The European Journal of Technical and Natural Sciences 2023, No 4–5
ISSN 2414-2352

PREMIER Publishing
ppublishing.org

Section 2. Biology

DOI:10.29013/EJTNS-23-4.5-8-16

UNMASKING GENETIC VULNERABILITIES IN BREAST CANCER THROUGH SNP ANALYSIS

Jiayi Zhu [1]

[1] City of London School for Girls

Cite: *Jiayi Zhu. (2023). Unmasking Genetic Vulnerabilities in Breast Cancer Through SNP Analysis. European Journal of Technical and Natural Sciences 2023, No 4–5*. https://doi.org/10.29013/EJTNS-23-4.5-8-16

Abstract

Breast cancer is a prevalent and severe malignancy with significant morbidity and mortality rates worldwide. This investigation sought to elucidate the relationship between single nucleotide polymorphisms (SNPs) and breast cancer. Genome-wide sequencing data from the Sequence Read Archive were harnessed, and comprehensive pipelines were developed to align sequences against chromosome 10 in a cohort of individuals with a history of breast cancer. The study found that while the PTEN gene exhibited just a single unique SNP, suggesting its genetic resilience, other genes presented with a notably higher number of SNPs. Specifically, genes without a defined function harbored the most significant number of unique SNPs. Prior research has underscored its role as a tumor suppressor and its critical association with various malignancies, including breast cancer. These insights offer a deeper understanding of the genomic intricacies of breast cancer, revealing potential genetic vulnerabilities and emphasizing the significance of particular genes and SNP contributions to the disease.

Keywords: *breast cancer, single nucleotide polymorphisms (SNPs), PTEN*

Introduction

Breast Cancer

Breast cancer, a prevalent and life-threatening disease, is characterized by the uncontrolled growth of cells in the breast tissue, leading to the formation of abnormal masses or lumps (Wilkinson & Gathani, 2022). These growths can often be detected through palpable breast lumps or thickening, which feel distinguishable from the surrounding tissue. Breast cancer can manifest in both women and men, although the incidence is significantly higher in women. In the United States, approximately 264.000 cases of breast cancer are diagnosed annually in women, along with approximately 2.400 cases in men (Centers for Disease Control and Prevention, n.d.). Breast cancer remains a major public health concern globally, with a staggering 685,000 reported deaths in 2020 (World Health Organization, n.d.).

Stages

Breast cancer is classified into distinct stages, illustrated in Figure 1, that denotes its progression and severity, offering crucial insights for diagnosis and therapeutic strategies. Starting with stage 0, or ductal carcinoma *in situ* (DCIS), the cancer remains non-invasive, localized within the breast's ductal structures, yet, around 40% of DCIS cases can evolve into invasive forms (Trayes & Cokenakes, 2021). Stage I marks the onset of invasive breast cancer, subdivided into stages IA and IB. Specifically, stage IA pertains to tumors up to 2 cm contained within the breast and lacking lymph node involvement. Conversely, stage IB is characterized by the absence of a primary breast tumor but features small cancer cell clusters (0.2 mm to 2 mm) in the lymph nodes (*Breast Cancer Stages*, 2019).

Figure 1. *Stages of Breast Cancer*

The stages of breast cancer range from 0 to IV numerically. Stage 0 denotes a cancer-free breast clear of any cancerous migration of abnormal cells. This stage demonstrates that the cancer is *in situ*, or present where it first appeared. The strength of the tumor's development increases from stages I through IV. Stage IV indicates that the cancer has progressed to nearby or distant body organs (Coughlin, 2019).

Stage II of breast cancer is categorized into two distinct sub-stages: IIA and IIB. In stage IIA, the tumor exceeds 2 mm but not 5cm in size and involves one to three axillary lymph nodes near the breast bone. Stage IIB is characterized by a tumor either more prominent than 5cm or 2 cm — 5cm with involvement of four to nine axillary lymph nodes, signifying a more extensive spread (Giammarile *et al.*, 2022). Stage III, on the other hand, indicates a more advanced stage where cancer has invaded the skin of the breast or the chest wall, exceeding 5cm in size, with the possible involvement of ten or more axillary lymph nodes or lymph nodes above or below the collarbone. The severity and spread continue to escalate through stages I to IV (*Breast Cancer Treatment*, 2021). Stage IV, known as metastatic breast cancer, marks the progression where the cancer cells have metastasized beyond the breast to distant organs such as the lungs, liver, or brain. This pattern of progression illustrates the systematic manner in which breast cancer evolves and expands, with each stage signifying a more complex and extensive spread of the disease (*Breast Cancer Treatment*, 2021).

Treatments

The treatment paradigms for breast cancer are stratified based on the stage and molecular characteristics of the malignancy. In cases of DCIS, management options may include lumpectomy followed by radiation therapy or mastectomy, with additional endocrine therapy if the lesion is estrogen receptor-positive (*Breast Cancer Treatment*, 2021). For early invasive stages (Stages I, IIa, IIb) and locally advanced stages (Stages IIIa, IIIb, IIIc) that are nonmetastatic, a three-phase approach is typically employed. The preoperative phase may involve systemic therapies such as endocrine or immunotherapies, contingent on the expression of estrogen, progesterone, or ERBB2 receptors (Kerr *et al.*, 2022). Conversely, preoperative chemotherapy is indicated for tumors lacking these receptors. Surgical intervention may encompass a lumpectomy, accompanied by radiation if complete excision with satisfactory cosmetic outcomes is achievable, or a mastectomy otherwise. The postoperative phase integrates a multidisciplinary approach, consisting of radiation, endocrine therapy, immunotherapy, and chemotherapy,

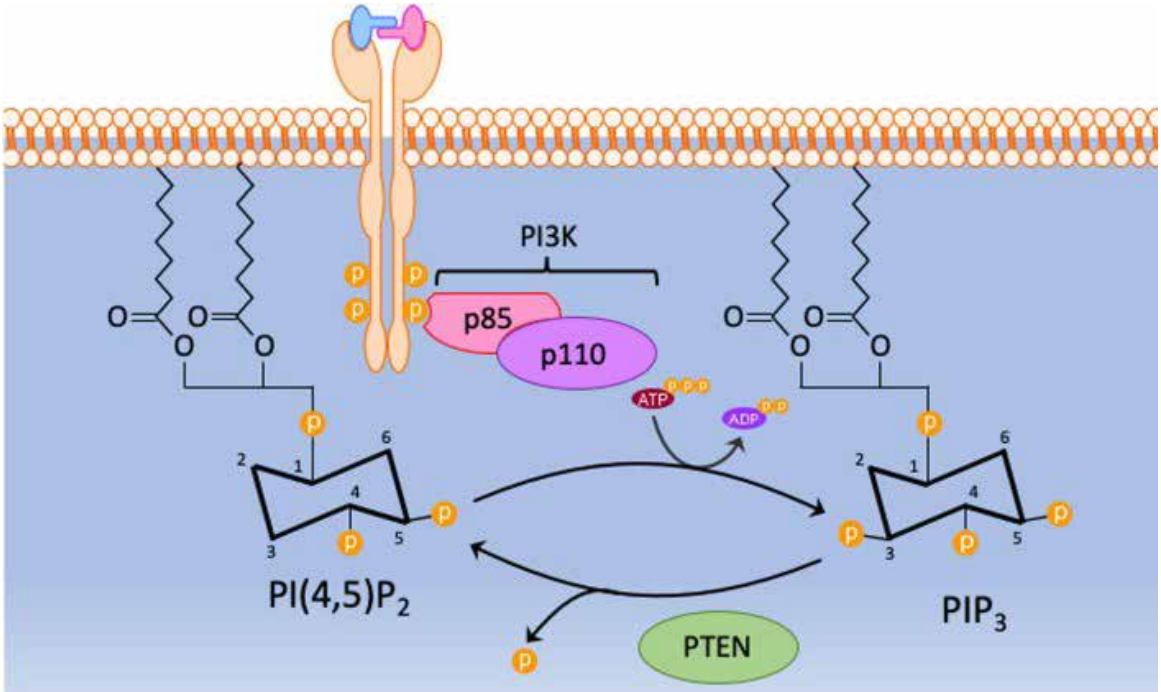
tailored to the tumor's unique molecular profile and clinical context (*Breast Cancer Treatment*, 2021).

These therapeutic interventions, each with its unique pharmacological mechanisms, carry distinct adverse effects that vary in severity and manifestation. Immunotherapy may lead to fatigue and nausea, but can also result in more critical complications such as left heart dysfunction and myelosuppression (Fisusi & Akala, 2019). Chemotherapy, targeting rapidly dividing cells, can induce a broad spectrum of side effects ranging from bone marrow suppression, electrolyte abnormalities, gastrointestinal distress, alopecia, and myelosuppression to acute and delayed cardiotoxicity and peripheral neuropathy (Rossi *et al.*, 2019). Endocrine therapy, which modulates hormonal pathways, may be associated with hot flashes, an elevated risk of thromboembolism and uterine cancer, myalgias, and osteoporosis-related bone fractures. Additionally, agents that modify bone metabolism can induce fatigue, heartburn, gastrointestinal symptoms, peripheral edema, hypophosphatemia, and osteonecrosis of the jaw. The diverse nature of these side effects underscores the complexity of cancer treatment and necessitates a personalized, multidisciplinary approach to manage and mitigate these challenges (Rossi *et al.*, 2019).

Gene

The phosphatase and tensin homolog (PTEN) gene, situated on chromosome 10q23.31, has been the focus of our investigation for its relationship with breast cancer (Yehia *et al.*, 2020). PTEN, under normal physiological conditions, functions as a tumor suppressor by controlling cellular proliferation (see Figure 2). Its germline mutations are implicated in Cowden syndrome, a rare disorder characterized by an increased predisposition to both malignant and benign tumors in multiple organs, including breasts, digestive tract, thyroid, uterus, and ovaries. In a separate investigation conducted by a different laboratory, (Zhang *et al.*, 2013), PTEN expression was detected in 57.5% of patients diagnosed with breast carcinoma. Their analysis revealed a low occurrence of PTEN mutations, with only one instance identified among 45 sporadic breast cancer cases. The researchers in that study postulated that PTEN promoter methylation might have been the primary mechanism contributing to the decreased expression of PTEN. The findings from this distinct study further reinforce the critical role that PTEN plays in the tumorigenesis, progression, and prognostic evaluation of breast cancer, and provide additional insights into the complex genetic landscape of this disease (Alvarez-Garcia *et al.*, 2019).

Figure 2. *Detailed schematic of PTEN lipid phosphatase activity*



PTEN, a critical tumor suppressor protein, functions by selectively targeting the inositol ring at the 3rd position of phosphatidylinositol-(3,4,5)-triphosphate (PIP3). Through its enzymatic action, PTEN dephosphorylates PIP3, effectively converting it into phosphatidylinositol-4,5-bisphosphate (PI(4,5) P2). This activity serves as a crucial regulatory mechanism in cellular pathways, especially those related to cell growth and survival (Chow & Salmena, 2020).

SNPs

Single Nucleotide Polymorphisms (SNPs) represent individual positions in the human genome where the nucleotide varies across different individuals, constituting the most prevalent form of genetic variation. In the context of non-familial breast cancer, SNPs are significant contributors, accounting for approximately 16% of genetic risk (He *et al.*, 2019). Specific to SNP18, its potential as a predictive marker for breast cancer (including invasive and ductal carcinoma *in situ*) was investigated in a cohort of 9363 women (mean age of 59, ranging from 46 to 73 years), (Su *et al.,* 2021) Among these women, 466 were diagnosed with breast cancer (271 prevalent; 195 incidents). The predictive power of SNP18 remained consistent whether unadjusted or adjusted for mammographic density and traditional risk factors, with odds ratios per interquartile range of 1.56 (95% CI, 1.38–1.77) and 1.53 (95% CI, 1.35–1.74), respectively.

Importantly, the observed risks are closely aligned with expected values, as indicated by an adjusted observed-to-expected odds ratio of 0.98 (95% CI, 0.69–1.28) (Roberts *et al.*, 2023).

The continued study and identification of SNPs may revolutionize personalized care in breast cancer management. This offers a further refinement of risk classification and holds the potential to integrate seamlessly with established risk-assessment strategies such as family history and phenotypic evaluations (Fagny *et al.*, 2020). SNP analysis is especially pertinent for women at high risk, who may seek genetic information to inform their choices about preventive or risk-reducing interventions. This approach to personalized risk assessment opens new avenues in breast cancer care, harnessing genetic insights to augment clinical decision-making, particularly among those most vulnerable to the disease (Howe *et al.*, 2014).

Methods

The human genome reference sequence is an invaluable asset for contemporary genomics research, allowing for the examination of genetic polymorphisms across different individuals. In the present study, sequence reads from both BRCA patients and healthy controls were analyzed. The human reference genome, specifically chromosome 12 from Ensembl Release 104, was downloaded to facilitate the comparison of genetic variants relevant to our study (Cunningham *et al.*, 2021).

The Sequence Read Archive (SRA) sequences (PRJNA933635) were selected, adhering to the library strategy and comprehensive study design. The files were acquired using the fastq-dump tool from the SRA Toolkit (v2.10.7) (NCBI, 2021) and processed using terminal commands. The quality of the sequence reads was scrutinized with the FastQC tool (v0.11.9) to ensure the robustness of our analysis (Andrews, 2010). Following this, the sequences were refined using Trimmomatic (v0.39), and regions with poor base quality (Phred quality score < 33) were identified and addressed (Bolger *et al.*, 2014).

For alignment with the human reference genome, Bowtie2 (v2.4.2) was employed, followed by indexing of the reads (Langmead and Salzberg, 2012). The output in SAM format was then converted into a more succinct Binary Alignment/Map (BAM) file using SAMtools (v1.11) (Li *et al.*, 2009). Subsequent sorting and read coverage calculations enabled the assessment of coverage depth and identification of regions with potential genetic polymorphisms. Single nucleotide polymorphisms (SNPs) were discerned utilizing the BCF tools from the SAMtools suite, with subsequent filtering for high-quality variants through BCFTools (v1.11).

Statistical associations between variants in the BRCA cohort and the control cohort were appraised via RStudio, utilizing chi-square tests for categorical variables evaluation. The contingencies were structured, and chi-square statistics and p-values were calculated to quantify discrepancies and ascertain

statistical significance. A significant association ($p < 0.05$) emerged between the variants and the BRCA cohort, furnishing substantial evidence to refute the null hypothesis.

In RStudio, necessary libraries were loaded, and the datasets for both cohorts were prepared and merged for statistical testing. Specific code implementation details are described, including the condition check for saving significant association data to a file named "significant_association.csv".

To correlate SNP accession numbers with genetic consequences, Ensembl was accessed via a Python script. SNP information was retrieved from the BCF file and cross-referenced with Ensembl REST API, including attributes such as genomic location, alleles, and potential consequences. The process was automated using Python, ensuring efficiency and accuracy, and the results were integrated into a tab-separated file for further inquiry.

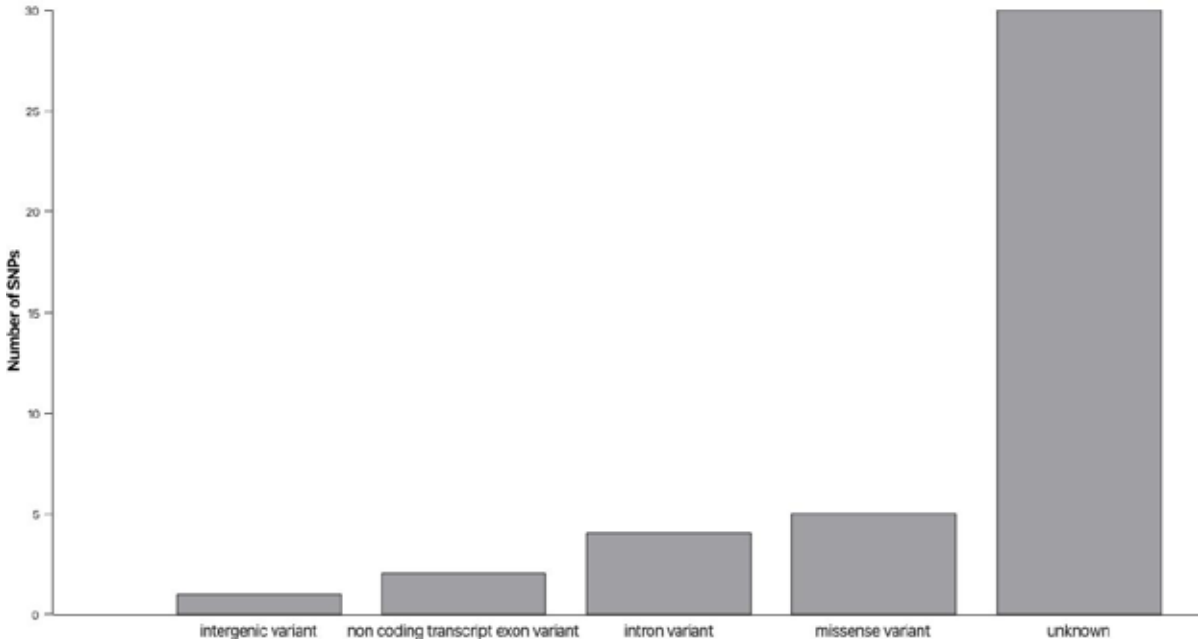
All Python scripts, including those employed for sequence read analysis and Ensembl access, are publicly hosted on GitHub (https://github.com/crisprmax/SNP-identifier-Python), complete with documentation and execution instructions.

Results

SNP Distribution Across Genetic Variants

Upon analysis of the SNP distribution (Figure 3), it is evident that the highest prevalence of SNPs is associated with unknown variants. This is succeeded by the missense variant in terms of SNP frequency. Interestingly, the intergenic variant demonstrated the minimal number of SNPs. While intergenic variants are typically common, the observed low SNP count could be an outcome of stochastic variation or may warrant further investigation into the sampling or sequencing processes.

Figure 3. *Distribution of SNPs across distinct genetic variants. The data reveals a predominant occurrence of SNPs in unknown variants, succeeded by missense variants, with the intergenic variants exhibiting the lowest frequency*



Characterization of Genetic Variants

Four principal genetic variants were delineated in this study:

1. Intergenic Variant: This variant represents sequence variations situated between genes within the intergenic regions.

2. Non-coding Transcript Exon Variant: Predominantly, these variations arise due to exon skipping events at either the first or last exon, potentially leading to the absence of start or stop codons.

3. Intron Variant: Introns play a pivotal role in diversifying the proteins produced from a gene's mRNA molecules. They can give rise to non-coding RNA and enable a plethora of protein varieties or differential protein levels specific to a cell type. Their

presence augments the evolutionary rate, facilitating the genesis of novel genes via exon duplication.

4. Missense Variant: Missense mutations can modulate DNA-transcription factor interactions, subsequently altering protein expression patterns.

Analysis of Unique SNPs in Genes

From the comprehensive analysis delineated in Table 1, it becomes evident that a significant portion of the unique SNPs, amounting to 127, are linked with genes that remain uncharacterized or have not been extensively studied in the current genetic landscape. This highlights a vast realm of the genome that warrants further investigation for its potential roles in various biological processes. In stark contrast, the PTEN gene, a pivotal regulator integral to numerous cellular pathways including cell growth, division, and apoptosis, showcased a mere single unique SNP. The limited genetic variability within PTEN is indicative of its conserved nature through evolutionary timelines. Such conservation suggests that any perturbation or mutation within this gene could lead to significant cellular anomalies, reinforcing its indispensable role in maintaining cellular homeostasis and integrity.

Table 1. *Distribution of unique SNPs across various genes. Notably, the PTEN gene exhibits a single unique SNP, while a significant fraction of SNPs are associated with genes that remain uncharacterized*

Gene Name	Gene Function	Total Unique SNPs
none	none	127
none	novel transcript	50
none	general transcription factor IIi (GTF2I) pseudogene	42
MTPAP	mitochondrial poly(A) polymerase	27
none	zinc finger protein pseudogene	24
SGMS1-AS1	SGMS1 antisense RNA 1	22
C10orf143	chromosome 10 open reading frame 143	20
BMS1	BMS1 ribosome biogenesis factor	18
AGGF1P2	angiogenic factor with G-patch and FHA domains 1 pseudogene 2	17
IMPDH1P5	inosine monophosphate dehydrogenase 1 pseudogene 5	13
GOLGA2P6	GOLGA2 pseudogene 6	13
OLMALINC	oligodendrocyte maturation-associated long intergenic non-coding RNA	13
CTNNA3	catenin alpha 3	10
LRRC37A6P	leucine rich repeat containing 37 member A6, pseudogene	9
ACTA2	actin alpha 2, smooth muscle	8
PTEN	phosphatase and tensin homolog	1

Discussion:

The exploration into various genetic variants and their influence on breast cancer provides critical insights into the intricate dynamics of the genome. Genetic variants, as showcased by this study, can have multifaceted consequences such as altering protein function.

Variants and Their Implications

- **Intergenic Variants**: The observed reduced number of SNPs in intergenic regions, as delineated from Figure 3, raises intriguing possibilities specific to breast cancer genetics. Given that these regions might be evolutionarily conserved, alterations within them could be indicative of crucial regulatory or structural roles that, when disrupted, may predispose individuals to breast cancer. Alternatively, changes in these regions might not manifest

immediately in the breast tissue phenotype, thereby evading early detection and potentially allowing for unnoticed progression of the disease.

- **Non-Coding Transcript Exon Variants**: In the context of breast cancer, potential alterations, such as the loss of start or stop codons, can lead to aberrant protein synthesis. These truncated or elongated proteins may disrupt normal cellular pathways, potentially driving oncogenesis or promoting tumor progression. Recognizing these variants is vital as they could be linked to specific breast cancer subtypes or influence responsiveness to treatments.
- **Intron Variants**: Introns, given their role as recombination hotspots, can be instrumental in breast cancer's genetic landscape. Their capacity to enable new exon combinations suggests they might contribute to the genetic heterogeneity observed in breast tumors. Such diversity can impact treatment outcomes, where certain combinations could confer resistance to standard therapies or lead to more aggressive disease forms;
- **Missense Variants**: These variants hold particular importance. A single amino acid change, especially in genes pivotal to breast cell regulation, can profoundly influence the cell's behavior. Whether it leads to loss of tumor suppressor functions, enhancement of oncogenic pathways, or introduces novel, detrimental functionalities, understanding these missense mutations becomes paramount. Their study can not only aid in early diagnosis but also in tailoring treatments specific to the genetic makeup of the tumor.

Insights from SNP Distribution

The SNP distribution across various genes offers some intriguing observations. The observation that PTEN, a gene integral to many cellular functions, exhibited just a single unique SNP suggests its genetic resilience. This limited variability further underscores the likely catastrophic consequences mutations in this gene could precipitate. On the other hand, genes with a higher number of SNPs could either be mutating rapidly or have regions that don't impact their function significantly when altered.

Limitations and Future Directions

While this study has provided valuable insights, it is essential to acknowledge its limitations. For instance, the number of SNPs in a gene does not necessarily correlate with its importance or functionality. Additionally, the effects of these SNPs at a phenotypic level were not explored. Future studies could delve deeper into the functional implications of these SNPs, especially in genes with high SNP counts. It would also be worthwhile to investigate the broader evolutionary significance of these variants and their role in species adaptation and survival.

As advancements in technology continue to drive down the costs of DNA sequencing, it is anticipated that an increasing number of individuals will have access to detailed genetic profiling, enabling the identification of specific SNPs. If their genetic profiles exhibit SNPs aligned with those identified in this study as predisposing factors for breast cancer, these individuals could benefit from more frequent screenings, enhancing early detection and diagnosis. Empowered with this knowledge, they can proactively adopt lifestyle modifications, such as tailored exercise regimens and dietary changes, to mitigate risks and potentially prevent the onset of breast cancer.

Investigating these genetic variants holds significant importance in the realm of medical science. Such variants can equip clinicians with the tools to detect breast cancer at earlier stages, given that genetic modifications can predispose cells to aberrant growth patterns that culminate in malignancies. It is noteworthy that most DNA alterations precipitating cancer manifest within genes. These genes harbor essential instructions for the synthesis of proteins or specialized RNA entities, such as microRNA, underscoring their pivotal role in cellular function and integrity.

Conclusion:

This investigation offers an in-depth exploration of the genomic nuances linked to breast cancer, elucidating the roles of distinct genetic variants in both the initiation and advancement of the disease. The pronounced

SNP patterns in genes, particularly in the likes of PTEN, delineate potential genomic regions of vulnerability and stability pertinent to breast cancer. The observed constrained genetic variability in pivotal genes accentuates the profound impact that even subtle genomic alterations can exert on breast cancer susceptibility and its subsequent trajectory. These genetic variations transcend mere random genomic aberrations; they serve as central determinants in the breast cancer continuum, shaping individual predisposition, disease progression, and therapeutic responsiveness. As we progressively decode the multifaceted breast cancer genomic landscape, we edge closer to tailored diagnostic and treatment modalities, envisioning a future where breast cancer's predictability and management are significantly enhanced, if not its outright prevention.

References:

Andrews, S. (2010). FastQC: a quality control tool for high throughput sequence data.

Bolger, A. M., Lohse, M., & Usadel, B. (2014). Trimmomatic: a flexible trimmer for Illumina sequence data. Bioinformatics,— 30(15).— P. 2114–2120.

Breast cancer risk factors you can't change. (n.d.). Retrieved from https://www.cancer.org/cancer/types/breast-cancer/risk-and-prevention/breast-ca ncer-risk-factors-you-cannot-change.html#:~: text=BRCA1%20and%20BRCA2%3 A%20The%20most, proteins%20that%20repair%20damaged%20DNA.

Breast cancer stages. (2019b, September 17). Retrieved from: URL: https://www.breastcancer.org/pathology-report/breast-cancer-stages

Breast cancer treatment. (2021, August 1). Retrieved from: URL: https://pubmed.ncbi.nlm.nih.gov/34383430/

Centers for Disease Control and Prevention. (n.d.). Basic Information About Breast Cancer. Retrieved from: URL: https://www.cdc.gov/cancer/breast/basic_info/index.htm#:~: text=Each%20year% 20in%20the%20United, breast%20cancer%20than%20White%20 women.

Chow, J. T., & Salmena, L. (2020). Recent advances in PTEN signalling axes in cancer. *Faculty reviews*, *9*, 31. URL: https://doi.org/10.12703/r/9–31

Coughlin S. S. (2019). Social determinants of breast cancer risk, stage, and survival. *Breast cancer research and treatment*,— *177*(3).— P. 537–548. URL: https://doi.org/10.1007/s10549–019–05340–7

Cunningham, F., et al. (2021). Ensembl 2021. Nucleic Acids Research,— 49(D1).— D884-D891.

Fagny, M., Platig, J., Kuijjer, M. L., Lin, X., & Quackenbush, J. (2020). Nongenic cancer-risk SNPs affect oncogenes, tumour-suppressor genes, and immune function. *British journal of cancer*,— *122*(4).— P. 569–577. URL: https://doi.org/10.1038/s41416–019–0614–3

Fisusi, F. A., & Akala, E. O. (2019). Drug Combinations in Breast Cancer Therapy. *Pharmaceutical nanotechnology*,— 7(1).— P. 3–23. URL: https://doi.org/10.2174/2211738507666190122111224

Giammarile, F., Vidal-Sicart, S., Paez, D., Pellet, O., Enrique, E. L., Mikhail-Lette, M., Morozova, O., Maria Camila, N. M., Diana Ivonne, R. S., Delgado Bolton, R. C., Valdés Olmos, R. A., & Mariani, G. (2022). Sentinel Lymph Node Methods in Breast Cancer. *Seminars in nuclear medicine*,— 52(5).— P. 551–560. URL: https://doi.org/10.1053/j.semnuclmed.2022.01.006

He, Y., Liu, H., Chen, Q., Shao, Y., & Luo, S. (2019). Relationships between SNPs and prognosis of breast cancer and pathogenic mechanism. *Molecular genetics & genomic medicine*,— 7(9),— e871. URL: https://doi.org/10.1002/mgg3.871

Howe, R. B., Miron-Shatz, T., Hanoch, Y., Omer, Z. B., O'Donoghue, C., & Ozanne, E. M. (2014). Personalized Medicine through SNP Testing for breast cancer risk: Clinical implementation. Journal of Genetic Counseling,— 24(5).— P. 744–751. URL: https://doi.org/10.1007/s10897–014–9803–7

Kerr, A. J., Dodwell, D., Mc Gale, P., Holt, F., Duane, F., Mannu, G., Darby, S. C., & Taylor, C. W. (2022). Adjuvant and neoadjuvant breast cancer treatments: A systematic review of their effects on mortality. *Cancer treatment reviews*,— 105.— 102375 p. URL: https://doi.org/10.1016/j.ctrv.2022.102375

Langmead, B., & Salzberg, S. (2012). Fast gapped-read alignment with Bowtie 2. Nature Methods,— 9(4).— P. 357–359.

Li, H., et al. (2009). The Sequence Alignment/Map format and SAMtools. Bioinformatics,— 25(16).— P. 2078–2079.

NCBI (2021). SRA Toolkit. National Center for Biotechnology Information.

Roberts, E., Howell, S., & Evans, D. G. (2023). Polygenic risk scores and breast cancer risk prediction. *Breast (Edinburgh, Scotland)*,— *67*.— P. 71–77. URL: https://doi.org/10.1016/j.breast.2023.01.003

Rossi, L., Mazzara, C., & Pagani, O. (2019). Diagnosis and Treatment of Breast Cancer in Young Women. Current treatment options in oncology,— 20(12).— 86 p. URL: https://doi.org/10.1007/s11864–019–0685–7

Su, Y., Yao, Q., Xu, Y., Yu, C., Zhang, J., Wang, Q., Li, J., Shi, D., Yu, B., Zeng, Y., Zhu, X., Bai, Q., & Zhou, X. (2021). Characteristics of Germline Non-BRCA Mutation Status of High-Risk Breast Cancer Patients in China and Correlation with High-Risk Factors and Multigene Testing Suggestions. *Frontiers in genetics*,— *12*.— 674094 p. URL: https://doi.org/10.3389/fgene.2021.674094

Trayes, K. P., & Cokenakes, S. E. H. (2021). Breast Cancer Treatment. *American family physician*,— 104(2).— P. 171–178.

Van Veen, E. M., Brentnall, A. R., Byers, H., Harkness, E. F., Astley, S. M., Sampson, S.,. . . Evans, D. G. (2018). Use of Single-Nucleotide polymorphisms and mammographic density plus classic risk factors for breast cancer risk prediction. JAMA Oncology,— 4(4).— 476 p. URL: https://doi.org/10.1001/jamaoncol.2017.4881

Wilkinson, L., & Gathani, T. (2022). Understanding breast cancer as a global health concern. *The British journal of radiology*,— 95(1130). 2021.— 1033 p. https://doi.org/10.1259/bjr.20211033

World Health Organization. (n.d.). Breast Cancer: Key Facts. Retrieved from: URL: https://www.who.int/news-room/fact-sheets/detail/breast-cancer#:~:text=Key%20facts, every%20country%20in%20the%20world.

Yehia, L., Keel, E., & Eng, C. (2020). The Clinical Spectrum of *PTEN* Mutations. *Annual review of medicine*,— 71.— P .103–116. URL: https://doi.org/10.1146/annurev-med-052218–125823

Zhang, H., Feng, L., Zhou, J., Song, S., & Jiang, Z. (2013). PTEN mutation, methylation and expression in breast cancer patients. Oncology Letters,— 6(1).— P. 161–168. URL: https://doi.org/10.3892/ol.2013.1331

submitted 22.08.2023;
accepted for publication 20.09.2023;
published 8.10.2023

Contact: 14zhuj@clsg.org.uk