REVIEW ARTICLE

BREAST CANCER IN PAKISTAN-AN UPDATED OVERVIEW

GHAZALA RUBI[1], MARIA AMIR[2], NAEEM ASHRAF[3], AMIR BASHIR[4], HINA ANDALEEB[5]
[1]Director Research, Postgraduate Medical Institute / Lahore General Hospital, Lahore

ABSTRACT
Breast cancer is a leading cause of mortality in Pakistan due to cancer in females. Breast cancer has subtypes that inflict differently and owe to various factors that include our lifestyle and genetics. Pakistan has enhanced percentage in developing breast cancer in fourth decade of life in women. Numerous genomics and proteomics studies are being conducted in Pakistan for prognosis, diagnosis and treatment of breast cancer. This review focuses on the mutations in BRCA1/2 genes and other such genomic biomarkers. Moreover, this review emphasizes the advancements made in Pakistan for proteomic and metabolomics diagnosis of carcinoma.

How to cite this article: Rubi G, Amir M, Ashraf N, Bashir A, Andaleeb H. Breast cancer in Pakistan - An updated overview. Pak Postgrad Med J 2022;33(4): 120-123

DOI: https://doi.org/10.51642/ppmj.v33i04.531

Correspondence to: *Ghazala Rubi*
Director Research,
Postgraduate Medical Institute / Lahore General Hospital, Lahore, Pakistan

Email: *rubighazala@yahoo.com*

INTRODUCTION
Every one out of nine woman is at risk to develop breast cancer in Pakistan[1]. Limitless division of cells in breast tissue forms a malignant tumor that can invade neighboring tissues[2]. Risk factors for breast oncogenes include insulin resistance, ethnicity, dense breast tissue, hormonal therapy, aging and lifestyle. Biological carcinogens include viral infections like bovine leukemia virus, Epstein - Barr virus, papilloma-virus, bovine leukemia virus and Human Herpes Virus-8 [3].

BURDEN OF BREAST CANCER IN PAKISTAN
Asia accounts for 39% of the globally diagnosed cases of breast cancer[4]. It is a metastatic cancer that has the potential to spread in other tissues like liver, bone, lung and brain[5]. A study revealed that breast cancer presents itself in 4th decade of life in Pakistani breast cancer patients[6]. Thus, screening should be done earlier before the disease shows itself. Pakistan records about 30.8% female cancer patients who die have breast cancer[7]. 20% of these patients have Triple-negative breast cancer that is recurrent and aggressive type of breast carcinoma[8]. Pakistan has the highest incidence of breast cancer among four Asian countries (India, China, Thailand). Enhanced burden of breast cancer in Pakistan owes to various factors like lifestyle, social issues, reproductive abnormalities and demographic issues[9]. Higher mortality rate in Pakistan is due to delayed prognosis and socioeconomic barriers. An advanced statistical method using Lee-Carter model estimated a trend in mortality rate due to breast cancer during the period of 1990-2030 in Pakistan. GHDx is a health-database that records the burden of deaths due to several diseases (including breast cancer). Age-standardized death rate of breast cancer patients in Pakistan is predicted to be increased by 62% till 2030[10]. Delayed detection of breast cancer enhances death rate due to the involved lymph nodes and distant metastasis[11].

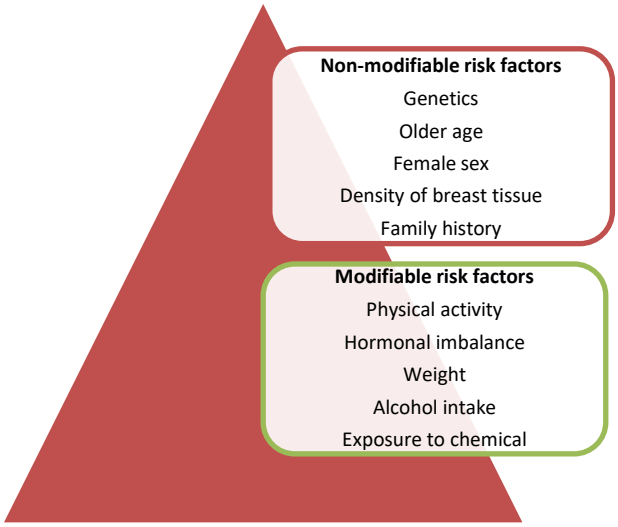

Figure 1: Risk factors of breast cancer.

PROGNOSTIC BIOMARKERS OF BREAST CANCER IN GENOME

Breast cancer susceptibility genes BRCA1 and BRCA2

These genes maintain the genomic stability by repairing DNA, gene transcriptional control and cell cycle maintenance. Alterations in these genes contribute to the oncogenic process in breast tissue. Recently, mutations in BRCA1 (rs1799950), BRCA2 (rs 144848) and TP53 (rs1042522) were found to significantly contribute to the breast cancer risk in population of KPK, Pakistan[12]. About 30% of all inherited or genetic breast cancer attributes to the BRCA1/2 mutations[13]. 185delAG, a frame shift mutation, has been reported to be a founder mutation of breast cancer in population of Punjab, Pakistan by Rashid.et al[14]. Another study revealed 133 deleterious mutations–110 & 23 in BRCA1 and BRCA2 respectively[15]. A next-generation sequencing strategy was adopted to map mutations in 27 breast cancer-associated genes that revealed 7 novel germ-line mutations in 3 high penetrance genes i.e., BRCAI &BRCAII and TP53[16]. DNA sequence analysis of samples from patients with infiltrating ductal carcinoma from KPK, Pakistan unveiled novel non-sense mutation in exon 11 of BRCA2[17]. 2 frame shift mutations, 6 missense and 2 intronic mutations were detected in patients of breast cancer that caused protein truncation from population of Islamabad, Pakistan[18]. List of identified mutations in BRCA1/2 is tabulated in Table#1

.

Table 1: Observed BRCA1/2 mutations in Pakistani patients of breast cancer

Gene	Exon	Mutation	Population	Reference
BRCA1				
	2	185insA	Punjab	[15]
	2	185delAG	Punjab	[15]
	2	68-69del	Sindh	[16]
	7	454delA	Punjab	[15]
	7	Y130X	Punjab	[15]
	10	1753GT	Sindh	[16]
	11	804delT	Punjab	[15]
	11	1014delGT	Punjab	[15]
	11	1127delA	Punjab	[15]
	11	1307delT	Punjab	[15]
	11	2080insA	Punjab	[15]
	11	2433delGT	Punjab	[15]
	12	Q1395X	Punjab	[15]
	13	R1443X	Punjab	[15]
	15	4784delG	Punjab	[15]
	16	4981delA	Punjab	[15]
	17	5154delC	Punjab	[15]
	21	5429dupG	Punjab	[15]
	22	5480delTG	Punjab	[15]
	24	5503CT	Sindh	[16]
BRCA2				
	9	993delCACAA	Punjab	[15]
	10	1528delAAAA	Punjab	[15]
	11	3048delA	Punjab	[15]
	11	3063delA	Punjab	[15]
	11	4088delA	Punjab	[15]
	11	5950delCT	Punjab	[15]
	11	6696delTC	Punjab	[15]
	11	5642delAATC	Sindh	[16]
	20	8773delAA	Punjab	[15]
	21	8897insT	Punjab	[15]
	23	9090delA	Sindh	[16]

Fanconi anemia complementation group M (FANCM) gene

This is found to be a potential gene in European countries. FANCM germ-line mutations were investigated in Pakistan recently. DHPLC and DNA sequencing un veiled 2 variants of uncertain significance (p.V1857M and p. K1780delinsNGIT). These variants were found in breast cancer patients who had family history of lymphomas[19]. However, further studies need to be done to confirm the contribution of this gene.

1. MSH2 EXONIC DELETIONS

Mismatch repair (MMR) pathway is a significant mechanism in oncogenes is of breast cancer**.** Mutations in the MMR genes like MLH1, MSH2, MSH6, and PMS2 have been found to be involved in colorectal

cancer, skin, brain, endometrial carcinoma and malignancies of stomach and ovarian cancer[20]. Two exonic deletions in MSH2 (Exon 3 and 9) have been evidenced to be associated with breast cancer etiology in cohort of Pakistani population[21]. These deletions alter the primary and secondary structure of the proteins as well.

2. miRNAs

MicroRNAs are the non-coding RNAs that repress translation to regulate protein production from mRNA. miRNAs are the emerging factors to study in cancer progression and its therapy. miR-140, miR-148, and miR-29a target an important pathway that is *TGF-β1* pathway. The level of *TGF-β1 enhances risk of* breast cancer, and its level is related to the grade and stage of cancer. A study was conducted to predict the correlation of miRNAs with the grade and stage of cancers in population of Pakistan. Effect of miRNA on TGF-beta pathway was studied via TargetScanHuman and correlation was depicted through Mindjet Manager[22].

PROGNOSTIC BIOMARKERS IN PROTEOME

Differentially-expressed proteins from samples of breast carcinomas were found in population of Bahawalpur, Pakistan via mass spectrometry. These can serve as significant biomarkers. The identified proteins are e-HBB, GNA13, enhancer of the rudimentary homologue, CCPG1, ALDOA, TRFL, TRP1, RAB1A, Ras-related protein Rab-7a, RPL21 60S ribosomal protein L21, ACTC1, ribosomal protein S25, Ras related protein Rab-8A, heat shock protein HSP 90-beta, beta-subunit of prolyl 4-hydroxylase (P4HB), carbamoyl phosphate synthetase I, pyrroline-5-carboxylate reductase 1 etc [23].

Nano LC/MS revealed 29% differentially-expressed proteins in serum of breast cancer patients. Most of the proteins were organelle-specific and low-weighed that can serve as prognostic biomarkers[24].

Another study revealed higher levels of calreticulin protein in patients of invasive ductal carcinoma in Pakistani population[25]. Calreticulin is a soluble protein that binds Calcium ions and works as a 2nd messenger in signaling.

Metabolomic profile of breast cancer

Altered metabolites depict the abnormal metabolic pathways in cancer. GC/MS provided the metabolomic profile of the serum of breast cancer patients from Karachi population. Increased metabolites of glycolysis, lipogenesis and other such pathways were observed that can help in cancer grading and staging[26].

CONCLUSION

Pakistan is registering more and more cases of breast cancer since few years owing to certain genetic and socioeconomic factors. The devastating mortality rate due to this disease in Pakistan is majorly because of late diagnosis and lack of awareness. Insight of genetic contributors of disease can help in treatment strategies. Mutations in certain protective genes like BRCA1/2 render genomic instability and hence, contributes in carcinogenesis. Advanced facilities and new government policies need to be introduced at national level to cope with the alarming situation of the breast cancer prevalence in Pakistan.

REFERENCES

1. Zaheer, S., Shah, N., Maqbool, S.A. *et al.* Estimates of past and future time trends in age-specific breast cancer incidence among women in Karachi, Pakistan: 2004–2025. *BMC Public Health* **19**, 1001 (2019).
2. Łukasiewicz, Sergiusz, et al. "Breast Cancer—Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies—An Updated Review." *Cancers* 13.17 (2021): 4287.
3. Fozuni, Elaheh, et al. "Evaluation frequency of human herpes virus type 8 in patients with breast cancer." (2020).
4. Fan, Lei, Paul E. Goss, and Kathrin Strasser-Weippl. "Current status and future projections of breast cancer in Asia." *Breast care* 10.6 (2015): 372-378.
5. Ahmad, Aamir. "Breast cancer statistics: recent trends." *Breast Cancer Metastasis and Drug Resistance* (2019): 1-7.
6. Soomro, Rufina, et al. "Age and stage of breast cancer in Pakistan: An experience at a tertiary care center." *J Pak Med Assoc* 68.11 (2018): 1682-1685.
7. GLOBOCAN. Fact sheets by Cancer-GLOBOCAN 2018. http://gco.iarc.fr/today/data/factsheets/populations/586-pakistan-fact-sheets.pdf (Accessed on 14/11/2019).
8. Boyle, P. "Triple-negative breast cancer: epidemiological considerations and recommendations." *Annals of oncology* 23 (2012): vi7-vi12.
9. Mubarik, Sumaira, et al. "Recent insights into breast cancer incidence trends among four Asian countries using age-period-cohort model." *Cancer management and research* 11 (2019): 8145.
10. Mubarik, Sumaira, et al. "Breast cancer mortality trends and predictions to 2030 and its attributable risk factors in East and South Asian Countries." *Frontiers in nutrition* 9 (2022).
11. Shamsi, Uzma, et al. "Patient delay in breast cancer diagnosis in two hospitals in Karachi, Pakistan: preventive and life-saving measures needed." *JCO Global Oncology* 6 (2020): 873-883.

12. Khan, Najeeb Ullah. "88. Significant association of BRCA1, BRCA2 and TP53 gene polymorphisms with breast cancer risk in Khyber Pakhtunkhwa, Pakistan." *Cancer Genetics* 268 (2022): 28-29.
13. Kharel, Sanjeev, et al. "BRCA1/BRCA2 mutation spectrum analysis in South Asia: a systematic review." *Journal of International Medical Research* 50.1 (2022): 03000605211070757.
14. Rashid, Muhammad U., et al. "Prevalence of BRCA1 and BRCA2 mutations in Pakistani breast and ovarian cancer patients." *International journal of cancer* 119.12 (2006): 2832-2839.
15. Rashid, Muhammad Usman, et al. "Spectrum and prevalence of BRCA1/2 germline mutations in Pakistani breast cancer patients: results from a large comprehensive study." *Hereditary cancer in clinical practice* 17.1 (2019): 1-13.
16. Ajaz, Sadia, et al. "Germline mutation analysis in sporadic breast cancer cases with clinical correlations." *Frontiers in genetics* 13 (2022).
17. Ullah, Lateef, et al. "Detection of novel infiltrating ductal carcinoma-associated BReast CAncer gene 2 mutations which alter the deoxyribonucleic acid-binding ability of BReast CAncer gene 2 protein." *Journal of Cancer Research and Therapeutics* 16.6 (2020): 1402.
18. Majeed, Ayesha Isani, et al. "Screening, diagnosis and genetic study of breast cancer patients in Pakistan." *Pakistan Journal of Medical Sciences* 36.2 (2020): 16.
19. Rashid, Muhammad Usman, et al. "Prevalence of FANCM germline variants in BRCA1/2 negative breast and/or ovarian cancer patients from Pakistan." *Familial Cancer* (2022): 1-11.
20. Engel, Christoph, et al. "Associations of pathogenic variants in MLH1, MSH2, and MSH6 with risk of colorectal adenomas and tumors and with somatic mutations in patients with Lynch syndrome." *Gastroenterology* 158.5 (2020): 1326-1333.
21. Malik, Saima Shakil, et al. "Correlation of MSH2 exonic deletions and protein downregulation with breast cancer biomarkers and outcome in Pakistani women/patients." *Environmental Science and Pollution Research* 28.3 (2021): 3066-3077.
22. Ahmed, Fayyaz, et al. "Perception of breast cancer risk factors: Dysregulation of TGF-β/miRNA axis in Pakistani females." *Plos one* 16.7 (2021): e0255243.
23. Manzoor, Yasmeen, et al. "Incubating Green Synthesized Iron Oxide Nanorods for Proteomics-Derived Motif Exploration: A Fusion to Deep Learning Oncogenesis." *ACS Omega* (2022).
24. Zafar, Ayesha, et al. "Quantifying Serum Derived Differential Expressed and Low Molecular Weight Protein in Breast Cancer Patients." *Protein and Peptide Letters* 27.7 (2020): 658-673.
25. Tariq, Asma, et al. "Calreticulin is Differentially Expressed in Invasive Ductal Carcinoma: A Comparative Study." *Current Proteomics* 16.2 (2019): 148-155.
26. Hadi, Naila Irum, et al. "Serum metabolomic profiles for breast cancer diagnosis, grading and staging by gas chromatography-mass spectrometry." *Scientific reports* 7.1 (2017): 1-11.