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Breast Cancer

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Abstract

Breast cancer is the most prevalent cancer in the world. Approximately one in every nine Pakistani women is likely to suffer from breast cancer showing an incidence rate of 50/100,000 and breast cancer is growing at an alarming rate in Pakistan. The main causative element remain unknown yet primary risk factors identified are sex, age, parity, genetics, lack of child bearing, breast feeding, higher hormonal levels individual lifestyle etc. in Indian and Asian women as compared with western women. Knowledge of this factor emphasizes the need to modify the timing of modalities of detection of early carcinoma and its management Inherited mutations in the breast cancer susceptibility gene1 (BRCA1) [MIM 113705] and breast cancer susceptibility gene2 (BRCA2) [MIM 600185] are associated with a high risk of developing breast cancers in females of different age and ethnic group.

Abbreviations: BRCA1: Breast Cancer Susceptibility Gene1; BRCA2: Breast Cancer Susceptibility Gene2; SKP2: S-Phase Kinase Protein-2; FFPF: Formalin-Fixed; Paraffin-Embedded; LOH: Loss Of Heterozygosity; HER2: Human Epidermal Growth Factor Receptor 2; ER: Estrogen Receptor; PR: Progesterone Receptors; ALN: Axillary Lymph Node

Introduction and Review of Literature

Breast cancer was first documented in Egypt around 1600 BC. In 1860 in an ancient Egyptian tomb, eight cases of tumor or ulcers of the breast were described by the Edwin Smith papyrus [1]. Breast cancer mostly occurred in female due to unlimited growth of breast tissue. Hormonal imbalance, genetic mutation and environmental factor are the major source of breast cancer. Previous studies reported that 23% of all cancer types diagnosed in females [2]. While until 2012 globally 1.4 million breast cancer cases are diagnosed every year [3]. Breast cancer was the most common malignancy with 6.6% are diagnosed in young women below 40 years [4]. The ratio of breast cancer was high in developing countries (71.7/100,000) as compared to under developing countries (29.3/100,000) [5]. According to the research conducted by Indian Medical council predicts that the cases of breast cancer patients were 106,124in 2015 and it is estimated that the cases will rise to 123,634 in 2020 [6]. Karachi Cancer Registry reported breast cancer as the most common cancer (34.6% of cancer cases) among females. The age-standardized incidence rate (to the world population) was 69.1 per 100,000 averaged over the years 1998–2002, the highest recorded rate of breast cancer in Asia [7]. In Pakistan, breast cancer was the most common malignancy in females [3].

One of nine women suffers from breast cancer [2]. In a study from Shaukat Khanum Memorial Cancer Hospital, Pakistan, breast cancer accounted for 21.5% out of all cancers in general population and for 45.9% of all the cancers in females [8]. Cancer data collected from Karachi during 1995-1997 revealed that breast cancer incidence is 53.1% as compared to 69.1% incidence in 1998-2002 [9]. This might be due to the lack of early screening programs which can detect the tumor at an early stage [2]. The maximum number of breast cancer patients in KPK Pakistan from Bannu area 78/120 (65%). The other areas are Lakki Marwat 17/120 (14.166%) and Karak 19/120 (15.833%). Besides these, other places included Kohat 1/120 (0.83%), North Waziristan Agency (NWA) 3/120 (2.5%) and South Waziristan Agency (SWA) 2/120 (1.66%). Age wise the number of cases between 15-30 and

31-60 years is maximum and equal i.e. 55/120 (45.83%) while from 61-90 there are minimum number of cases [10].

In Pakistani children, Parental consanguinity has been implicated in 60% of mortality and severe morbidity (Powell et al. 1995). In Britain, an excess of childhood cancers was also reported among children of the consanguineous marriage (Powell et al. 1995). In adult cancer, there is little information on the possible role of recessive genes. One study from Pakistan has described an association between consanguinity and the risk of breast cancer (Shami et al. 1991). Affected women are typically young and often present with advanced disease (Usmani et al.1996; Ahmad et al. 1997). Inbreeding increased the risk of disease caused by homozygosity of deleterious recessive genes [11]. Interestingly, studies from Pakistan and India showed an increased incidence of breast cancer with more Estrogen receptor (ER) and Progesterone receptors (PR) negative profiles. In breast cancer, ER expression is 80-90% while PR expression is 70-80%. [12]. Because most of the cases present at a very advanced stage. Our study asserts the importance of early diagnosis to prevent ALN metastasis. Axillary lymph node (ALN) status was the most important prognostic factor associated with disease-free survival and the overall survival rate for breast cancer [13]. Prognostic subgroups of breast cancer based on their immunohistochemical expression of estrogen receptor, progesterone receptor and Her2/Neu status and their association with ALN metastasis in a group of Northern Pakistani women [14].

Triple-negative breast cancers have a more aggressive clinical course than other forms of breast cancer [15]. BRCA1 and BRCA2 are called high penetrance genes. The proteins encoded by these genes are suggested to act as tumor suppressors and involved in the maintenance of genomic integrity[16]. They participate in repairing DNA damage by homologous recombination and also proposed to regulate transcription [17]. The carriers of the BRCA1 and BRCA2 develops breast cancer at younger ages compared to non-carriers [18]. Cumulative breast cancer risks among BRCA1 and BRCA2 families are estimated to be equally high (87% and 84% by age 70 years, respectively) [19]. The carriers of BRCA1 and BRCA2 variant alleles in Finnish breast cancer families are reported to represent a much lower proportion of the total (altogether 21%) compared to other populations [20]. The syndrome of Li-Fraumeni and Cowden disease is associated with increased susceptibility of developing tumors (also in breast tissue). These hereditary cancer syndromes are caused by mutations in tumor suppressor genes p53 and PTEN [21]. These genes play only a small proportion of all hereditary breast cancers (<1%) [22]. The Genome Atlas increase the expression of RAC1 and VASP in breast cancer. They are associated with a decrease in cancer cell differentiation and inhibit cancer cell migration [23]. Four common subtypes of breast cancer identified. The two subtypes are derived from ER-negative tumors and the other two are derived from ER-positive tumors [24-25].

Symptoms

Breast cancer symptoms include a lump in the breast or armpit, bloody nipple, breast pain or sore nipple discharge, orange-peel texture or dimpling of the breasts skin, inverted nipple, swollen lymph nodes change in the breast size and shape [26].

BRCA1

BRCA1 plays an important role in DNA repair, genome stability, and checkpoints of the cell cycle. BRCA1 association with different adaptor proteins forms several complexes, and each complex forms in a mutually exclusive manner [18]. The BRCA1 present on chromosome 17q 21.13. The BRCA1 gene contains 22exons, 110 kb of DNA Miki et al. (1994). BRCA1 act as a tumor suppressor/ encodes nuclear Phospho-protein play role in genome stability, gene product associate with DNA-polymerase II through C-terminal domain, histone deacetylase complex. 40% chances of inherited after mutation in the gene

[27]

BRCA2

In families with breast cancer linked to chromosome 13q12, Wooster et al. (1995) identified 6 different germ line mutations in the BRCA2 gene (see, e.g., 600185.0001), each causing serious disruption to the open reading frame of the transcriptional unit Inherited mutations in BRCA1 and this gene, BRCA2, confer increased lifetime risk of developing breast or ovarian cancer. Both BRCA1 and BRCA2 involved in the maintenance of genome stability, specifically the homologous recombination pathway for double-strand DNA repair. The BRCA2 protein contains several copies of a 70 a.a motif called the BRC motif, and these motifs mediate binding to the RAD51 recombinase which functions in DNA repair. BRCA2 is considered a tumor suppressor gene, as tumors with BRCA2 mutations generally exhibit loss of heterozygosity (LOH) of the wild-type allele [28].

Human Epidermal Growth Factor Receptor 2

The HER2 is a transmembrane glycoprotein, encodes by ERBB2 [29]. HER2 status can be determined in formalin-fixed, paraffin-embedded (FFPF) by assessing protein expression on the membrane of the tumor cells using IHC. In situ hybridization methods use for HER2 diagnosis. Some assay use single probes [30].

Spk2

F-box protein skp2 (S-phase kinase protein-2) plays an important role in breast cancer pathogenicity. Skp2 related to the system of ubiquitin-proteasome that plays an important role in different biological processes. P27 is a substrate for skp2, its lower level caused by Skp2 overexpression which shows expression of cancer in humans. Skp2 act as a prognostic marker, an important

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factor in cell growth, invasion, apoptosis, and metastasis in breast cancer [31].

Treatment

Beta-blocker, propranolol inhibit norepinephrine-induced breast cell migration[32]. Doxorubicin and Anthracyclines are chemotherapies. Doxorubicin prevents topoisomerase activity and DNA synthesis. Doxorubicin is more similar structure to Daunorubicin. It is more abundant, produced by wild types strains of Streptomyces [4].

Neupogen

(Filgrastim) Granulocyte-colony stimulating factors help the body make more neutrophils, neutrophils are a type of white blood cell. Neupogen is used to reduce the risk of infection during chemotherapy treatment [33].

Aromasin (Exemestane)

Aromatase is a hormonal therapy. Aromatase inhibitors lower the amount of estrogen in women. Aromasin used to treat postmenopausal women and to reduce the risk of early-stage, hormone-receptor-positive breast cancer coming back after surgery and other treatments [34].

Xeloda (Capecitabine)

Capecitabine is an Antimetabolite chemotherapy, kill cancer cells. It is used to treat metastatic breast cancer that has stopped responding to Taxol, Taxotere, and Adriamycin. Xeloda is taken orally as a pill [35].

Vitamins and antioxidants

Treatment with beta-carotene, vitamin A, and vitamin E may increase death. The potential role of vitamin C on mortality remains unsettled [36]. The relationship between vitamin D levels and breast cancer risk or prognosis is controversial [37].

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