in Women and Risk Factors

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Abstract.

Most common cancers in the United States are those of breast, prostate, lung, colon rectum and blood. Among Asian countries, Pakistan has the highest rates of breast and ovarian cancer. Breast cancer is the fourth leading cause of mortality by cancer in women. Symptoms of breast cancer include a breast lump and nipple discharge. Cancer is a disease characterized by uncontrolled, uncoordinated and undesirable cell division. Unlike normal cells, cancer cells continue to grow and divide for their whole lives, replicating into more and more harmful cells. The abnormal growth and division observed in cancer cells is caused by damage in these cell's DNA. Environmental factors can initiate a chain of events that results in cellular DNA defects that lead to cancer. There are well-established risk factors for breast cancer, most of which relate to estrogens and growth hormones in females. These include early-age menarche, late-age menopause, postmenopausal obesity and use of hormone therapy. Certain occupational exposures also increases the risk of developing postmenopausal cancer, as breast tissue is more sensitive to adverse effects if exposure occurs during the breast cell proliferation. Human papillomaviruses, mouse mammary tumor virus and Epstein-Barr virus are the prime candidate viruses as causes of human breast cancer. BRCA1 and BRCA2 are major cancer predisposition genes, responsible for a large percentage of hereditary breast and ovarian cancer (HBOC) families. Weight and carbohydrate intakes are associated with risk of ER-positive breast cancer. The recent emphasis on health education, early diagnosis of cancers, and more public facilities for cancer treatment are expected to bring about the much needed improvement in breast cancer care in India. In present paper an attempt has been made to overview the breast cancer in woman and risk factors causing cancer.

Keywords: *Breast cancer, Risk factors, Environmental and genetic, BRCA1 &BRCA2genes.*

Breast Cancer in Women and Risk Factors.

Breast cancer is the commonest cancer of urban Indian women and the second commonest in the rural women. About 13% of the annual deaths worldwide are cancer related. Cancer is the second most common cause of death in the developed world. Most common cancers in the United States are those of breast, prostate, lung, colon rectum and blood. Among Asian countries, Pakistan has the highest rates of breast and ovarian cancer. The incidence of breast cancer is low in India, but rising. Owing to the lack of awareness of this disease and in absence of a breast cancer screening program, the majority of breast cancers are diagnosed at a relatively advanced stage.

Cancer is a group of diseases characterized by cell proliferation. It is not a single disease; rather, it is a heterogeneous group of disorders characterized by the presence of cell that do not respond to the normal controls on division. Cancer occurs when this cellular reproduction process goes out of control. In other words, cancer is a disease characterized by uncontrolled, uncoordinated and undesirable cell division. Unlike normal cells, cancer cells continue to grow and divide for their whole lives, replicating into more and more harmful cells. The abnormal growth and division observed in cancer cells is caused by damage in these cell's DNA. There are a variety of ways that cellular DNA can become damaged and defective. For example, environmental factors (such as exposure to tobacco smoke) can initiate a chain of events that results in cellular DNA defects that lead to cancer. Alternatively, defective DNA can be inherited from your parents. Tumors come in two forms; benign and malignant. Benign tumors are not cancerous, thus they do not grow and spread to the extent of cancerous tumors. Benign tumors are usually not life threatening. Malignant tumors, on the other hand, grow and spread to other areas of the body. The process whereby cancer cells travel from the initial tumor site to other parts of the body is known as metastasis. It is a class of neoplastic diseases in which a group of cells display uncontrolled growth, invasion and sometimes metastasis (Spread to other locations in the body via lymph or blood) Neoplasm means a new growth as an abnormal mass of tissues which grow in an uncontrolled way that of normal tissues in the some excessive manner after cessation of stimuli that evoked the change. (Willlis,1952).

All cells contain cancer genes, which when de repressed cause cancer . In normal cells these genes are repressed (Bush, 1962). Genes present in all cells which are important in the induction of cancer are oncogenes. They are responsible for basic cellular functions in normal cells, but when mutated, they become oncogenes that contribute to the development of cancer. Der et al., (1982) found that activated oncogenes become homologous of retroviral transforming genes. The development of a fully malignant tumor appears to involve the activation or altered expression of proto-oncogene to oncogenes and the loss or inactivation of tumor suppressor genes the function of which is to control normal cellular activity (Fearon et al., 1990; Sagar, 1989; Stanbridge, 1990).

Breast cancer is the fourth leading cause of mortality by cancer in women. Symptoms of breast cancer include a breast lump and nipple discharge. There are well-established risk factors for breast cancer, most of which relate to estrogens and growth hormones in females. These

include early-age menarche, late-age menopause, postmenopausal obesity and use of hormone therapy. Human papillomaviruses, mouse mammary tumor virus and Epstein-Barr virus are the prime candidate viruses as causes of human breast cancer.

Human papillomaviruses and the mouse mammary tumor virus have hormone responsive elements that appear to be associated with enhanced replication of these viruses in the presence of corticosteroid and other hormones. This biological phenomenon is particularly relevant because of the hormone dependence of breast cancer. Germline point mutations in BRCA1 and BRCA2 genes account for about 30% of the inherited breast and ovarian cancers. Germline genomic rearrangements have been found in both BRCA1 and BRCA2 genes, but the extent to which these alterations might contribute to increasing the actual mutation detection rate is still debated.

BRCA1 and BRCA2 are major cancer predisposition genes, responsible for a large percentage of hereditary breast and ovarian cancer (HBOC) families. Many studies indicate that fat in foods also increases one's risk for cancer, and it may adversely affect breast cancer survival rates for those who have cancer (Wynder et al.,1986).

Alcohol intake has been reported to be positively associated with an increased risk of postmenopausal breast cancer; however, the association with the estrogen receptor (ER) and progesterone receptor (PR) status of the breast tumors remains unclear. The observed association between risk of developing postmenopausal ER+ breast cancer and alcohol drinking, especially among those women who use postmenopausal hormones, may be important, because the majority of breast tumors among postmenopausal women overexpress ER(Suzuki et al.,2005).

There are well-established risk factors for breast cancer, most of which relate to estrogens and growth hormones in females. These include early-age menarche, late-age menopause, postmenopausal obesity and use of hormone therapy. Hormone-responsive viruses have become major suspects as etiological agents for human breast cancer. Human papillomaviruses and the mouse mammary tumor virus have hormone responsive elements that appear to be associated with enhanced replication of these viruses in the presence of corticosteroid and other hormones (James et al., 2006).

Obesity is one of the established risk factors for postmenopausal breast cancer, excess endogenous estrogen due to obesity contributes to an increased risk of ER+ PR+ postmenopausal breast cancer(Suzuki et al.,2006)

Viruses are considered to be one of the high-risk factors closely related to human breast cancer. DNA viruses, such as specific types of human papillomavirus (HPV), Epstein-Barr virus (EBV), human cytomegalovirus (HCMV), herpes simplex virus (HSV), and human herpes virus type 8 (HHV-8), have emerged as causal factors of some human cancers. Virus factor is significantly related to human breast cancer, not only in terms of the oncogenetic process, but also in overall and relapse-free survivals (Ju-Hsin et al.,2007).

All breast cancers are not the same. Different characteristics in gene expression profiles result in differential clinical behavior. With the use of gene micro arrays, different subtypes of breast cancer have been characterized. The basal subtype is characterized by high expression of keratins 5 and 17, laminin, and fatty acid-binding protein 7. The ERBB2+ subtype is characterized by high expression of genes in the ERBB2 amplicon. The luminal A subtype is characterized by the highest expression of the ER alpha gene. The luminal B and C subtypes have a lower expression of the ER cluster (Virginia et al., 2006).

Breast cancer is currently regarded as a heterogeneous disease classified into various molecular subtypes using gene expression analysis. These molecular subtypes include: basal cell-like, Her-2/neu, luminal A, and luminal B. In a study the luminal A subtype was the most prevalent in the study sample (55.4%) compared with (11.8%) luminal B, (21.2%) basal cell-like, and (11.6%) Her-2/neu subtypes. The molecular subtypes did not differ by menopausal status. The basal cell-like subtype (57.1%) was the most prevalent in the age group <35 y compared with luminal A, luminal B, and Her-2/neu subtypes at 25.0%, 14.3%, and 3.6%, respectively. The basal cell-like subtype also showed an age-specific bimodal distribution with a peak in the <35 yrs and 51 to 65 yrs age groups. The basal cell-like and the Her-2/neu subtypes showed an increased association with clinico pathologic variables portending a more aggressive clinical course when compared with luminal A subtype (Chukwuemeka et al. 2007).

In some families an association exists between breast and prostate cancer. Several reports have suggested that BRCA2 mutations may be associated with an increased risk of these cancers. Three cases of early onset of prostate cancer in families with female and male breast cancers have been reported in a study. In each case, the familial phenotype is found associated with a mutation of the BRCA2 gene cancers (Abdel-Rahene et al.,2007).

In a national study of BRCA1 and BRCA2 mutations in Danish HBOC (Hereditary Breast Ovarian Cancer) families revealed (64%) BRCA1 and (36%) BRCA2 positive families Most of the mutations were frame shift or nonsense mutations, while large genomic rearrangements were rare. In BRCA1 the most common mutations were: 2594delC (16%), 3438G>T (9%), 5382insC (8%), 3829delT (5%). In BRCA2 the most common mutations were: 6601delA (11%), 1538del4 (10%), 6714del4 (9%). There was a tendency towards a higher frequency of BRCA2 mutations in West Denmark compared to East Denmark. The frequencies of specific BRCA1 and BRCA2 mutations were slightly different in the two regions (Mads et al., 2008).

There is a risk model based on population averages. Each woman's breast cancer risk may be higher or lower, depending upon a several factors, including family history, genetics, age of menstruation, and other factors that have not yet been identified (American Cancer Society Breast Cancer Facts & Figures, 2008-2009).

Probability of Developing Breast Cancer Within the Next 10 years

By age 20—1 out of 1,760
By age 30—1 out of 229
By age 40—1 out of 69
By age 50—1 out of 42
By age 60—1 out of 29
By age 70—1 out of 27
Lifetime—1out of 8

While breast cancer is less common at a young age (i.e., in their thirties), younger women tend to have more aggressive breast cancers than older women, which may explain why survival rates are lower among younger women.

(American Cancer Society Breast Cancer Facts & Figures, 2008-2009).

Five Year Survival Rate By Age
Younger than 45-81%
Ages 45-64-86%
Ages 65 and older-85%

History of migraine may be associated with a reduced risk of breast cancer and this relationship holds for both premenopausal and postmenopausal women and is independent of exposure to common migraine triggers. Women with a history of migraine may have a reduced risk of breast cancer (odds ratio, 0.74; 95% confidence interval (CI), 0.66-0.82). This risk may not differ by menopausal status, age at migraine diagnosis, use of prescription migraine medications, or when analyses may be restricted to women who avoid various migraine triggers including alcohol, exogenous hormones, and smoking (Christopher et al., 2009).

Daily use of tamoxifen estrogen receptor modulator (SERM) for five years helps to reduce the risk of developing breast cancer in high –risk women by 50% Tamoxifen either prevents or shows no effect on the bone and liver function as well as on cholesterol in post menarche patients. While in case of perimenopausal and postmenopausal breast cancer patients who received tamoxifen, it may induce increase in cholesterol level and bone resorption, which may be due to decreased level of estrogen. However, further research is needed to reach better conclusions (Muniza, 2009).

In a study comparisons of the epidemiologic and clinical outcome data of women with breast cancer show significant similarities, but the striking difference is that the peak age is between 40 and 50 years in Asian countries, but is between 60 and 70 years in Western

countries. The incidence of breast cancer in Asia is rising and is associated with increased mortality. In the West, although the incidence is also increasing, the mortality rate is definitely decreasing(Leong et al.,2010).

Certain occupational exposures also increases the risk of developing postmenopausal cancer, as breast tissue is more sensitive to adverse effects if exposure occurs during the breast cell proliferation (France-Labreche et al., 2010).

Analysis of food records show that fat intake at baseline and after randomization is not associated with total breast cancer incidence. Greater weight and lower carbohydrate intake at baseline and after randomization are associated with an increased risk of estrogen receptor (ER)-positive breast cancer. Weight and carbohydrate intakes are associated with risk of ER-positive breast cancer (Martin et al., 2011).

References:

Abdel-Rahene, Azzouz-iDominique Stoppa-Lyonnet, Morgan-Roupre, Stephane-Larre, Philippe-Mangin and Oliver-Cussenot. (2007). *BRCA2 mutation screening is clinically relevant in breast and early prostate cancer families.* *Int. J. Urology.* ***14****(5):445-6.*

American Cancer Society. (ACS). (2009)*. Breast Cancer Facts & Figures 2009-2010. Atlanta: American Cancer Society, Inc.*

Busch H.(1962). *An introduction to the Biochemistry of the cancer cell. Academic Press .New York* ***pp.****11.*

Christopher, Li, Robert, W., Mathes- Kathleen, E., Malone, Janet, R., Daling, Leslie, Bernstein, Polly, A., Marchbanks, Brian, L., Strom, Michael, S., Simon, Michael, F., Press, Dennis, Deapen, Ronald, T., Burkman, Suzanne, G., FolgerJill, A., McDonald and Robert Spirtas. (2009). *Relationship between Migraine History and Breast Cancer Risk among Premenopausal and Postmenopausal Women Cancer. J. Epide. Biom. Prev.* ***18****(7):2030–4.*

Chukwuemeka Ihemelandu, U., LaSalle Leffall, D., Robert Dewitty, L., Tammey Naab, J., Haile Mezghebe, M., Kepher Makambi, H., Lucile Adams-Campbell and WayneFrederick, A. (2007). *Molecular breast cancer subtypes in premenopausal and postmenopausal African-American women: age-specific prevalence and survival. J. Surg. Res.* ***143****(1):109-18*

Der, C. J., Krouteres, T. G and Cooper, G.M. (1982). *Transformng genes of human bladder and lung carcinoma cell lives are homologous to the ras-genes of Harvey and Kristen Sarcoma Viruses. J. Proc. Hatl. Acad. Sci.* ***79:*** *3637-40.*

Fearon,E.R.,Cho,K.R.,Nigro,J.M.,Kern,S.E.,Sinon,J.W.,Ruppert,J.M.,Hamilton,S.R.,Preisnger,A.C.,Thomas, G.,Kingler,K.WandVogelstein,B.(1990). *Identification of a chr.18qgene. J. Science.**247**:49*

France,Labreche.,Mark,S.Goldberg.,MarieFrance,Valois.andLouis,Nadon.(2010). *Postmenopausal breast cancer and occupational exposures .J.Occup.Environ.Med **67**:263-269.*

James Lawson, S., Walter Gunzburg, H and Noel Whitaker, J. (2006). *Viruses and human breast cancer. J. Fut. Microbiol. **1**:33-51.*

Leong, S.P., Shen, Z.Z., Liu, T.J.,Agarwal, G., Tajima, T., Paik, N.S., Sandelin, K., Derossis, A., Cody, H and Foulkes, W.D (2010). *Is breast cancer the same disease in Asian and Western countries. Journal of Oncology. **34**(10):2308-24.*

Ju-Hsin Tsai, Chun-Sen Hsu, Chung-Hung Tsai, Jang-Ming Su, Yin-Tso Liu, Min-Hsiung, Cheng- James, Cheng-Chung Wei, Fong-Lin Chen, Chi-Chiang Yang. (2007). *Relationship between viral factors, axillary lymph node status and survival in breast cancer. J. Res. Clin. Oncol. **133**(1):13-21.*

Mads Thomassen, Thomas V O Hansen, Ake Borg, Henriette Theilmann Lianee, Friedrik Wikman, Inge Sokilde Pedersen, Marie Luise Bisgaard, Finn C Nielsen, Torben A Kruse and Anne-Marie Gerdes. (2008). *BRCA1 and BRCA2 mutations in Danish families with hereditary breast and/or ovarian cancer. J.Acta. Oncol. **47**(4):772-7.*

Martin ,L.J.,Li, Q., Melnichouk, O.,Greenberg, C., Minkin, S., Hislop, G and Boyd, N.F. (2011). *A randomized trial of dietary intervention for breast cancer prevention.J. Cancer. Res. **71**(1); 123-33.*

Muniza-Qayyum,Malik. (2009). *Breast cancer.J.Prof. Med. **16**:3-316.*

Sagar,R. (1989). *Tumor Suppressor genes: the puzzle and the promise. J. Science.**246**:1406-1412.*

Stanbridge, C. (1990). *Identifying tumor supperessor genes in Human colorectal cancer. J. Science.**247**:12-13.*

Suzuki R, Ye W, Rylander-Rudqvist T, Saji S, Colditz GA, Wolk A(2005). *Alcohol and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status: a prospective cohort study. J Natl Cancer Inst. 2;97(21):1563-4.*

Suzuki, R.,Rylander-Rudqvis,t T., Ye ,W., Saji, S and Wolk, A.(2006). *Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: A prospective cohort study. 1;119(7):1683-9*

Virginia Kaklamani, G., William, J and Gradisha(2006).*Gene expression in breast cancer.J. Cur. Treat.Opt. Oncol.**7**(2): 123-8*

Wynder, E.L. (1980). *Reflection on diet.J. Nutr.Cancer.Res.**43**:3024-3027.*

Willlis, R.A (1952). *The spread of tumor in Human Body.J. Cancer. **26**:204-211.*