International Journal of Endorsing
HEALTH SCIENCE RESEARCH

IJEHSR

Original Article

Genetic Analysis for Early Diagnosis of Breast Cancer.

Amna Amin Sethi & Nisar Ahmed Shar

Department of Biomedical Engineering, NED University of Engineering & Technology, Karachi-Pakistan.

Doi: 10.29052/IJEHSR.v12.i2.2024.90-98

Corresponding Author Email: amnasethi@neduet.edu.pk

Received 02/09/2023
Accepted 25/03/2024
First Published 15/04/2024

Abstract

Background: Breast cancer is the most prevalent cancer type among women globally, constituting approximately 25% of all cancer cases. While germline mutations in BRCA1/BRCA2 genes are well-established risk factors for breast cancer, there remains a need to identify additional genes contributing to disease development. Understanding the genetic landscape beyond BRCA1/BRCA2 is crucial for elucidating disease heterogeneity and developing targeted therapies.

Methodology: This study aimed to identify novel genes implicated in breast cancer development by analyzing genomic and clinical data from patients with six different breast cancer types. Utilizing various databases including NCBI, ENSEMBL, Clinical Variance, cBioPortal, COSMIC, DAVID, and OMIM, we conducted a comprehensive genetic analysis. Additionally, a survey was conducted to assess public perception of breast cancer.

Results: Our genetic analysis revealed a significant overlap in genes associated with different breast cancer types, identifying NF1, PIK3CA, and TP53 as common genes across all types. Furthermore, the survey highlighted a lack of awareness regarding breast cancer causes and preventive measures among the general population.

Conclusion: Beyond BRCA1/BRCA2, identifying common genes like NF1, PIK3CA, and TP53 sheds light on potential targets for therapeutic interventions across various breast cancer types. Promoting awareness and education, particularly on self-examination procedures, is imperative to empower individuals in breast cancer prevention and early detection efforts.

Keywords

Breast Cancer, Genes, Pathogenic Alleles, Mutations, BRCA1/BRCA2.

Check for updates

Introduction

Breast cancer stands as a significant global health concern, accounting for a substantial portion of cancer-related mortality worldwide[1]. With approximately 25% of the Global Cancer Burden attributed to breast cancer, its impact on public health cannot be understated. Among women, breast cancer is the most commonly diagnosed cancer, representing around 30% of all cases. In 2022 alone, it was estimated that there were 287,850 new cases of breast cancer and 43,250 associated deaths[2]. Particularly in Pakistan, breast cancer prevalence is notably high compared to other Asian countries, with approximately 1 in 9 women at risk of developing the disease at some point in their lives[3]. Despite these alarming statistics, reliable data on breast cancer in Pakistan is lacking, and existing data often lacks scientific rigor.

Survival rates for breast cancer vary significantly based on the stage at diagnosis, with early-stage diagnoses (stage 0, I, and II) typically associated with higher survival rates compared to advanced stages (III and IV)[4]. Notably, more than 90% of women diagnosed at the earliest stage survive for at least five years, underscoring the importance of early detection and intervention. Understanding the risk factors associated with breast cancer, including hormonal influences, age, obesity, reproductive history, and genetic predisposition, is crucial for effective prevention and management strategies[5].

Genetic factors play a pivotal role in breast cancer susceptibility, with inherited DNA mutations significantly increasing the risk of developing the disease. Among the identified breast cancer susceptibility genes, BRCA1 and BRCA2 are particularly notable for their involvement in regulating cell cycle processes, DNA repair mechanisms, and transcriptional activity[6]. Germline mutations in these genes have been linked to hereditary breast cancer, with implications for both female and male individuals[7]. Additionally, several other genes, including PTEN, TP53, STK11/LKB1, ATM, and NBS1, contribute to breast cancer development, highlighting the complexity of the genetic landscape[8].

Recent advancements in cancer genomics have shed light on the molecular pathways and genetic modifiers associated with breast cancer[9,10]. Molecular targeted therapies, immunotherapies, and HER2 protein targeting have emerged as promising treatment modalities, yet challenges such as tumor resistance and molecular alterations persist[11-14]. Therefore, a deeper understanding of cancer-predisposing genes and their associated pathways is crucial for the development of novel therapeutic interventions and prognostic markers.

This study aims to delve into the classification of mutations, polymorphisms, and variations in genes linked to breast cancer beyond BRCA1 and BRCA2. By exploring additional genes that may contribute to disease development, the research seeks to enhance early detection strategies and inform targeted treatment approaches. Leveraging large-scale cancer genomics datasets, this study endeavors to advance our understanding of breast cancer pathogenesis and improve clinical outcomes for patients at risk.

Methodology

Inclusion Criteria

The study included genetic data pertaining to breast cancer from various databases, namely NCBI, ENSEMBL, Clinical Variance, cBioPortal, COSMIC, DAVID, and OMIM as shown in figure 1. The inclusion criteria focused on genes associated with breast cancer and relevant genomic information.

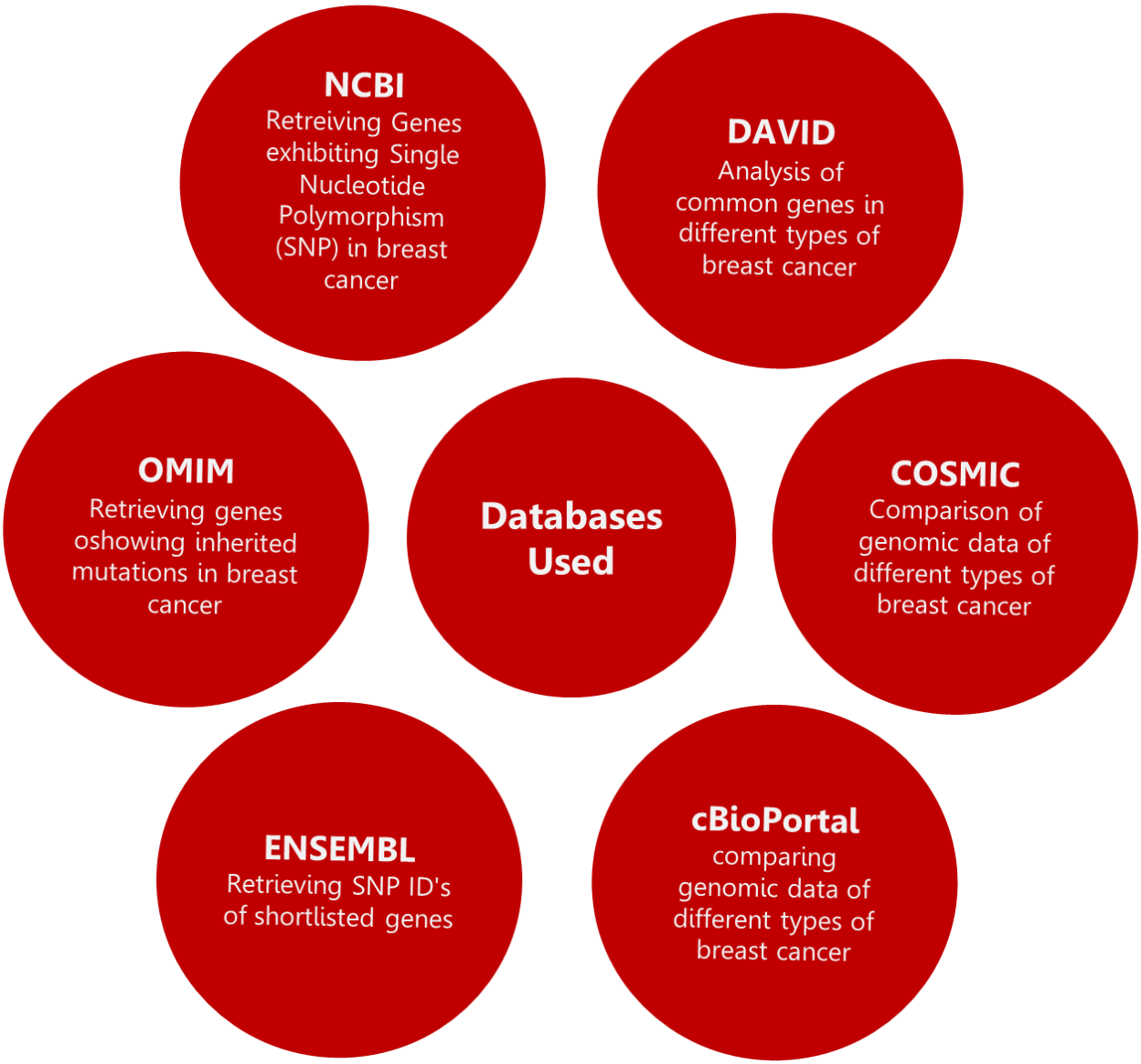

Figure 1: Schematic Representation of the Databases used in this study.

Genetic Investigation

The genetic investigation involved the identification and analysis of specific genes implicated in breast cancer pathogenesis. Initial screening using NCBI yielded a pool of forty-three candidate genes, which underwent further refinement based on single nucleotide polymorphism (SNP) analysis. Sixteen genes exhibiting variations in non-intron regions were prioritized for subsequent analysis.

Genomic Data Analysis

ENSEMBL provided essential genomic information and SNP IDs for the identified genes, facilitating precise gene mapping and annotation[15]. cBioPortal served as an interactive platform for the comparative analysis of genomic data across different types of breast cancer, including invasive ductal carcinoma, invasive lobular carcinoma, and others[16,17]. Comparative analysis identified common genes across various cancer subtypes.

Comparison with COSMIC Database

The identified genes were compared with entries in the COSMIC Cancer Database to assess somatically acquired mutations prevalent in human cancers[18]. This comparative analysis provided insights into shared genetic alterations between breast cancer subtypes and existing cancer mutations.

Functional Annotation and Pathway Analysis

DAVID database tools were utilized for functional annotation and visualization of the gene set[19]. Gene Ontology analysis and pathway mapping facilitated the categorization of genes based on their functional roles and interactions. Protein domain analysis elucidated evolutionary aspects of gene function and pathway involvement.

Survey

A supplementary survey was conducted to gauge public perception of breast cancer, particularly among residents of Karachi, Pakistan. Utilizing an online questionnaire, societal attitudes and awareness regarding breast cancer were assessed, providing valuable insights into the socio-cultural context of the disease.

Results

General Characteristics & Survey Results

The study comprised participants from diverse age groups, with the majority falling below 25 years, followed by those aged 25 to 35, and a smaller proportion aged 35 or above. An overwhelming 98.4% of participants demonstrated awareness of breast cancer, primarily acquired through distant sources rather than familial experiences. Electronic media, especially the internet, was the predominant source of information (86.7%), followed by family/friends, books, and hospital visits (Figure 2).

The survey underscored varying levels of awareness and knowledge regarding breast cancer practices. While 43.2% were aware of breast self-examination (BSE), only 26.8% knew the correct procedure as shown in figure 3. Clinical breast examination (CBE) remained largely unfamiliar, with only 35.3% reporting awareness. Notably, 96.6% were unaware or had never undergone genetic testing for BRCA1 and BRCA2 mutations, indicating a substantial gap in understanding hereditary breast cancer risk. Awareness of alternative genetic tests was notably low (1.6%).

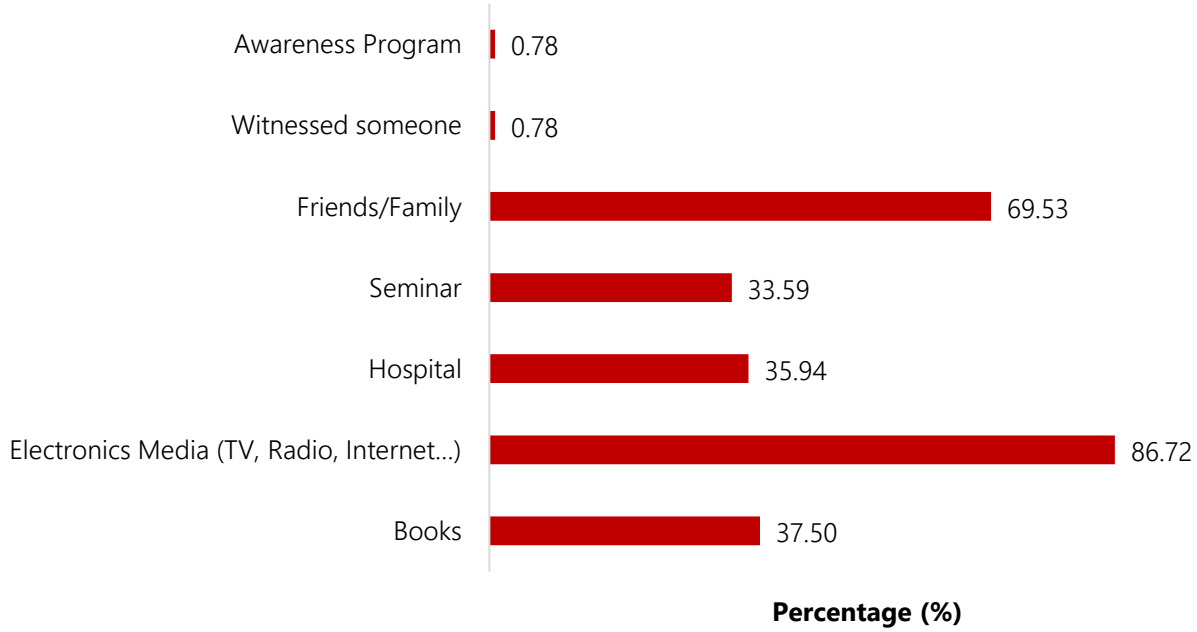

Figure 2: Response of survey participants regarding sources of information about Breast Cancer.

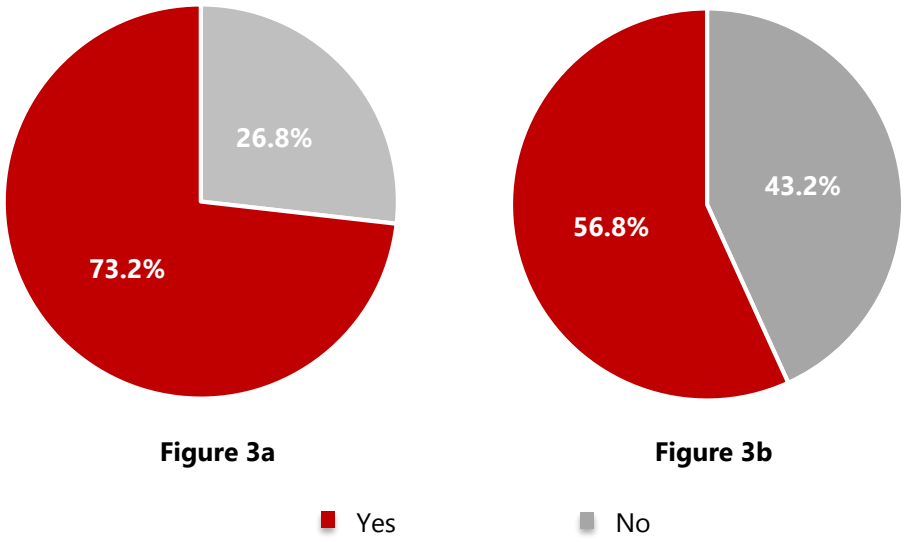

Figure 3: Response of survey participants regarding Breast Self-Examination. Figure 3a indicates awareness of Breast Self-Examination among participants and Figure 3b indicates knowledge of the procedure of Breast Self-Examination among participants.

Our survey revealed concerning gaps in awareness and knowledge related to breast cancer screening methods and genetic testing. While 43.2% of participants were aware of breast self-examination, only 26.8% knew the correct procedure. Additionally, only a minority (35.3%) were familiar with clinical breast examination (CBE). Surprisingly, 96.6% reported no awareness or experience with genetic testing for BRCA1 and BRCA2 mutations, crucial for assessing breast cancer risk. Among those tested, only 27.3% received positive results. Furthermore, alternative genetic tests beyond BRCA1 and BRCA2 were largely unknown, with only 1.6% of participants having undergone them. These findings emphasize the urgent need for comprehensive education and awareness initiatives regarding breast cancer screening and genetic testing to empower individuals in managing their breast health effectively.

Genetic Investigation

The genetic investigation identified key genes associated with various types of breast cancer. Initially, analysis of NCBI data revealed several genes with germline mutations, such as AKT1, BAP1, FLNA, among others. Notably, three genes—NF1, PIK3CA, and TP53—were found to be common across all six types of breast cancer studied, as summarized in Table 1.

Table 1: Number of common genes found among different types of breast cancer.

Types of Breast Cancer	Number of Identified Common Genes
Invasive ductal carcinoma & invasive lobular carcinoma	311
Invasive ductal carcinoma, invasive lobular carcinoma, & mixed invasive ductal lobular carcinoma	178
Invasive ductal carcinoma, invasive lobular carcinoma, mixed invasive ductal lobular carcinoma, & NOS	68
Invasive ductal carcinoma, invasive lobular carcinoma, mixed invasive ductal lobular carcinoma, general breast cancer, & NOS	17

Invasive ductal carcinoma, invasive lobular carcinoma, mixed invasive ductal lobular carcinoma, general breast cancer, metaplastic breast cancer, & NOS	3

Further analysis utilizing the COSMIC database identified seventeen common genes among invasive ductal carcinoma, invasive lobular carcinoma, mixed invasive ductal lobular carcinoma, general breast cancer, and NOS. While most of these genes were previously known to be mutated in breast cancer, three genes—DOT1L, FLT1, and PIK3C2G—had not been previously identified as mutated genes in breast cancer according to COSMIC. Additionally, twelve unique genes specific to breast cancer were identified through COSMIC that were not obtained through other sources (Table 2).

Table 2: Status of common genes between 5 types of breast cancer (Invasive ductal carcinoma, invasive lobular carcinoma, mixed invasive ductal lobular carcinoma, general breast cancer, and NOS) in the COSMIC database.

Genes Names	COSMIC Status
ARID1A	Present
KMT2C	Present
PTEN	Present
ARID2	Present
NF1	Present
RB1	Present
ATM	Present
PIK3C2G	Absent
TET1	Present
BCOR	Present
PIK3CA	Present
DOT1L	Absent
CDH1	Present
PMS1	Present
FLT1	Absent
FOXP1	Present
TP53	Present

Subsequent analysis in the DAVID tool (Figure 4) elucidated the functional significance of the identified common genes. These genes were associated with various pathways and enriched in specific Gene Ontology terms, indicating their involvement in distinct molecular functions and biological processes. The functional annotation of these genes categorized them into specific functional groups or clusters, shedding light on their known biological roles. Additionally, protein domain prediction provided further insights into the potential roles of these genes in breast cancer development.

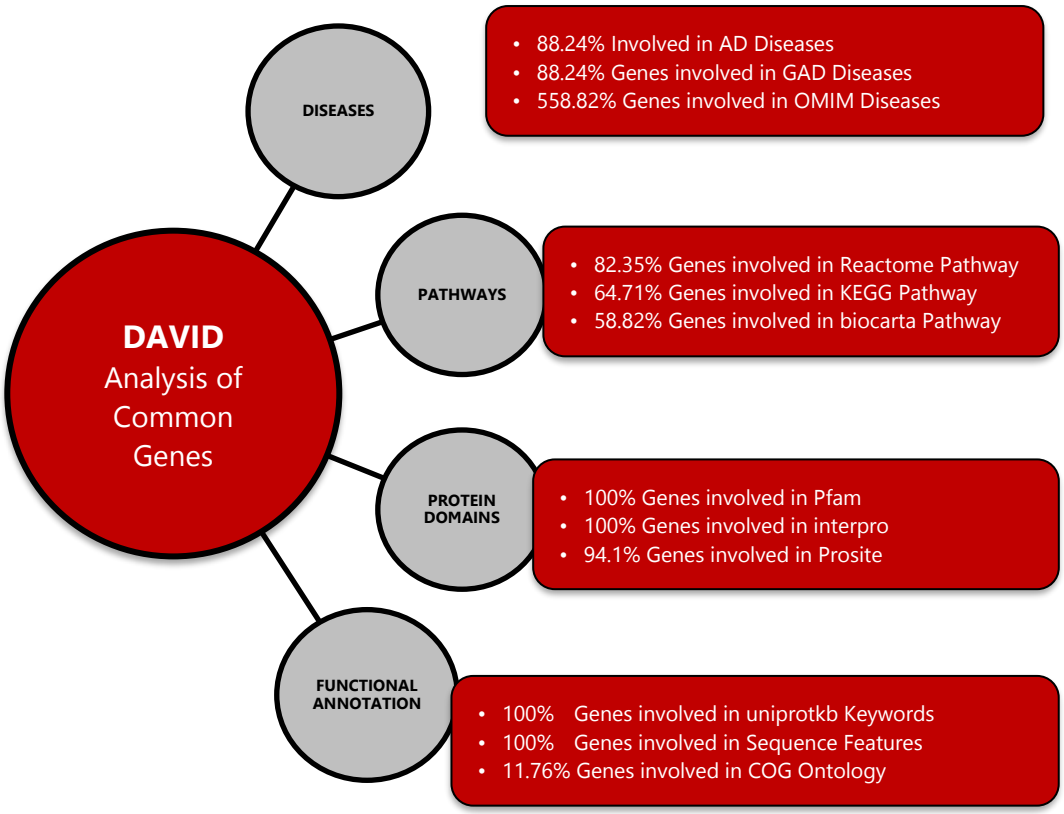

Figure 4: The analysis of common genes between 5 types of breast cancer (Invasive ductal carcinoma, invasive lobular carcinoma, mixed invasive ductal lobular carcinoma, general breast cancer, and NOS) in the DAVID tool. It shows the involvement of genes in causing disease, functional categories of selected genes, genes involved in pathways, and protein domains

Moreover, certain types of breast cancer—adenoid cystic breast cancer, breast invasive mixed mucinous carcinoma, and invasive breast carcinoma—did not share any common genes with the other types, likely due to their rarity and limited available patient data.

Discussion

Despite advancements in technology, breast cancer remains a formidable challenge in healthcare[20]. This study uncovered significant overlap among genes implicated in various subtypes of breast cancer, highlighting the complexity of the disease. However, discrepancies in gene recognition across databases underscore the need for comprehensive analyses to elucidate the full genetic landscape of breast cancer. Additionally, the multifaceted nature of gene pathways complicates targeted diagnostic and therapeutic strategies, necessitating a holistic approach to disease management.

Several genes, such as TP53, ATM, and CDH1, exhibit numerous pathogenic alleles associated with breast cancer, offering potential targets for early diagnosis and intervention[20]. While the involvement of TP53 mutations in various cancers is well-documented, the study underscores the significance of identifying additional genetic markers, such as NF1 and PIK3CA, for targeted treatment approaches[21-24]. The identification of non-progressive breast cancers through screening

emphasizes the importance of refining screening protocols to enhance early detection capabilities[25].

The survey findings underscore the need for enhanced public awareness and education regarding breast cancer risk factors, prevention strategies, and screening modalities. Leveraging digital media platforms for disseminating information and promoting self-examination practices can empower individuals to take proactive steps in managing their breast health. Furthermore, advocating for widespread adoption of mammography and genetic testing, particularly among high-risk populations, is essential for early detection and personalized treatment planning.

However, barriers to genetic testing accessibility, including cost constraints, pose significant challenges to equitable healthcare access. To address this issue, targeted genetic testing focusing on genes with the highest pathogenic allele prevalence could optimize resource allocation and expand testing accessibility. Moreover, efforts to reduce the cost of genetic testing through streamlined testing panels could improve affordability and uptake among vulnerable populations.

While this study sheds light on the genetic underpinnings of breast cancer and underscores the importance of public awareness and screening initiatives, several limitations must be acknowledged. The study's reliance on limited databases for genetic analysis necessitates further validation and exploration of additional genetic factors. Moreover, the survey's focus on a specific demographic limits the generalizability of the findings, highlighting the need for broader population-based studies to inform comprehensive breast cancer prevention and management strategies.

Conclusion

In conclusion, this study sheds light on the shared genetic components of various breast cancer types, offering potential targets for early detection and personalized treatment strategies. By identifying common genes and pathogenic alleles, there is a significant opportunity to develop diagnostic tools capable of detecting breast cancer in its early stages, ultimately reducing mortality rates. While the findings provide valuable insights, further research is needed to fully elucidate the complexities of breast cancer genetics and advance towards the ultimate goal of disease eradication, emphasizing the importance of ongoing research efforts in this field.

Conflicts of Interest

The Author(s) declare no conflicts of interest.

Acknowledgement

The author acknowledges support from the HEC sponsored Center: National Center of Big Data and Cloud Computing (Genomics domain of Exascale Open Data Analytics Lab), NED University of Engineering & Technology, Karachi, Pakistan.

Funding

None.

References

1. Hinzey A, Gaudier-Diaz MM, Lustberg MB, DeVries AC. Breast cancer and social environment: getting by with a little help from our friends. Breast Cancer Res. 2016;18(1):54. Doi: 10.1186/s13058-016-0700-x
2. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, Jemal A, Siegel RL. Breast Cancer Statistics, 2022. CA Cancer J Clin. 2022;72(6):524-541. Doi: 10.3322/caac.21754
3. Menhas R, Umer S. Breast Cancer among Pakistani Women. Iran J Public Health. 2015;44(4):586-587.
4. Koh J, Kim MJ. Introduction of a New Staging System of Breast Cancer for Radiologists: An Emphasis on the Prognostic Stage. Korean J Radiol. 2019;20(1):69-82. Doil: 10.3348/kjr.2018.0231
5. Shiovitz S, Korde LA. Genetics of breast cancer: a topic in evolution. Ann Oncol. 2015;26(7):1291-1299. Doi: 10.1093/annonc/mdv022
6. Mehrgou A, Akouchekian M. The importance of BRCA1 and BRCA2 genes mutations in breast cancer development. Med J Islam Repub Iran. 2016;30:369.
7. Elimimian EB, Elson L, Li H, Liang H, Bilani N, Zabor EC, Statler A, Nahleh Z. Male Breast Cancer: A Comparative Analysis from the National Cancer Database. World J Mens Health. 2021;39(3):506-515. Doi: 10.5534/wjmh.200164

8. van der Groep P, van der Wall E, van Diest PJ. Pathology of hereditary breast cancer. Cell Oncol (Dordr). 2011;34(2):71-88. Doi: 10.1007/s13402-011-0010-3
9. Graffeo R, Rana HQ, Conforti F, Bonanni B, Cardoso MJ, Paluch-Shimon S, Pagani O, Goldhirsch A, Partridge AH, Lambertini M, Garber JE. Moderate penetrance genes complicate genetic testing for breast cancer diagnosis: ATM, CHEK2, BARD1 and RAD51D. Breast. 2022;65:32-40. Doi: 10.1016/j.breast.2022.06.003
10. Flister MJ, Bergom C. Genetic Modifiers of the Breast Tumor Microenvironment. Trends Cancer. 2018;4(6):429-444. Doi: 10.1016/j.trecan.2018.04.003
11. Tai W, Mahato R, Cheng K. The role of HER2 in cancer therapy and targeted drug delivery. J Control Release. 2010;146(3):264-275. Doi: 10.1016/j.jconrel.2010.04.009
12. Teng X, Zhang J, Zhang X, Fan X, Zhou T, Huang YH, Wang L, Lee EYP, Yang R, Cai J. Noninvasive imaging signatures of HER2 and HR using ADC in invasive breast cancer: repeatability, reproducibility, and association with pathological complete response to neoadjuvant chemotherapy. Breast Cancer Res. 2023;25(1):77. Doi: 10.1186/s13058-023-01674-9
13. Yoshimura A, Imoto I, Iwata H. Functions of Breast Cancer Predisposition Genes: Implications for Clinical Management. Int J Mol Sci. 2022;23(13):7481. Doi: 10.3390/ijms23137481
14. Park AY, Han MR, Seo BK, Ju HY, Son GS, Lee HY, Chang YW, Choi J, Cho KR, Song SE, Woo OH, Park HS. MRI-based breast cancer radiogenomics using RNA profiling: association with subtypes in a single-center prospective study. Breast Cancer Res. 2023;25(1):79. Doi: 10.1186/s13058-023-01668-7
15. Ensembl genome browser 109. [Cited 2023 May 12]. Available at: https://asia.ensembl.org/index.html.
16. cBioPortal for Cancer Genomics. [Cited 2023 May 14]. Available at: https://www.cbioportal.org/.
17. Weigelt B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: how special are they? Mol Oncol. 2010;4(3):192-208. Doi: 10.1016/j.molonc.2010.04.004
18. COSMIC | Catalogue of Somatic Mutations in Cancer. [Cited 2023 June 02]. Available at: https://cancer.sanger.ac.uk/cosmic
19. DAVID Functional Annotation Bioinformatics Microarray Analysis. [Cited 2023 June 12]. Available at: https://david.ncifcrf.gov/
20. Lima ZS, Ghadamzadeh M, Arashloo FT, Amjad G, Ebadi MR, Younesi L. Recent advances of therapeutic targets based on the molecular signature in breast cancer: genetic mutations and implications for current treatment paradigms. J Hematol Oncol. 2019;12(1):38. Doi: 10.1186/s13045-019-0725-6
21. Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2010;2(1):a001008. Doi: 10.1101/cshperspect.a00100.
22. Pearson A, Proszek P, Pascual J, Fribbens C, Shamsher MK, Kingston B, O'Leary B, Herrera-Abreu MT, Cutts RJ, Garcia-Murillas I, Bye H, Walker BA, Gonzalez De Castro D, Yuan L, Jamal S, Hubank M, Lopez-Knowles E, Schuster EF, Dowsett M, Osin P, Nerurkar A, Parton M, Okines AFC, Johnston SRD, Ring A, Turner NC. Inactivating NF1 Mutations Are Enriched in Advanced Breast Cancer and Contribute to Endocrine Therapy Resistance. Clin Cancer Res. 2020;26(3):608-622. Doi: 10.1158/1078-0432.CCR-18-4044
23. Fusco N, Malapelle U, Fassan M, Marchiò C, Buglioni S, Zupo S, Criscitiello C, Vigneri P, Dei Tos AP, Maiorano E, Viale G. PIK3CA Mutations as a Molecular Target for Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer. Front Oncol. 2021;11:644737. Doi: 10.3389/fonc.2021.644737
24. Daneshmand M, Hanson JE, Nabavi M, Hilton JF, Vandermeer L, Kanji F, Dent SF, Clemons M, Lorimer IA. Detection of PIK3CA Mutations in Breast Cancer Bone Metastases. ISRN Oncol. 2012;2012:492578. Doi: 10.5402/2012/492578
25. Heggland T, Vatten LJ, Opdahl S, Weedon-Fekjær H. Non-progressive breast carcinomas detected at mammography screening: a population study. Breast Cancer Res. 2023;25(1):80. Doi:10.1186/s13058-023-01682-9