The Research of Medical Science Review

Received: 23 October, 2024
Accepted: 9 November, 2024
Published: 21 November, 2024

ISSN: 3007-1208 | 3007-1216
Volume 2, Issue 3, 2024

ASSOCIATION OF ATM GENETIC VARIANT (rs3092856) POLYMORPHISM WITH BREAST CANCER IN KHYBER PAKHTUNKHWA

Muhammad Nouman[*1], Afaq Ahmad[2], Faiza Shams[3], Abdul Qadeer Khan[4], Hafiz Fazal Mahmood[5], Muhammad Ashraf[6], Jabir Khan[7], Javeria Begum[8]

*[*1]Master Of Philosophy In Biotechnology Department Of Biotechnology, Faculty Of Chemical And Life Sciences Abdul Wali Khan University Mardan.*
[2,3,6]Department Of Biotechnology, Faculty Of Chemical And Life Sciences Abdul Wali Khan University Mardan.
[4]Department Of Allied Health Science, Iqra National University Peshawar
[5]Institute Of Allied Health Science, Sarhad University Of Science And Information Technology, Peshawar.
[7]Institute Of Allied Health Science, Sarhad University Of Science And Information Technology, Peshawar
[8]Institute Of Biotechnology And Microbiology, Bacha Khan University Charsadda

[*1]noumanbiotch555@gmail.com, [2]Afaq92623@gmail.com, [3]Faizashams25@gmail.com, [4]aqkh562@gmail.com, [5]fazalmahmood1988@gmail.com, [6]mashrafjadoon@gmail.com, [7]aliahmadkhan9001@gmail.com, [8]javeriabiotech615@gamil.com

ABSTRACT

Currently, breast cancer is a major health concern among the women population. It is caused by the abnormal proliferation of cells inside the breast resulting in the formation of lumps, which can metastasize to other areas in the body. Annually, there are almost a million females diagnosed with breast cancer worldwide. In most cases breast cancer results from some mutations of a few genes such as Ataxia telangiectasia Mutated (ATM), which is found to be over-expressed in nearly 50% of breast cancers. In this study, we obtained a total of 334 blood samples from Khyber Pakhtunkhwa, out of which 184 were past Breast cancer symptomatic while 150 were healthy controls. In this way, we obtained pure blood from diseased and healthy individuals using the Phenol-Chloroform method to extract DNA from whole blood. Similarly, genotyping was done using Allele-Specific PCR (AS-PCR) by utilizing specially designed tetra primers for each allele and statistical analysis was done using IBM SPSS software. The amplification product was localized on 2% agarose gel using a UV illuminator. The polymorphism distribution of the ATM Genetic variant rs3092856 in breast cancer patients and healthy controls indicates the SNP (rs3092856) has a significant ($P=0.0079$, $\chi2=8.970,2$) role in breast cancer protective mechanism in Khyber Pakhtunkhwa. Besides, the heterozygous dominant genotypes in patients with breast cancer and the CC genotypes in homozygous dominant genotypes had statistically higher prevalence compared to healthy controls. However, patients with breast cancer had significantly less frequency of homozygous recessive Genotype (GG) than healthy controls. Additionally, we noted that the cases had a similar low frequency of the minor allele (G) compared to the controls, which showed the same trend of associations. The above-mentioned findings infer that the risk associated with developing breast cancer is associated with the C allele while the G allele exerts a strong protective effect in the Khyber Pakhtunkhwa population afflicted with breast cancer.

Keywords: *Breast cancer, SNP, ATM, rs3092856 C> G ARMS-PCR, Khyber Pakhtunkhwa*

INTRODUCTION

Breast cancer is a type of cancer that affects women globally and is one of the most common types of cancer that affects women. In 2023, there were approximately 900.000 new cases reported globally. The disease accounts for nearly 60% of deaths due to cancer. In rich societies, more than 80% of patients diagnosed with breast cancer survive for more than five years. In a poor society, this number is lower than 40%. The aim is to improve the annual survival rates through advancements in diagnosis and treatment. In developing countries, however, there is more challenge to achieve better treatment results because of their weak, and inadequately funded health systems (Komata D et al., 2016). Estrogen promotes the mutations that ultimately cause breast cancer. Among these, specific single nucleotide polymorphisms (SNPs) associated with breast cancer are identified by Genome-Wide Association Studies (GWAS).

Even though their impacts are quite often less severe than the impacts of rare gene-associated mutations, including BRCA1, BRCA2, and ATM. These common genetic imperfections also constitute the breast cancer genetic makeup and help in the classification of people into different levels of risk. (Deng & Associates, 2017). SNP rs3092856 is located within the ATM gene on chromosome 11. The ATM gene is found at chromosome 11 in region 22.3 of the long arm of chromosome 11 (11q22.3). (Shan et al., 2019).

The ATM gene contains 66 coding segments which cover approximately 150 kilobases of DNA and produce a 13 kilobase long messenger RNA with a coding sequence of 9168 base pairs from multiple tissues investigated. GWAS identified several candidate single nucleotide polymorphisms (SNPs) that are implicated with breast cancer. The impact of such common genetic alterations is often lower when contrasted with the atypical mutations like the ATM, BRCA1 and BRCA2 genes. All these features, however, together form the genetic framework of breast cancer, and assist in determining different levels of risk in the patients (Janavicius. 2011). The GWAS has also identified certain specific SNPs, such as rs3092856 linked with breast cancer.

This study aims to assess the burden of breast cancer alongside its symptoms among the patients and analyze the relationship between ATM genetic variation rs3092856 and the danger of breast cancer in Khyber Pakhtunkhwa's patients.

Research Methodology

Ethical Approval

The ethical review board of the Biotechnology Department permitted us to conduct the research processes and methods in the Abdul Wali Khan University health biotechnology lab.

Area Selection, Sample Size, and Information Collection

In the study, we have taken blood samples at the Mardan Medical Complex (MMC) situated near Sheikh Maltoon Town in Mardan, Khyber Pakhtunkhwa, Pakistan. A total of 300 people had their blood collected wherein 150 were of breast cancer and 150 were healthy. A comprehensive questionnaire and an informed consent form were developed and implemented to collect patient information such as demographics, health history, and lifestyle preferences. Approximately 3-4 cc of blood were collected from each participant. Deposited in an EDTA vacutainer and stored at the health biotechnology laboratory.

Inclusion Criteria for Patients

We have collected blood specimens from the patients showing signs similar to breast cancer, who consented to be part of the study and were diagnosed using imaging and serum tests. Healthy subjects were included in the study on the basis that the individuals did not have any family stories of breast cancer.

Exclusion Criteria for Patients

The exclusion criteria consist of: All participants in the study were those who refused to participate in the research, those with diagnoses other than breast cancer, those with impaired immune systems, those who did not have typical symptoms, and those who did not undergo a breast cancer screening.

Extraction of DNA:

Genomic DNA was extracted from 4-5ml of the blood samples utilizing standard Phenol-chloroform methods. Proceeding extraction, DNA was confirmed on 1% agarose followed by quantification by nanodrop.

DESIGNING OF PRIMERS

The ATM sequence was obtained from the NCBI, and the SNP (rs3092856 C>G) was identified using the NCBI db-SNP data source. Two outside primers and two interior primers for each allele were designed using the NCBI primer design tool.

PROCEDURE of PCR Amplification

For the amplification of PCR, we utilized a thermocycling T100. The developed primers were employed in this experiment. The final PCR reaction needs nine microliters of blue master mix, two microliters of PCR grade water, three microliters of genomic DNA, 1.5 microliters of outer primers, and 1.5 microliters of inner primers.

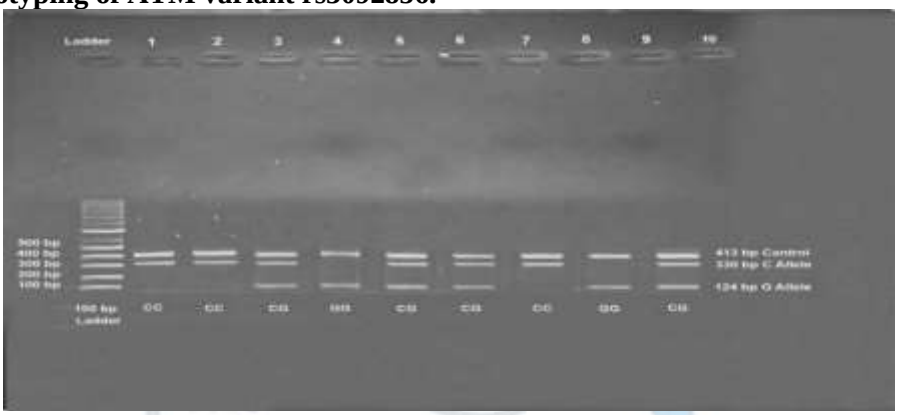
GENOTYPING OF ATM VARIANT RS3092856 C>G

The ATM variant rs3092856 was genotyped using an allele-specific PCR method. Table 3.4 shows the requirements for PCR thermocycling.

HORIZONTAL GEL ELECTROPHORESIS

Electrophoresis of amplified PCR products was performed on a 2% agarose gel.

Figure 3.1 Genotyping of ATM variant rs3092856.



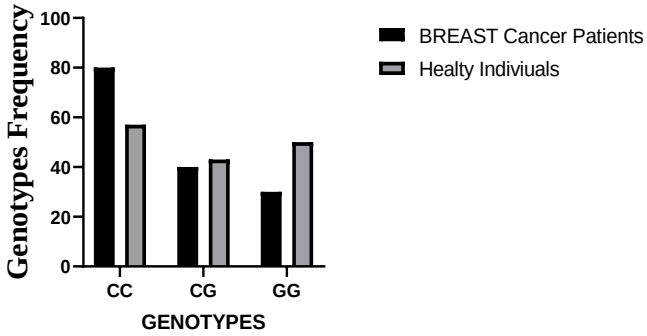
STATISTICAL ASSESSMENT

We have carried out all statistical procedures and assessments using GraphPad Prism 8.0.1.

Result

ATM Genetic Variant (RS3092856 C>G) GENOTYPING

We have studied the ATM genetic variant rs3092856 in 150 breast cancer patients and 150 healthy people to assess its association with the illness. Each case-control study's genotype frequency differs significantly from the others. The tests were conducted using the statistical software SPSS.



CO-DOMINANT MODEL

The study found significant differences in genotypes between the patient and control group in the co-dominant model. Patient genotype, C/G (38%), G/G (20%) C/C (53%). Controlled genotypes, G/G (38%), C/C (28%), C/G (33%). An important connection between patient status and genotype was found(x2=8.9720). P= (0.0079).

HOMOZYGOUS DOMINANT MODEL

The study found an important association between patient status and the C/C genotype. 46% of patients had the C/G+G/G genotype while 53% had the C/C genotype. In control group there were 62% C/G+G/G genotype and 38% C/C genotype. In this case, the odds ratio was 1.8647 (95% CI 1.771—2.9538) P = 0.0079.

HOMOZYGOUS RECESSIVE MODEL

The genotype distribution in the homozygous recessive model showed significant differences. 20% of patients and control had G/G genotype, while the remaining 80% had C/C or C/G. An important link was found between the G/G genotype and the status of the patient (OR=0.5000, 95% CI= 0.2959-0.8450, P=0.0096).

HETEROZYGOUS DOMINANT MODEL

There were no significant association found in the genotype distribution between control and patients using the heterozygous dominancy paradigm. Both the groups had 26% C/G and 73% C/C or G/G genotypes. The OR for the G/C genotype and patient status was 0.8295 (95% CI: 0.5014), with a P-value of 0.4665, representing no important association.

ADDITIVE MODEL

In the additive model, affected individuals had C allele frequency of 66.66% and G allele frequency of 33.33%, while controls had C allele frequency of 47.66%. The C allele was significantly associated with the patient status (OR= 1.8217, 95% CI: 1.3095-2.5341, P=0.0004).

DISCUSSION

The main causes of breast cancer include genetic changes and DNA damage, and estrogen exposure may exacerbate these diseases. BRCA1, BRCA2, and ATM are among the genes connected to BC that are being studied in an attempt to make them uncommonly inherited. Breast cancer is associated with a 5- 10% hereditary predisposition. The increased risk linked with the BRCA1 and BRCA2 genes has gained a lot of attention recently, however, it is likely that this represents just a minor share of the total hereditary risk. (Kastan and Shiloh 2001).

The rest could be clarified by less significant but more prevalent genes. For instance, the ATM gene is changed in the human disorder ataxia-telangiectasia. The current clinical practice involves gene panel testing for women with ATM gene mutations who are thought to be at moderate risk of getting breast cancer due to a family history of the disease. It is suggested that these women undergo screening and MRIs at the age of forty. Currently, physicians are unable to test the general public with gene panels, and ATM mutations are typically detected after a breast cancer diagnosis. (L. Dorling and colleagues, 2021).

As a result, a family history of ovarian or breast cancer predisposes to development of this disease. Mammography has been reported to claim the

highest percentage of deaths of women worldwide due to cancers. Siegel et al. (2018) indicated that women are hundreds of times more probably to grow breast cancer as compared to men. It was estimated that 2.3 million new cases of breast cancer will be diagnosed in 2022, and half of the population who suffer from this disease will die because of it. The share of deaths was 60%, which falls under emerging nations. In developed countries, the rate of survival for breast cancer after 5 years is about 80%. However, this is less than 40% in emerging nations (Khan et al. (2023)). Khokher et al. opine that breast cancer is on the rise in Pakistan. A higher incidence of breast cancer is found in South Asian low-income countries of high population density. Badar and others, 2011. Male breast cancers have also been linked with Pakistan's northern regions. Jiao et al., 2023.

Since Swift et al.'s first study showed that breast cancer was most clearly linked with AT heterozygosity, ATM has been identified as a factor of risk in sporadic cases of breast cancer in the general population. This topic remains throughout the literature. (Kaur & others, 2022).

Among the patients reporting BC symptoms, we calculated the prevalence of BC symptoms. A high prevalence of BC was reported amongst those with BC symptoms; on the whole, of 184 patients with symptoms, 150 (81.52%) as shown in Figure 4.1 were given biopsies whose confirmation is their diagnosis, and there were those left at 34 or 18.48%. The individuals also had gynecomastia, breast engorgement, breast cysts, and abscesses.

This study explores genotypic and allelic frequencies in symptomatic patients and control. It found that homozygous-dominant gene, CC was significantly high for breast cancer patients than the health controls, implying that it may have a negative effect.

However, frequencies of the CG genotype (Figure 4.5) were similar in breast cancer patients and controls from British Columbia. Frequency of the homozygous recessive genotype, or GG genotype (Figure 4.4) was greater in the control group than in the breast cancer patients indicating that Khyber Pakhtunkhwa's disproportionately large population was resistant to breast cancer. In addition, in the suspected patients, the minor frequency for the minor allele G revealed linkage and parallel trends. Thus, this research finds that those with the C allele have a higher risk of BC than subjects with the G allele. The G allele confers protection against BC in Khyber Pakhtunkhwa subjects. However, the homozygous recessive genotype GG in ATM SNP Rs 3092856 has been associated with a high risk of throat, prostate, and breast cancer (Jiao et al., 2023; Kaur et al., 2022; Liu et al., 2018). Compared to previously existing statistics in the world, this study differs significantly.

However, this case-control study may possess a few probably flaws that are worth mentioning. The size of the enormous sample may give proof that ATM Genetic Variation SNP rs3092856 is associated with breast cancer. Moreover, the use of only one facility in collecting all blood samples may have been exposed to selection bias hugely influencing this particular study. However, further research has to confirm these findings with larger datasets.

CONCLUSION:

The findings of this study revealed a substantial link between the illness and the breast cancer SNP, such as rs3092856. It is the first study to investigate the link between breast cancer and the ATM genetic variant, such as rs3092856 in the Khyber Pakhtunkhwa population. According to the results, those with the CC genotype are more size is needed to better understand the effect of the ATM genetic variation on breast cancer.

REFERENCES

Ahmad, H., Ali, A., Ali, R., Khalil, A. T., Khan, I., Khan, M. M., & Alorini, M. (2023). Genatic antirational landscape and in-silico analysis of TP53, PIK3CA, and PTEN in patients with breast malignancy from khyber Pakhtunkhwa. ACS omega, 8(45), 43318-43331.

Ahmad, W., Firasat, S., Akhtar, M.S., Afshan, K., Jabeen, K., & Amjad, R.A. 2021. Demographic variation and risk factors regarding breast malignancy among females in Southern Punjab, Pakistan. Jouribonucleic acidl of the Pakistan Medical Association, 1(3), pp. 91-95.

Aitmagambetova, M.A., Smagulova, G.A., Tuhvatshin, R.R., Zheksenova, A.N. and Amanzholkyzy, A., 2022. Genetic and clinical characteristics of BRCA-

associated hereditary breast malignancy in the West region of Kazakhstan. Carcinogenesis, 43(9), pp.838-841.

Akram, M., Iqbal, M., Daniyal, M. and Khan, A.U., 2017. Awareness and current knowledge of breast malignancy. Biological research, 50, pp.1-23.

Akram, M., Iqbal, M., Daniyal, M. & Khan, A. U. 2017. Awareness And Current Knowledge of Breast Cancer. Biological Research, 50, 1-23.

Ali, A., 2019. Frequency locally advanced and metastatic breast malignancy at the time of presentation in a private hospital in Peshawar. The Professional Medical Jouribonucleic acidl, 26(10), pp.1693-1696.

Aliya, B., Azeem, F. and Ullah, R., 2019. Knowledge, attitude, and practice of breast malignancy screening among female health care professionals of a tertiary care hospital of Peshawar. Jouribonucleic acidl of Rehman Medical Institute, 5(4), pp.03-06.

American Malignancy Society. 2021. Breast Malignancy Early Detection and Diagnosis. Available at: https://www.malignancy.org/malignancy/breast-malignancy/screening-tests-and-early-detection.html

Aziz, Z., & Sana, S. Estimation of malignancy incidence in Karachi. 2004. Malignancy Research, 64(4), 906-911.

Baselga, J., Cortés, J., Kim, S.B., Im, S.A., Hegg, R., Im, Y.H., Roman, L., Pedrini, J.L., Pienkowski, T., Knott, A. and Clark, E., 2012. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast malignancy. New England Jouribonucleic acidl of Medicine, 366(2), pp.109-119.

Behl, A., Wani, Z. A., Das, N. N., Parmar, V. S., Len, C., Malhotra, S., & Chhillar, A. K. 2023. Monoclonal antibodies in breast malignancy: A critical appraisal. Critical reviews in Oncology/hematology, 183, 103915.

Bhardwaj, P.V., Dulala, R., Rajappa, S. and Loke, C., 2024. Breast malignancy in India: screening, detection, and management. Hematology/Oncology Clinics, 38(1), pp.123-135.

Bjerke set, E., Röhrl, K. and Schou-Bredal, I., 2020. Signs cluster of pain, fatigue, and psychological distress in breast malignancy survivors: prevalence and characteristics. Breast malignancy research and treatment, 180, pp.63-71.

Brewer, H.R., Jones, M.E., Schoemaker, M.J., Ashworth, A. and Swerdlow, A.J., 2017. Family history and risk of breast malignancy: an analysis accounting for family structure. Breast malignancy research and treatment, 165, pp.193-200.

Cordo Russo, R.I., Chervo, M.F., Madera, S., Charreau, E.H. and Elizalde, P.V., 2019. Nuclear ErbB-2: a novel therapeutic target in ErbB-2-positive breast malignancy? Hormones and Malignancy, 10(2), pp.64-70.

Cuzick, J., Sestak, I., Bonanni, B., Costantino, J.P., Cummings, S., DeCensi, A., Dowsett, M., Forbes, J.F., Ford, L., LaCroix, A.Z. and Mershon, J., 2013. Selective oestrogen receptor modulators in prevention of breast malignancy: an updated meta-analysis of individual participant data. The Lancet, 381(9880), pp.1827-1834.

De Bruin, M.A., Ford, J.M. and Kurian, A.W., 2012. Genetic polymorphisms as predictors of breast malignancy risk. Current Breast Malignancy Reports, 4, pp.232-239.

Decker, M., Kortüm, M., Zimmer, S., & Langer, F. 2011. Functional characterization of ATM variants identified in breast malignancy patients undergoing genetic testing. Endoribonuclease acidtional Jouribonucleic acidl of Malignancy, 129(11), 2803-2810.

Derakhshan, F., & Reis-Filho, J. S. (2022). Pathogenesis of triple-negative breast malignancy. Annual Review of Pathology: Mechanisms of Disease, 17(1), 181-204.

DeVita, V.T., Lawrence, T.S. and Rosenberg, S.A. eds., 2019. DeVita, Hellman, and Rosenberg's malignancy: principles & practice of oncology. Wolters Kluwer.

Dorling L, Carvalho S, Allen J, et al. 2021. Breast Malignancy Association Consortium,

Breast malignancy risk genes—association analysis in more than 113,000 females. New England Jouribonucleic acidl of Medicine, 384(5), pp.428-439.

Drukteinis, J.S., Mooney, B.P., Flowers, C.I. and Gatenby, R.A., 2015. Beyond mammography: new frontiers in breast malignancy screening. The American jouribonucleic acidl of medicine, 126(6), pp.472-479.

Elizalde, P.V., Russo, R.I.C., Chervo, M.F. and Schillaci, R., 2016. ErbB-2 nuclear function in breast malignancy growth, metastasis and resistance to therapy. Endocrine-related malignancy, 23(12), pp.T243-T257.

Feng, Y., Spezia, M., Huang, S., Yuan, C., Zeng, Z., Zhang, L., ... & Ren, G. (2018). Breast malignancy development and progression: Risk factors, malignancy stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes & diseases, 5(2), 77-106.

Gohar, L., Riaz, B., Nadeem, M.S., Abbas, S., Afsar, T., Razak, S., Muccee, F., Husain, F.M., & Shafique, H. 2024. Body mass index and altered lipid profile as major risk markers for breast malignancy progression: A cross-sectional study of postmenopausal females in Pakistan. BMC Females's Health, 24(1), pp. 29.

Gøtzsche, P.C. and Jørgensen, K.J., 2013. Screening for breast malignancy with mammography. Cochrane Database of Systematic Reviews, (6).

Greenwood, H.I., Heller, S.L., Kim, S., Sigmund, E.E., Shaylor, S.D. and Moy, L., 2013. Ductal carcinoma in situ of the breasts: review of MR imaging features. Radiographics, 33(6), pp.1569-1588.

Hu, C., Hart, S.N., Gnanaolivu, R., Huang, H., Lee, K.Y., Na, J., Gao, C., Lilyquist, J., Yadav, S., Boddicker, N.J. and Samara, R., 2021. A population-based study of genes previously implicated in breast malignancy. New England Jouribonucleic acidl of Medicine, 384(5), pp.440-451.

Ikram, A., Pervez, S., Khadim, M.T., Sohaib, M., Uddin, H., Badar, F., Masood, A.I., Khattak, Z.I., Naz, S., Rahat, T. and Murad, N., 2023. National malignancy registry of Pakistan: first comprehensive report of malignancy statistics 2015-2019. J Coll Physicians Surg Pak, 33(6), pp.625-32.

Jiao, Y., Truong, T., Eon-Marchais, S., Mebirouk, N., Caputo, S. M., Dondon, M.-G., Karimi, M., Le Gal, D., Beauvallet, J. & Le Floch, É. 2023. Association And Performance Of Polygenic Risk Scores For Breast Cancer Among French Women Presenting Or Not A Familial Predisposition To The Disease. European Journal Of Cancer, 179, 76-86.

Johnson N, Fletcher O, Palles C, Rudd M, Webb E, Sellick G. 2007. Counting potentially functional variants in BRCA1, BRCA-2 and ATM predicts breast malignancy susceptibility. Hum Mol Genet 16:1051–1057. https://doi.org/10.1093/hmg/ddm050

Kaur, H. B., Vidotto, T., Mendes, A. A., Salles, D. C., Isaacs, W. B., Antonarakis, E. S. & Lotan, T. L. 2022. Association Between Pathogenic Germline Mutations In Brca2 And Atm And Tumor-Infiltrating Lymphocytes In Primary Prostate Cancer. Cancer Immunology, Immunotherapy, 1-9.

Kawai, M., Ohtani, S., Iwasaki, M., Yamamoto, S., Takamatsu, K., Okamura, H., Arai, M., Nomura, T., Ozaki, S., Shibata, K.I. and Akabane, A. 2022. The Japanese Breast Malignancy Society clinical practice guidelines for epidemiology and prevention of breast malignancy, edition. Breast Malignancy, 31(2), pp.166-178.

Khan, Y., Khan, N. U., Ali, I., Khan, S., Khan, A. U., Iqbal, A., & Adams, B. D. (2023). Significant association of BRCA-1 (rs1799950), BRCA-2 (rs144848) and TP53 (rs1042522) polymorphism with breast malignancy risk in Pashtun population of Khyber Pakhtunkhwa, Pakistan. Molecular Biology Reports, 50(7), 6087-6096.

Kretschmer, C., Sterner-Kock, A., Siedentopf, F., Schoenegg, W., Schlag, P.M. and Kemmner, W., 2011. Identification of early molecular markers for breast

malignancy. Molecular malignancy, 10, pp.1-11.

Koo, M. M., Von Wagner, C., Abel, G. A., Mcphail, S., Rubin, G. P. & Lyratzopoulos, G. 2017. Typical And Atypical Presenting Symptoms Of Breast Cancer And Their Associations With Diagnostic Intervals: Evidence From A National Audit Of Cancer Diagnosis. Cancer Epidemiology, 48, 140-146.

Liu, J., Tang, X., Shi, F., Li, C., Zhang, K., Liu, J., Wang, G., Yin, J. & Li, Z. 2018. Genetic Polymorphism Contributes To 131i Radiotherapy-Induced Toxicities In Patients With Differentiated Thyroid Cancer. Pharmacogenomics, 19, 1335-1344.

Ma, F., Guan, Y., Yi, Z., Chang, L., Li, Q., Chen, S., Zhu, W., Guan, X., Li, C., Qian, H. and Xia, X., 2020. Assessing malignant heterogeneity using ctDEOXYRIBONUCLEIC ACID to predict and monitor therapeutic response in metastatic breast malignancy. Interibonucleic acidtional jouribonucleic acidl of malignancy, 146(5), pp.1359-1368.

Majid, M. A., Achmad, A., Holik, H. A., & Kartamihardja, A. H. S. (2019). Breast Malignancy Awareness among Bandung Adolescents. Juribonucleic acidl Pengabdian kepada Masyarakat (Indonesian Jouribonucleic acidl of Community Engagement), 8(1), 35-39.

Mansoori, B., Mohammadi, A., Gjerstorff, M.F., Shirjang, S., Asadzadeh, Z., Khaze, V., Holmskov, U., Kazemi, T., Duijf, P.H. and Baradaran, B., 2019. miR-142-3p is a malignant suppressor that inhibits estrogen receptor expression in ER-positive breast malignancy. Jouribonucleic acidl of cellular physiology, 234(9), pp.16043-16053.

Matouk, I.J., Raveh, E., Abu-lail, R., Mezan, S., Gilon, M., Gershtain, E., Birman, T., Gallula, J., Schneider, T., Barkali, M. and Richler, C., 2014. Oncofetal H19 RIBONUCLEIC ACID promotes malignant metastasis. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1843(7), pp.1414-1426.

Montalto, F. I. & De Amicis, F. 2020. Cyclin D1 In Cancer: A Molecular Connection For Cell Cycle Control, Adhesion And Invasion In Tumor And Stroma. Cells, 9, 2648.

Naeem, M., et al. 2021. Challenges in the treatment of breast malignancy in Pakistan. Malignancy Treatment Reviews, 54, pp. 45-53.

Naz, N., Khanum, S., Dal Sasso, G.T.M. and De Souza, M.D.L., 2016. Females's Views on Handling and managing their breast malignancy in Pakistan: a qualitative study. Diseases, 4(2), p.17.

Neagu, A.N., Jayaweera, T., Corrice, L., Johnson, K. and Darie, C.C., 2024. Breast Malignancy Exposomics. Life, 14(3), p.402.

Nicholson, W.K., Silverstein, M., Wong, J.B., Barry, M.J., Chelmow, D., Coker, T.R., Davis, E.M., Jaén, C.R., Krousel-Wood, M., Lee, S. and Li, L., 2024. Screening for Breast Malignancy: US Preventive Services Task Force Recommendation Statement. JAMA.

O'Mahony, M., Comber, H., Fitzgerald, T., Corrigan, M.A., Fitzgerald, E., Grunfeld, E.A., Flynn, M.G. and Hegarty, J., 2017. Interventions for raising breast malignancy awareness in females. Cochrane Database of Systematic Reviews, (2).

Orrantia-Borunda, E., Anchondo-Nuñez, P., Acuña-Aguilar, L. E., Gómez-Valles, F. O., & Ramírez-Valdespino, C. A. (2022). Subtypes of breast malignancy. Breast Malignancy [Internet]. Exon Publications; 2022 Aug 6. Chapter 3. Available from: https://www.ncbi.nlm.nih.gov/books/NBK583808/ doi: 10.36255/exon-publications-breast-malignancy-subtypes

Pagenstecher, C., Wehner, M., Friedl, W., Rahner, N., Aretz, S., Friedrichs, N., Sengteller, M., Henn, W., Buettner, R. & Propping, P. 2006. Aberrant Splicing In Mlh1 And Msh2 Due To Exonic And Intronic Variants. Human Genetics, 119, 9-22.

Pakistan Atomic Energy Commission (PAEC). 2020. Breast malignancy statistics in

Pakistan. [Online] Available at: PAEC website.

Pisano, E.D., Gatsonis, C., Hendrick, E., Yaffe, M., Baum, J.K., Acharyya, S., Conant, E.F., Fajardo, L.L., Bassett, L., D'Orsi, C. and Jong, R., 2005. Diagnostic performance of digital versus film mammography for breast-malignancy screening. New England Jouribonucleic acidl of Medicine, 353(17), pp.1773-1783.

Prodosmo, A., Buffone, A., Mattioni, M., Baribonucleic acidbei, A., Persichetti, A., De Leo, A., Appetecchia, M., Nicolussi, A., Coppa, A., Sciacchitano, S. and Giordano, C., 2016. Detection of ATM germline variants by the p53 mitotic centrosomal localization test in BRCA1/2-negative patients with early-onset breast malignancy. Jouribonucleic acidl of Experimental & Clinical Malignancy Research, 35, pp.1-10.

Putti, S., Giovinazzo, A., Merolle, M., Falchetti, M.L. and Pellegrini, M., 2021. ATM kinase dead: From ataxia telangiectasia syndrome to malignancy. Malignancys, 13(21), p.5498.

Rashid, M., et al. 2020. Genetic profiling of breast malignancy patients in Pakistan. Interibonucleic acidtional Jouribonucleic acidl of Malignancy Research, 129(11), pp. 2803-2810.

Renwack, A., Thompson, D., Seal, S., Kelly, P., Chagtai, T. & Ahmed, M. ATM genatic alterations that cause ataxia-telangiectasia are breast malignancy susceptibility allele, 2006 Nature Genetics, 38(8), 873-875.

Rosato, V., Bosetti, C., Negri, E., Talamini, R., Dal Maso, L., Malvezzi, M., Falcini, F., Montella, M. and La Vecchia, C., 2014. Reproductive and hormonal factors, family history, and breast malignancy according to the hormonal receptor status. European jouribonucleic acidl of malignancy prevention, 23(5), pp.412-417.

Reeder, J. G. & Vogel, V. G. 2008. Breast Cancer Prevention. Advances In Breast Cancer Management, Second Edition, 149-164.

Saini, A., Kumar, M., Bhatt, S., Saini, V. & Malik, A. 2020. Cancer Causes And Treatments. International Journal Of Pharmaceutical Sciences And Research, 11, 3121-3134.

Shah, R., Rosso, K. & Nathanson, S. D. 2014. Pathogenesis, Prevention, Diagnosis And Treatment Of Breast Cancer. World Journal Of Clinical Oncology, 5, 283.

Salahuddin, Arifullah , Najma , Mehreen, 2018. Risk Assessment Model of Rural and Urban Breast Malignancy Patients of Khyber Pakhtunkhwa Province, Pakistan, Pakistan Jouribonucleic acidl of Medical Research, 57(2).

Shanazarov, N., Zhapparov, Y., Kumisbekova, R., Turzhanova, D. & Zulkhash, N. 2023. 'Association of Gene Polymorphisms with Breast Malignancy Risk in the Kazakh Population', Asian Pacific Jouribonucleic acidl of Malignancy Prevention, 24(12), pp. 4195-4201.

Shoukat, Z. and Shah, A.J., 2023. Breast malignancy awareness and associated factors among females in Pakistan: A cross-sectional descriptive study. Asian Pacific Jouribonucleic acidl of Malignancy Prevention: APJCP, 24(5), p.1561.

Siagel, R. L., Miller, K. D. & Jemal, A. (2021). Malignancy statistics, 2021. CA: A Malignancy Jouribonucleic acidl for Clinicians, 71(1), 7-33.

Slamon, D.J., Leyland-Jones, B., Shak, S., Fuchs, H., Paton, V., Bajamonde, A., Fleming, T., Eiermann, W., Wolter, J., Pegram, M. and Baselga, J., 2001. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast malignancy that overexpresses HER2. New England Jouribonucleic acidl of Medicine, 344(11), pp.783-792.

So, W.K., Law, B.M., Ng, M.S., He, X., Chan, D.N., Chan, C.W. and McCarthy, A.L., 2021. Signs clusters experienced by breast malignancy patients at various treatment stages: a systematic review. Malignancy Medicine, 10(8), pp.2531-2565.

Soomro, R., Faridi, S., Khurshaidi, N., Zahid, N. and Mamshad, I., 2018. Age and stage of breast malignancy in Pakistan: An experience at a tertiary care center. J Pak Med Assoc, 68(11), pp.1682-1685.

Sørlie, T., Tibshirani, R., Parker, J., Hastie, T., Marron, J.S., Nobel, A., Deng, S., Johnsen, H., Pesich, R., Geisler, S. and Demeter, J., 2003. Repeated observation of breast malignant subtypes in independent gene expression data sets. Proceedings of the national academy of sciences, 100(14), pp.8418-8423.

Tabár, L., Vitak, B., Chen, T.H.H., Yen, A.M.F., Cohen, A., Tot, T., Chiu, S.Y.H., Chen, S.L.S., Fann, J.C.Y., Rosell, J. and Chen, H.H., 2011. Swedish two-county trial: impact of mammographic screening on breast malignancy mortality during 3 decades. Radiology, 260(3), pp.658-663.

Tavtigian, S. V., Oefner, P. J., Babikyan, D., Hartmann, A., Healey, S., Le Calvez-Kelm, F., & Hutter, P. 2009. The ataxia-telangiectasia gene (ATM) variant c.7271T>G (p.Val2424Gly) is a high-risk genatic alteration,. Jouribonucleic acidl of Medical Genetics, 46(10), 686-693.

Thompson, D., Duedal, S., Kirner, J., McGuffog, L., Last, J., Reiman, A., & Byrd, P. 2012. Malignancy risks and mortality in heterozygous ATM genatic alteration carriers. Jouribonucleic acidl of the National Malignancy Institute,. 97(11), 813-822.

Thorat, M.A. and Balasubramanian, R., 2020. Breast malignancy prevention in high-risk females. Best Practice & Research Clinical Obstetrics & Gynaecology, 65, pp.18-31.

Thorstanson, Y. R., Huang, H., Teraoka, S. N., Capanu, M., Reiner, A. & Ford, J. M.. ATM sequence variants in patients with ataxia-telangiectasia. 2003. Human Genatic alteration, 21(2), 123-131.

Tufail, M. & Wu, C. 2023. Exploring the burden of malignancy in Pakistan: An analysis of 2019 data. Jouribonucleic acidl of Epidemiology and Global Health, 13(2), pp. 104-115.

Ullah, Z., Khan, M.N., Din, Z.U. and Afaq, S., 2021. Breast malignancy awareness and associated factors amongst females in Peshawar, Pakistan: a cross-sectional study. Breast Malignancy: Basic and Clinical Research, 15, p.11782234211025346.

WHO. https://www.who.int/news-room/fact-sheets/detail/breast-malignancy

Xiao, W., Zheng, S., Yang, A., Zhang, X., Zou, Y., Tang, H. and Xie, X., 2018. Breast malignancy subtypes and the risk of distant metastasis at initial diagnosis: a population-based study. Malignancy management and research, pp.5329-5338.

Yoshimura, A., Imoto, I. and Iwata, H., 2022. Functions of breast malignancy predisposition genes: implications for clinical management. Interibonucleic acidtional jouribonucleic acidl of molecular sciences, 23(13), p.7481.

Zaib, S., Masood, N., Khan, J.S. and Yasmin, A., 2024. Breast Malignancy: Epidemiology, Risk Factors and Survival Analysis in the Pakistani Population. Jouribonucleic acidl of University College of Medicine and Dentistry, pp.18-23.