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Breast cancer in Pakistan: evaluating the health crisis and the path forward for women's wellbeing

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Abstract: Breast cancer (BC) is the most prevalent malignancy among women globally. Historically

regarded as a disease affecting older, middle-aged women, recent years have seen a growing incidence of BC among younger females, a trend also observed in studies conducted in Pakistan. This paper reviews the mutant functions of tumor suppressor genes (BRCA1, BRCA2, p53, ATM, and PTEN), epigenetic alterations, and the role of estrogen receptors in breast cancer development. Additionally, we examine the current BC scenario in Pakistan, highlighting a notably higher incidence among younger women. Data from SKMCH and RC indicate that women aged 45-49 years exhibit the highest incidence rate of 45.42%. Limited studies have reported a high expression of ER, PR, and HER-2/neu in Pakistani women. Furthermore, the presence of the BRCA1 (c.1961dupA) mutation in Pakistan aligns with global findings. However, no comprehensive studies have been conducted to investigate epigenetic transformations in breast tumors within the Pakistani population. This critical area of research warrants further exploration to provide a more complete understanding of BC in Pakistan.

Keywords: Breast Cancer, p53, BRCA1, BRCA2, Epigenetic Transformation, Estrogen Receptor.

Introduction: Breast Anatomy and Function

Breast development starts at puberty and is completed during pregnancy. [1] The internal structure of the breasts is unique in that it contains mammary glands for the subsequent nourishment and immunity for a newborn during lactation. [2] The mammary glands continue to develop throughout the different ages of a woman's life. The end buds of the primitive ductal system in an infant's breast gradually evolve into a branched ductal system with a concurrent decrease in fatty tissue during puberty. Further development will remain in a dormant state until pregnancy hormones stimulate it.

The fundamental ductal system develops through the differentiation of two cell types: luminal epithelial cells and myoepithelial cells. These cells are the so-called milk-producing structures. microcavities surrounded by cells myoepithelial epithelium, luminal arteries surround the breast milk sac with antibodies, nutrients, and certain toxins. Alveoli bundle together to form lobules, which connect to the nipple through the milk ducts.

Milk ejection is initiated by the nipple stimulation that triggers a nerve impulse that activates the release of oxytocin through the hypothalamus and posterior pituitary gland. Under the influence of oxytocin, the myoepithelial cells contract and create intraductal pressure to facilitate milk ejection. [2]

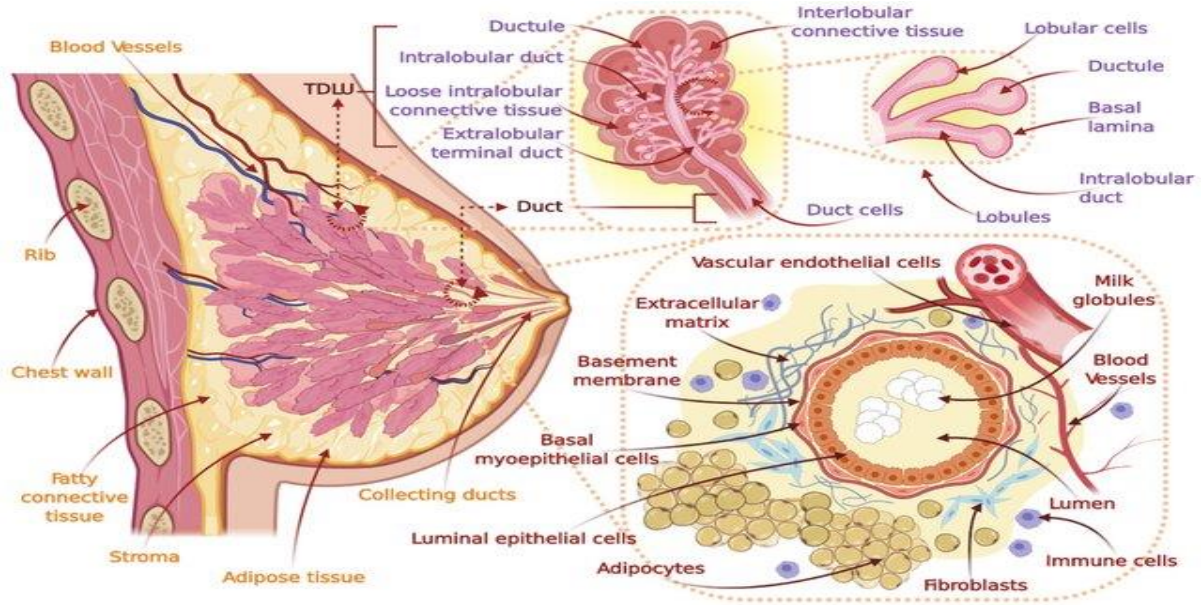


Figure 1. Schematic representation of the human female breast and the many kinds of interacting cells found inside the breast tissue. The breast tissue overlaps the ribs and chest muscles. The mature woman's breast includes glandular epithelium (~10–15%) and this milk producing epithelia is housed inside the surrounding adipose tissue. Multiple lobules (terminal ductules, acini, milk producing lobules) collectively make up the lobes of the breast. The functional units of the breast are the terminal duct lobular units. All lobules and lobes are linked to the nipple by a branching system of ducts. Terminal ductal lobular units (TDLUs), which is a cluster of ductules, intralobular duct, loose intralobular connective tissue, and extralobular terminal duct, are frequent sites of genesis for numerous. Within the stroma, two kinds of fibroblasts are found. Loosely linked intralobular fibroblasts surround the epithelial cells and they are

eventually surrounded by the more condensed interlobular fibroblasts. The second key biological component of the mammary stroma is adipocytes (i.e., fat cells). The parenchymal tissue comprises of epithelial and myoepithelial cells. In addition, the stromal compartment comprises vascular endothelial cells and invading immune cells. Stromal cells release components of the extracellular matrix (e.g., collagens, hyaluronic acid, tenascins, fibronectins, proteoglycans) that are vital for the breast's three-dimensional architecture. Mammary ducts consist of polarized apically directed columnar luminal epithelial cells that line (within) ducts together with alveolar structures at the ends, as well as contractile myoepithelial cells that are orientated basally. This is contained by the basement membrane (BM), which provides a physical barrier that divides the epithelial and stromal compartments. BM (i.e., basal lamina) largely consists of laminin, collagen, entactin, and proteoglycans. Myoepithelial cells that exhibit contractile qualities and stem cells (i.e., mammary repopulating units) compose the functionally different basal layer. Constituents of milk are generated by secretory cells that create the alveoli, followed by secretion into the alveolar lumen.

Structure of the Breast

The breast is composed of adipose and glandular tissues supported structurally by Cooper ligaments. The glandular tissue is associated with 15–20 lobes consisting of 10–100 alveoli (0.12 nm in diameter). Each alveolus opens into 15–25 ducts that then coalesce to form a single principal duct, ultimately forming lactiferous sinuses which lead to the nipple surface. There is some disagreement over the average number of ducts per nipple. [3].

Breast relies on the internal mammary artery's blood supply and the posterior mammal branches of the lateral thoracic arteries, as well as other branches like the pectoral branch of this vein and then the intercostal vascular branch. The regulation of veneous drainage is both deep and superficial systems. Deep veins, as they follow the mammary arteries, drain blood towards internal thoracic, cephalic, and other vessels. Sub-areolar veins drain into surrounding vasculature from the nipple to the surface and communicate superficial and deep venous plexuses. [4]. The breast receives supply from the 2nd to 6th intercostal nerves. The nerves follow variable penetration and courses, in that the anterior nerves take a superficial course to provide innervation to subcutaneous tissue, whereas the lateral nerves make deeper connections. The areola and nipples receive supply from the lateral and anterior cutaneous branches of the 3rd to 5th intercostal nerves [1,3]. Lymph drainage of the breast is carried out through two main pathways: the axillary and the internal mammary nodes. The axillary nodes drain the majority (75%) of the lymph from both the medial and lateral portions of the breast, while the internal mammary nodes drain lymph primarily from the deeper portions [5].

Breast Cancer

Cancer is a disease in which there is abnormal and excessive cell growth, resulting in the formation of a mass or lump called a tumor. Cancer is named based on the affected cells. BC (Breast Cancer), one of the most frequently reported cancers in the world can be invasive or non-invasive. It arises because of mutations in the cells of the lobules and linking ducts, while the rest of the breast is made up of fatty connective and lymphatic tissues.[6] Ductal carcinoma in situ (DCIS), a form of BC arising from mutations in the ductal cells, is reported to be non-invasive but may become an invasive form if not treated (Allred).

Classification Systems of Breast Cancer

Invasive breast cancer invades cellular boundaries, spreading to the nearby normal tissue, and its prognosis is primarily based on the diagnosis of the tumor as well as the extent of metastasis. Two principal cancer staging systems are widely used for the disease classification. The TNM system considers tumor size (T), spread to the nearby lymph nodes (N), and the presence or absence of distant metastasis (M) (Edge and Compton). Based on these parameters, BC is staged from 0 to IV, with stage 0 indicating in situ cancer, stage I being early invasive cancer, and stage IV being the highest stage. The system is largely utilized for clinical purposes. Meanwhile, the Surveillance, Epidemiology, and End Results (SEER) system is utilized for public health research, planning, and cancer registry statistics. SEER stages disease progression into three levels from local to regional to distant categories that reflect TNM stage I and some parts of stage II thereby restricting cancer growth within the breast. The TNM classification for stages II and III belongs to the regional stage because the cancer spreads to regional lymph nodes or tissue. The distant stage of cancer matches the TNM stage IIIc and IV definitions which indicate that cancer has spread to distant lymph nodes and organs. BC holds different categories which stem from analysis of gene expression profiles. [7] while specific biomarkers such as ER+/ER- receptors alongside PR+/PR- receptors alongside HER2+/HER2- receptors serve as diagnostic and therapeutic indicators. [5]

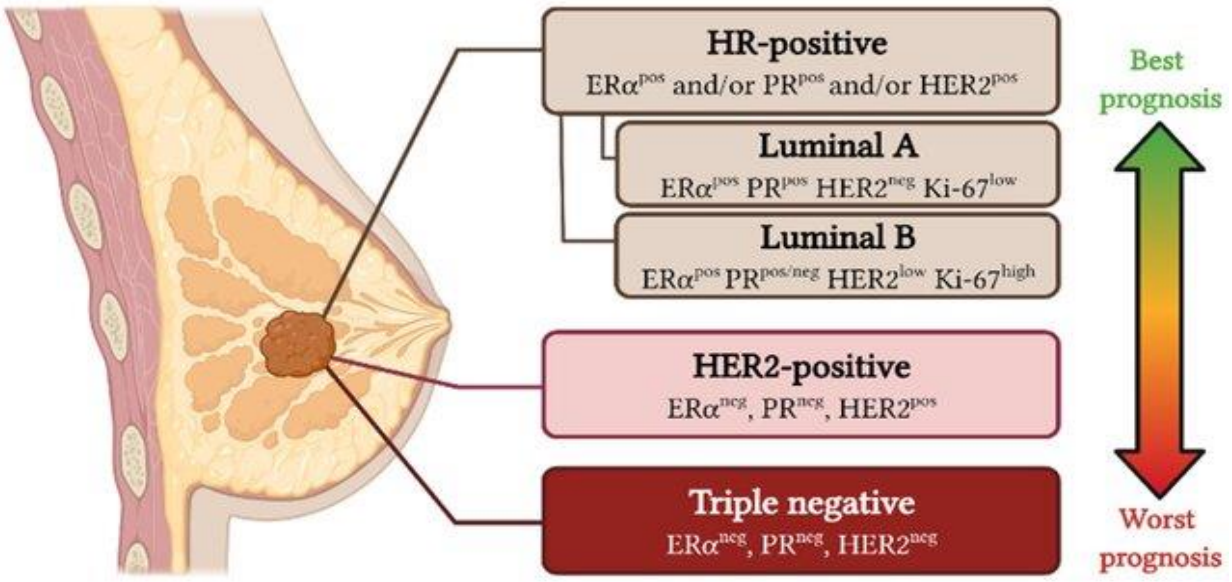


Figure 2

Molecular classification of BC subtypes. BC can be divided into three main subtypes depending on the histological expression of four markers (ERα, PR, HER2, and Ki-67): hormone receptor (HR)-positive, HER2-positive, and triple-negative. This figure was created with Biorender.com.

Epigenetic Transformation

Breast cancer develops because deregulated genes build up and stimulate both uncontrolled cell proliferation along with growth. Epigenetics together with gene mutation functions as a fundamental contributor to the development of BC. Scientists actively investigate cancer molecular mechanisms yet they also try to establish biomarkers for BC aggressiveness assessment along with studying epigenetic therapeutic potential. Cancer development together with prognostic outlooks depends heavily on epigenetic changes. These include DNA methylation, which modifies CpG dinucleotides covalently at the 5' position of the cytosine rings, and histone modifications, which are post-translational covalent modifications that occur on the N-terminal tails of the four core histones. Gene expression can also be modified by certain non-coding RNA molecules that degrade target RNAs or inhibit their translation. [8]

Genes that regulate important cellular mechanisms such as the cell cycle, angiogenesis, apoptosis, tissue invasion, hormone signaling, and metastasis, are fundamental in the development of BC when their expression is inactivated through hypermethylation. [4,6] Hypermethylation of tumor suppressor genes like BRCA1 and p16 and DNA repair genes like GSTP1 and CHD1 has been reported in breast tumors, in which these genes have been involved in metastasis and invasion.[8]

The research showed that high-stage tumors presented increased ADAM23 gene hypermethylation which affects cell surface adhesion molecule transcription.[9] DSC3, KIF1 and NDRG1 genes from BC tumors undergo epigenetic silencing. The environmental risk factor estrogen receptor expression showed a positive correlation with hypermethylation of the tumor suppressor gene RASSF1A promoter. Research conducted on hereditary BC revealed identical results. [10] RASSF1A methylation serves as a potential biomarker to diagnose BC. In addition, post-translational histone modifications are a significant epigenetic change, and they play a crucial role in the development, aggressiveness, and prognosis of BC. Histone proteins influence the expression of various genes in different BC tumor subtypes. [11]

Histone modifications in invasive breast cancers have been shown to have significant lysine acetylation (H3K9ac, H3K18ac, H4K12ac, and H4K16ac), arginine methylation (H4R3me2), and lysine methylation (H3K4me2 and H4K20me3). Positive correlation of H4R3me2, H3K9ac, and H4K16ac levels with lower lymph node stage and negative correlation with tumor size were observed. High levels of histone modifications were also significantly associated with steroid receptor-positive tumors. [3,5,6] However, in Pakistan, no true studies have been identified that predict epigenetic changes in breast cancer tumors in the local population.

The terminal duct-lobular unit contains estrogen- and progesterone-sensitive stem cells, which proliferate during the menstrual cycle and pregnancy. These have the potential to form lactational lobules. During the prepubertal period, the terminal ductal-lobular stem cells in mutation carriers (germline or somatic) are dormant but remain vulnerable to malignancy. When the DNA of these cells becomes damaged, it proliferates

under the influence of puberty hormones. Mutations in p53 or other genes involved in the regulation of the replication process allow these cells to grow uncontrollably and activate proto-oncogenes. [12]

The oncogene activation in BC cells induces mutations in one or more of the tumor suppressor genes. These genes play roles in maintaining genomic integrity by preventing the passage of damaged DNA. Mutations in various tumor suppressor genes result in the loss of the cells' ability to sense and repair DNA damage. Under normal circumstances, these genes recognize damage to the DNA and halt the cell cycle until repair is done. Tumor suppressor genes also induce apoptotic cell death Mutations in the BRCA1 and BRCA2 genes are linked to approximately 80-90% of the familial BC cases. Inactivation of these tumor suppressor genes results not only in the development of BC but also in ovarian and prostate cancer. [13] BRCA1 is a very large 17q21 chromosome gene, spanning 100 kb, and encodes a protein of 1863 amino acids. BRCA1 expression is especially high in the thymus, testis, breast, and ovary. The gene products are involved in DNA repair, transcriptional transactivation, apoptosis, and cell cycle control. [13,14] There are two isoforms of BRCA1, BRCA1a and BRCA1b, that are phosphoproteins containing phosphoserine residues. Both BRCA1a and BRCA1b are p53 gene coactivators, and both were found to interact with p53 in vitro and in vivo studies. [15]

The BRCA2 gene, which is much larger than BRCA1, maps to chromosome 13q12-13, covers 10,254 base pairs, has 26 coding exons, and encodes a 3,418 amino acid protein. [8,12] Like BRCA1, BRCA2 proteins play regulatory roles in transcription and DNA repair. The BRCA2 mutations are moderately in the prostate and mammary glands and highly in the thymus and testis, indicating that they may be involved in differentiation and development. [16] One of the best-known genes in human cancer is the p53 tumor suppressor gene. It is located on chromosome 17p13.1 and acts as a transcription factor for regulating growth signals in damaged cells. Mutations of the p53 gene are found in approximately 20-40% of human breast cancers. Individuals who have a germline mutation of the p53 gene (Li-Fraumeni syndrome) are at high risk of getting breast cancer and other cancers as a result of the loss of growth-suppressive gene function. [17] p53 also shares extensive homology with p63 and p73, which encode transactivation and DNA-binding proteins with tetramerization domains identical to p53. Ataxia Telangiectasia (AT) gene or ATM, which is involved in DNA repair and cell-cycle checkpoints, can also be involved in breast cancer formation. The mutation of tumor suppressor gene PTEN results in improper PIP3 pathway activation that promotes uncontrolled cell growth while inhibiting apoptosis. [18]

Genetic and Reproductive Factors

Genetic predisposition plays a crucial role in determining BC risk among Pakistani females. Mutations in the BRCA1 and BRCA2 genes are relatively prevalent in this population, significantly increasing the likelihood of hereditary breast and ovarian cancers. Studies suggest that over one-third of early-onset BC cases in Pakistan may be linked to these genetic alterations. Moreover, reproductive factors substantially influence BC susceptibility. [19] Initial onset of menstruation, delayed menopause, and nulliparity have been associated with an elevated risk, while higher parity and younger maternal age at first childbirth have been correlated with a protective effect. Furthermore, the use of combined oral contraceptives has been associated to a minor increase in BC risk, which diminishes after discontinuation. [16,17]

Lifestyle and Environmental Factors

Breast cancer risks heavily depend on lifestyle preferences people make. The trio consisting of physical inactivity and elevated BMI values and smoking habits proves to be essential danger elements. A body mass index higher than 25 kg/m² shows a positive correlation with breast cancer development risk. Former and active smokers show sensitive breast cancer risk. Scientists have linked breast cancer susceptibility to both excessive consumption of fats in diet and inadequate consumption of fruits and vegetables. [18,20] The assessment of risk factors becomes complex because of exposure to environmental substances including chemicals that disrupt endocrine function and radiation elements. The limited research on environmental carcinogens in Pakistan's population needs expansion because it lacks data about their contribution to BC frequency. [21]

Estrogen-Receptor Positive (ER+) Breast Cancer

Estrogen receptor (ER) is both a nuclear hormone receptor and a transcribing transcription factor upon activation by its ligand. Ligand binding induces receptor conformational changes which allow the receptor to dimerize into homodimers. The receptor binds to special DNA sequences referred to as estrogen response elements to activate transcription of target genes. The functional regions of the ER include the N-terminally positioned hormone-independent transactivation domain (AF1) followed by the highly conserved central DNA-binding domain (DBD) that specifically binds to ERE DNA sequences and ends in the C-terminal LBD-followed by the hormone-dependent transactivation domain (AF2). A hinge domain divides the ligand-binding domain from the DNA-binding domain. There is

a hormone-binding pocket within the LBD and then comes the ligand-activated second transactivation domain (AF2) at the C-terminal end. [22]

Genes which control estrogen metabolism and intracellular transport operate through enzymes or receptors while mutations within these genes lead to an increased breast cancer (BC) risk. Three critical genes include 17β-hydroxysteroid dehydrogenase 2 (EDH17B2) and cytochrome P450c17a (CYR17) and estrogen receptor (ER). Through hormone-to-hormone response elements (HREs) DNA targets ER manages transcription by acting as a steroid receptor. Gene expression results in upregulation or downregulation following receptor-HRE binding which depends on the active state of tissue-specific auxiliary factors that bind to target genes. Polymorphisms of the ER and inefficient binding of estrogen to its receptor may affect gene transcription. Moreover, the AIB1 protein, a nuclear receptor coactivator, may be involved in the development of steroid-dependent cancers by binding to the estrogen receptor in a ligand-dependent manner and in the stimulation of estrogen-dependent transcription. [23]

Epidemiology of Breast Cancer in Pakistan

Cancer is the leading cause of death in economically developed countries and the second leading cause in developing countries. [16] Breast cancer is the most commonly diagnosed cancer globally, accounting for 23% (1.38 million) of all new cancer cases and 14% (458,400) of cancer-related deaths in 2008. The burden of cancer is rising in developing nations due to factors such as population aging, growth, and the adoption of cancer-related lifestyle habits, including smoking, physical inactivity, and "westernized" diets. [24] BC is most prevalent in middle-aged women (40–59 years). [14] The typical incidence curve for BC shows a rapid rise until the age of 40, after which the rate slows, but continues to increase with age until around 50, after which it begins to decline, especially in low-risk populations. Pakistan reports the highest BC incidence in Asia, excluding Israel, according to available data. [25] BC stands as the most frequently occurring cancer in females throughout Karachi where it represents one-third of all female cancer cases. The incidence of BC in Karachi represents the highest rates throughout Asia. BC ranks as a leading threat region in Pakistan, while it constitutes 40% of all female malignant tumors. [23,26] Patients diagnosed with BC in Pakistan usually develop the cancer after their 49th birthday but Western societies show median detection around 54 years of age. Based on data from Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH & RC) from December 29, 2014 to December 31, 2023 BC emerged as the main cancer type among Pakistani females with a total occurrence rate of 45.42% of cases. Most breast cancer cases documented for 2023 occurred within the 45–49-year age group. BC detected in younger patients shows higher aggressive behavior and inferior prognoses compared to BC diagnosed in older women. [27] The frequency of BC diagnosis in Pakistani women under 50 years old shows a continuous upward trend. Rise in Karachi's mean age of cancer diagnosis from 50.0 years old to 45.75 years old during the last decade emerged. Study in Karachi demonstrated that women received an average BC diagnosis at age 44.07 years while representing the ethnic groups of Sindhi 9%, immigrants 17%, Balochi 2%, KPK 2%, Minorities 2%, and Punjabi 2%. [22,28]

The study at Lady Reading Hospital Peshawar established that breast cancer (BC) predominantly affected 30.4% of women in the 40-49 years age group. [29] The disease spectrum of breast cancer in Pakistani women consists of a wide variety of different breast cancer types. Different regions of Pakistan show varied distributions of BC subtypes according to Table 1. A study documented the occurrence of invasive ductal carcinoma (IDC) at 88.7% while invasive lobular carcinoma (ILC) appeared at 5.4% and lymph node metastasis rates amounted to 80.8% among women aged 30 and above. The grading of tumors predominantly showed grade II (57.1%) with grade III (29.8%) while tumor dimensions were below 5 cm in 23.2% of cases, [27,30] identified IDC as the main cancer type in 82.6% of patients whose average age reached 56.52 years. Research showed IDC occurred in 78% of patients primarily affecting stages II and III tumor grades. Data shows Infiltrating ductal carcinoma (IDCA) represents the primary subtype of BC in Pakistan. [31] Revealed a substantial increase in IDCA prevalence compared to previous hospital data through their study which found 81% of patients diagnosed with tumor grading type II while their tumor sizes remained below 5 cm. A retrospective assessment of 3,279 BC specimens at Aga Khan University Hospital found IDCA affected 37% of patients while fibroadenoma occurred in 16.95% of cases and fibrocystic changes in 13.96% patients. Mastitis affected 6.83% of patients and duct ectasia occurred among 5.33% with diverse tumor sizes. [32]

A clinic study operating at the National Cancer Institute in Karachi surveyed various breast cancer presentation types during 2014-2020 using clinical-pathological examination criteria. The study reported 91% invasive ductal carcinoma (IDCA), 6% intraductal carcinoma, and 3% lobular carcinoma. Invasive intraductal carcinoma was found in 94% of patients with a mean age of 41.9±10.9 years and tumor grades III and IV, [33] which aligns with previous findings where the prevalence of intraductal carcinoma was 90%. Ductal carcinoma in

situ, commonly abbreviated as DCIS, refers to the malignant proliferation of epithelial cells in the duct-lobular system of the breast that cannot be detected with a light microscope. In the developing world like Pakistan, diagnosis of DCIS is very infrequently reported in contrast to the developed world mainly due to inadequate availability of the advance medical setups to detect DCIS. [34] Two Karachi-based studies documented DCIS rates of 1% and 1.2%, respectively. In addition, a high prevalence of palpable masses (92.1%) was also documented in Pakistani women. [34] Germline mutations in the BRCA1 and BRCA2 genes are established lifetime risk factors for developing BC. The BRCA1 c.1961dupA mutation has been identified in several families from different parts of the world. It was identified in Oman, China, Western Europe, Latin America, and the Caribbean. Very recently, this same mutation in BRCA1 has also been reported among Pakistani families, who have a history of a very high consanguineous marriages. [35]

A study conducted in 2005 reported that 9.17% of tumors in Pakistan were estrogen receptor positive (ER+ve). The behavior of ER and progesterone receptor (PR) positive tumors in the Pakistani female population is similar to that observed in Western data. Sharif MA et al. reported the expression of HER-2/neu, ER, and PR in 481 cases of invasive ductal carcinoma (IDCA) with a mean age of 48 years and a tumor size of 4.4 cm. Their findings showed high expressions of ER (72.3%), PR (62.6%), and 31% HER-2/neu. They also found an inverse association between ER and PR with HER-2/neu, while a positive association was observed with lymph node metastases ($p < 0.05$). A similar trend is observed in India, which shares genetic similarities with Pakistan. Breast cancer affects 100,000 Indians each year with projections suggesting this number will reach 131,000 by 2020. [37] The incidence of breast cancer in Indian women under 45 years shows a rising trend which mirrors a similar pattern reported in Pakistan.

Table

Breast Cancer Subtype	%	Area	Age Range
Infiltrating ductal carcinoma	82.60%	Peshawar	40-59
	81%	Rawalpindi/Islamabad	36-60
	45.41%	Lahore	>18
Mucinous carcinoma	2.17%	Peshawar	40-59
Infiltrating lobular carcinoma	6.50%	Peshawar	40-59
Papillary carcinoma	4.35%	Peshawar	40-59
Invasive lobular carcinoma	6.50%	Peshawar	40-59
Medullary carcinoma	2.17%	Peshawar	40-59
Benign lumps	30.91%	Rawalpindi/Islamabad	36-60
Luminal B (Grade 3)	60%	Lahore	>18
Luminal A (Grade 2)	37%	Lahore	>18

Breast Cancer Awareness and Early Detection in Pakistan

Breast cancer is still the most common cancer in women in Pakistan, and it has a high burden in areas such as Peshawar and Islamabad. Breast cancer is responsible for about 38.8% of all female cancers in the country, with 56,250 cases reported. In KP, which comprises Peshawar, breast cancer is 31.1% of all female cancers, with 1,000 cases in 2018. In Islamabad, breast cancer is 45% of all female cancers, with 1,500 cases in 2018. The above statistics demonstrate the high incidence of breast cancer in both KP and Islamabad, emphasizing the need for increased awareness and early detection in these areas. [36,38]

Awareness of breast cancer among Pakistani women is very low. A survey of 9,766 women in 18 studies revealed that 42.7% knew risk factors, 41.8% knew symptoms, and 36.3% knew diagnostic modalities. Furthermore, only 28.7% had ever done regular breast self-examination (BSE), and 15.3% had ever had a clinical breast exam (CBE). In Lahore, 80.2% of the population was not aware of the prevalence of breast cancer worldwide, and 65.3% thought that not everyone is at risk. Only 42.1% were aware of symptoms, and 13.9% did self-examination. These results highlight the need for specific educational interventions to enhance knowledge and practices regarding breast cancer. [39]

The World Health Organization (WHO) stresses self-examination to enable early detection of breast cancer. In Pakistan, there are about 90,000 new cases every year and 40,000 deaths resulting from delayed detection. Survival can be highly improved with early diagnosis, at 90% for early-stage invasive breast cancer. Despite this, cultural beliefs, fear, and cost prevent a lot of women from accessing timely medical care. [40]

To address these issues, a number of initiatives have

been implemented. To encourage early detection, the Women's Parliamentary Caucus and the WHO have arranged awareness seminars. with an emphasis on the local community, the Shaukat Khanum Memorial Cancer Hospital and Research Centre is also carrying out research to provide more effective methods of cancer detection and treatment. [41,44] Notwithstanding these initiatives, more thorough public education and awareness campaigns about breast cancer risk factors and the need of early diagnosis are still required. Mortality may be decreased and early detection rates greatly increased by putting in place routine screening programs and encouraging self-examination.

Causes of Breast Cancer

The spreading western lifestyle choices of smoking alongside alcohol use and unbalanced diets are thought to fuel the rising numbers of breast cancer cases in developing countries like Pakistan.[42] Obesity together with physical inactivity both increase BC risk through elevated extra-glandular estrogen and its metabolites along with hyperinsulinemia levels often found in obese women. The combination of decreased breastfeeding practices together with timing irregularities of menstruation and childbirth age throughout Pakistan and Bangladesh and India shows a connection to rising breast cancer incidence. The use of assisted reproductive technology (ART) produces hormonal exposure and delayed childbearing and serves as risk factors for BC development. Clinical evidence shows that assisted reproductive technology through VEGF upregulation stimulates tumor angiogenesis. [43,45]

Risk Factors for Breast Cancer in Pakistani Women

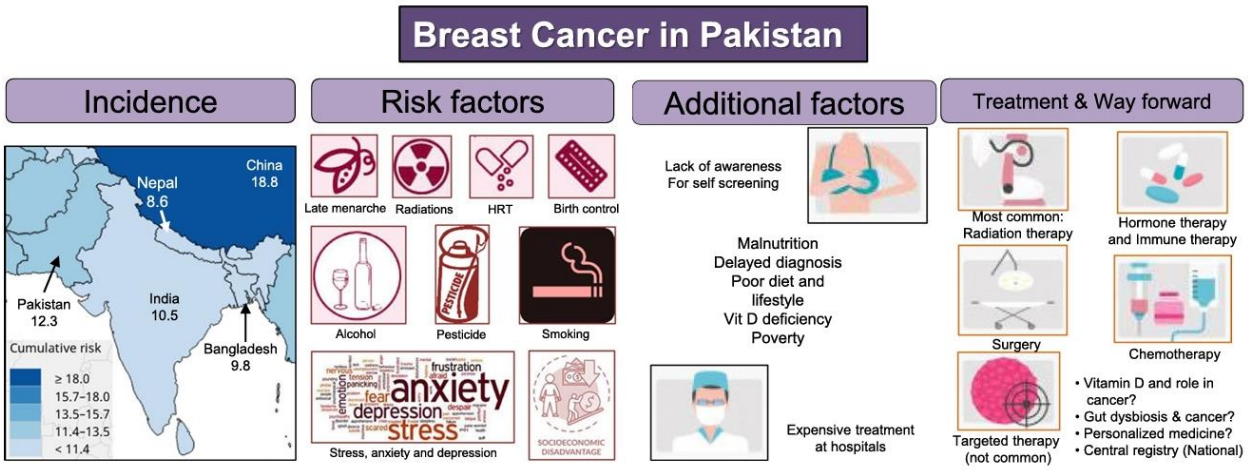
Multiplicity of risk factors are assumed to be related in getting BC in Pakistan [46]; Fig. 3. Breasts were related with personal modesty, humiliation and timidity among women in Lahore, where breasts were needed to be veiled at all times [47, 56, 58]. This reinforced the stigma linked to publicly discussing breast issues among women, mothers and daughters, husbands, and extended family members. BC may be seen as socially undesirable illness as a consequence of this [48]. It is also suggested that women are hesitant to do breast self-examination, either owing to lack of understanding and/or cultural concerns [49, 64]. As a consequence, fundamental social prejudice against the condition, based on shared beliefs has emerged. This technique has the potential to permeate society and dramatically alter breast wellness behavior, especially self-examination practice [50]. Social bias and misconceptions about screening criteria, family history, and sentiments of vulnerability are all impediments to breast health practices and self-examination, may also occur [54].

Worryingly, research reveal that women in Pakistan only seek medical care when their cancer has advanced to a critical level owing to an inability to recognize at an early stage [55, 67, 85]. According to several research, cancer victims are urged to study spirituality in order to properly manage the physical and psychological symptoms [14, 62]. Although not reporting BC has the potential to be catastrophic, it may signify the societal stigmatization connected with a BC diagnosis [14]. Emotional, bodily anguish, psychological, social, and spiritual sorts of suffering are all encountered by women [75].

The average age at which white American women acquire BC is 61 years, whereas the average age at which Pakistani women suffer the illness has been shown to be 51.4 years [68]. In compared to other parts of the globe, notably Western countries, it is roughly a decade sooner. Thus, it is vital to delve more into the reasons of this early age occurrence among Pakistani women. Apart from age, additional risk variables include tobacco use, physical inactivity, obesity and body mass index, and menopausal status [70]. Furthermore, reproductive characteristics such as parity and breastfeeding have previously been demonstrated to give protection against BC [56]. Encouraging results from a recent investigation found that the life expectancy for both sexes improved in Pakistan, yet these increases differed throughout the provinces and federal territories. Between 2014 and 2023, the life expectancy of women grew by 82%, while that of males climbed by 76% [42]. The leading risk factors for mortality and disability-adjusted life years at the national level in 2019 were smoking, air pollution, high systolic blood pressure, dietary risks, and malnutrition, which might be contributing factors to cancer as well [47].

In terms of lifestyle and diet, new evidence suggested that vitamin D deficiency may have a role in BC [63,65]. According to epidemiological study and laboratory data [74], vitamin D may have anti-cancer capabilities [84, 86]. Considering Karachi’s low latitude (about 67°00’36” east longitudes and 24°51’36” north latitudes), vitamin D insufficiency was detected in 60.2% of study respondents, with severe deficiency (12 ng/ml) in 34.8% of Pakistani women [81, 82]. This is despite the fact that Karachi gets substantial quantities of sunlight [81]. Public health initiatives are required to address high deficiency rates, including dietary fortification, with increased exposure to sunshine.

Figure 3



Despite a scarcity of data, a study of Pakistani women showed a relationship between endogamy (genetic related ness) and the incidence of BC [58]. Additionally, it has been argued that, owing to a lack of cosmetics regulatory monitoring, there are hundreds of cheap, unlicensed, and accessible products, some with high concentrations of parabens that may be involved in developing breast cancer [66]. Moreover, irrigating crops using sewage water is a widespread approach in underdeveloped nations. Heavy metal deposition in vegetables may be enhanced as a consequence of sewage water irrigation. Human health may be threatened if such polluted vegetables are ingested [78]. The crops planted with sewage irrigation are inappropriate for human consumption owing to the presence of hazardous components such as lead, cadmium and chromium. Chromium in high concentration may generate urogenital issues, heart difficulties, and carcinogenic repercussions [79]. When compared to non-cancerous persons, the hazardous element, cadmium was larger in female breast cancer patients in Pakistan [76,80].

Furthermore, poor dietary habits that cause inflammation contribute to both communicable and noncommunicable illnesses [82]. Obesity increases the risk of mortality by around 30% on average and the chance of BC by 35-40%. Not only should eating behaviours be prioritized, but also body weight control [83]. Physical activity, age, smoking, marital status, breastfeeding, menopausal status, oral contraceptives, body mass index, and parity may all increase risks [52, 54, 82].

The gut microbiome is well known to regulate the host's health and physiology. The gut microbiota and their metabolites stimulate cellular and immunological processes counter factors detrimental to human health [60]. Recent evidence points to a potential involvement for gut microbial dysbiosis in the development, management, and prognosis of BC. A recent study designated the "Biota Cancer Survivors" study sought to determine whether the gut microbiota of cancer survivors differed from a database of healthy controls [63]. Through comparison of differences between BC survivors and healthy controls, significant taxonomic differences were elucidated between the two groups. How ever, additional research is required to elucidate the contributing mechanisms and investigate the connection between microbiome and BC survival.

The role of gut microbiome and dysbiosis, as well as the research of the microbiota-gut axis in cancer is not fully under passed in Pakistan, and is a valuable field of exploration. A preliminary investigation of the oral microbiota (bacteria) and gastrointestinal tract (gut) in 32 urban Pakistani adults was recently completed utilizing 16S ribosomal RNA gene sequencing [65]. Interestingly, gender differences were detected in the gut microbiomes of Pakistani individuals, as well as a skewness toward Firmicutes and particularly large quantities of Proteobacteria in the males, which may lead to gut dysbiosis. It was also noticed that Pakistani women have considerably more Firmicutes [69]. Without a question, BC is a difficult condition, with various risk factors contributing to the disease's eventual appearance.

CONCLUSION

Current healthcare challenges and literacy issues persist in the diverse Pakistani population structure. The majority of breast cancer cases in Pakistan appear at higher stages because patients delay seeking medical assistance. Illiteracy along with fear and the absence of screening programs and cultural and economic factors are the main drivers behind this issue. Urban residents consume large amounts of inexpensive throwaway plastic products that consist primarily of bisphenol-A compounds with estrogenic activity thus leading to

premature menarche, obesity, cancer and problems with reproductive organ function. The traditional barbecuing practices in KPK increase the risk of BC and other cancer types through exposure to heterocyclic amines with carcinogenic potential. National screening programs require both awareness and cost-effective access to appropriate medical services following these important health statistics.

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