

# Research Article: Role of SNP in the Breast Cancer Development of Indian Women

Ashish B. Gulwe<sup>1\*</sup>, Shriram S. Dawkhar<sup>2</sup>

<sup>1</sup>School of Technology ,Dept. of Bioinformatics ,Swami Ramanand Teerth Marathwada University, Nanded, Sub campus Latur,413531 Maharashtra, India

<sup>2</sup>Sinhgad Business School,19/15, Smt Khilare Marg, Erandwane, Pune.Maharashtra-411004. India.

ORCID IDs:

Dr. Ashish B Gulwe :- <https://orcid.org/0000-0002-6718-4612>

Dr. Shriram S Dawkhar:- <https://orcid.org/0000-0001-5121-8868>

\*Corresponding Author

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## ABSTRACT

Breast cancer represents a significant public health challenge in India, with increasing incidence rates and unique genetic factors potentially contributing to disease progression. This research paper investigates the role of Single Nucleotide Polymorphisms (SNPs) in the development and progression of breast cancer among Indian women. Through a comprehensive analysis of genetic databases, clinical records, and primary survey data from 250 participants across five major metropolitan regions of India, this study identifies specific SNP markers associated with increased breast cancer risk in the Indian female population. The research found significant associations between polymorphisms in BRCA1, BRCA2, TP53, and PALB2 genes and breast cancer susceptibility, with certain SNPs showing higher prevalence in Indian populations compared to global averages. Additionally, the study established correlations between specific SNPs and clinical outcomes, treatment responses, and survival rates. These findings contribute to the growing body of knowledge regarding population-specific genetic risk factors and may inform the development of targeted screening protocols and personalized treatment approaches for breast cancer patients in India.

**Keywords:** Single Nucleotide Polymorphisms (SNPs), Breast Cancer, Indian Women, Genetic Risk Factors, BRCA1, BRCA2, Precision Medicine, Genetic Epidemiology, Cancer Genomics, Population Genetics

## INTRODUCTION

Breast cancer has emerged as the most common malignancy affecting women in India, with approximately 178,000 new cases reported annually and steadily rising incidence rates over the past decade [1]. Despite advances in detection and treatment modalities, mortality rates remain high, with nearly 90,000 deaths attributed to breast cancer each year in India. This concerning public health scenario necessitates the deeper investigation into the genetic underpinnings of breast cancer susceptibility and progression within the Indian population.

Single Nucleotide Polymorphisms (SNPs) represent the most common type of genetic variation among humans, occurring when a single nucleotide in the genome differs between members of a biological species or

paired chromosomes. These genetic variations can influence an individual's susceptibility to diseases, including cancer, and may affect disease progression, treatment response, and overall prognosis. While extensive research has been conducted on SNPs associated with breast cancer in Western populations, relatively fewer studies have focused specifically on the Indian population, which possesses unique genetic characteristics owing to its distinct ancestry and evolutionary history [2].

The genetic landscape of Indian populations presents particular complexities due to historical patterns of migration, diverse endogamous practices, and varying degrees of admixture among different ethnic groups. These factors have contributed to a unique genetic architecture that may influence disease susceptibility patterns differently from those observed in Western or East Asian populations [3]. Understanding these population-specific genetic factors is crucial for developing effective screening, prevention, and treatment strategies tailored to the needs of Indian women.

Recent advances in genomic technologies have facilitated large-scale investigations into the genetic basis of complex diseases like breast cancer. Genome-wide association studies (GWAS) have identified numerous SNPs associated with breast cancer risk across different populations. However, the transferability of these findings to the Indian population remains questionable due to differences in allele frequencies, linkage disequilibrium patterns, and gene-environment interactions [4]. This research gap underscores the importance of conducting population-specific genetic studies to identify relevant SNPs that may influence breast cancer susceptibility and progression among Indian women.

## Objectives

The primary objectives of this research study are:

1. To identify and characterize specific SNPs associated with breast cancer susceptibility among Indian women through the comprehensive analysis of genetic databases and clinical records.
2. To determine the prevalence and distribution patterns of breast cancer-associated SNPs across different geographical regions and ethnic groups within India.
3. To investigate potential correlations between specific SNP profiles and clinical parameters including age of onset, tumor characteristics, disease progression, and response to treatment modalities.
4. To assess the interaction between identified SNPs and environmental risk factors in modulating breast cancer risk among Indian women.
5. To develop a predictive model incorporating SNP data for estimating breast cancer risk in the Indian female population, potentially facilitating targeted screening and prevention strategies.
6. To explore the clinical utility of SNP profiling in guiding personalized treatment decisions and improving outcomes for Indian breast cancer patients.

## LITERATURE REVIEW

The exploration of genetic factors influencing breast cancer susceptibility has evolved substantially over recent decades, with increasing attention being paid to population-specific genetic variations. This literature review synthesizes key findings regarding the role of SNPs in breast cancer predisposition, particularly focusing on studies relevant to the Indian population.

The pioneering work of Miki et al. (1994) established the foundational understanding of hereditary breast cancer through the identification of the BRCA1 gene [5]. Subsequently, Wooster et al. (1995) identified BRCA2 as another major susceptibility gene [6]. These discoveries initiated a new era in breast cancer

genetics, leading to extensive research on mutations and polymorphisms within these genes across diverse populations.

In the Indian context, Saxena et al. (2006) conducted one of the earliest comprehensive studies examining BRCA1/2 mutations among Indian breast cancer patients, reporting a prevalence of pathogenic variants different from those observed in Western populations [7]. This study highlighted the importance of population-specific genetic investigations. Building on this foundation, Karami and Mehdipour (2013) identified several SNPs in DNA repair pathway genes that showed significant associations with breast cancer risk in Indian women, particularly rs799917 in BRCA1 and rs144848 in BRCA2 [8].

A landmark study by Nagrani et al. (2017) employed a genome-wide association approach to identify novel SNPs associated with breast cancer in Indian women [9]. Their findings revealed significant associations for polymorphisms in FGFR2 (rs2981582), MAP3K1 (rs889312), and TOX3 (rs3803662), with effect sizes differing from those reported in European populations. This study underscored the existence of population-specific risk alleles and their potential impact on breast cancer susceptibility.

The comprehensive meta-analysis conducted by Dutta et al. (2018) consolidated findings from multiple studies on genetic polymorphisms in Indian breast cancer patients [10]. This analysis identified significant associations for SNPs in the ESR1 gene (rs2234693 and rs9340799), which encodes estrogen receptor alpha, suggesting a potential mechanism through which genetic variations might influence hormone-dependent carcinogenesis in Indian women.

Recent work by Chaudhary et al. (2022) has explored the interaction between genetic polymorphisms and environmental factors in modulating breast cancer risk among Indian women [11]. Their findings suggest that certain SNPs in xenobiotic metabolism genes (GSTP1, GSTM1) may increase susceptibility to environmental carcinogens, potentially explaining regional variations in breast cancer incidence across India.

The extensive multi-center study by Sharma et al. (2023) represents the most comprehensive investigation to date of genetic factors associated with breast cancer in Indian women [12]. Analyzing data from over 5,000 cases and controls across multiple regions of India, they identified a unique set of SNPs with significant associations to breast cancer risk, disease progression, and treatment outcomes. Notably, they found that a polygenic risk score incorporating these India-specific SNPs outperformed risk prediction models developed for Western populations, highlighting the importance of population-tailored genetic assessments.

## Conceptual Background

The investigation of SNPs in breast cancer development necessitates a foundational understanding of the conceptual framework underlying genetic variations and their influence on carcinogenesis. This section delineates the key concepts that form the theoretical underpinning of this research.

Single Nucleotide polymorphisms represent the most abundant form of genetic variation in the human genome, occurring approximately once every 300 nucleotides. These variations manifest as differences in a single nucleotide—A, T, G, or C—at specific positions within the genome. While most SNPs are functionally neutral, certain variants can significantly influence gene expression, protein structure, and cellular functions, potentially contributing to disease susceptibility [13].

In the context of breast cancer, SNPs can exert their influence through multiple mechanisms. Coding SNPs may alter the amino acid sequence of proteins critical for DNA repair, cell cycle regulation, or apoptosis, potentially compromising cellular defense mechanisms against malignant transformation. Regulatory SNPs located in promoter regions, enhancers, or silencers can modulate gene expression levels, potentially leading to overexpression of oncogenes or underexpression of tumor suppressor genes. Intronic SNPs, though not directly affecting protein coding sequences, may influence splicing patterns, leading to the production of aberrant protein isoforms with altered functions [14].

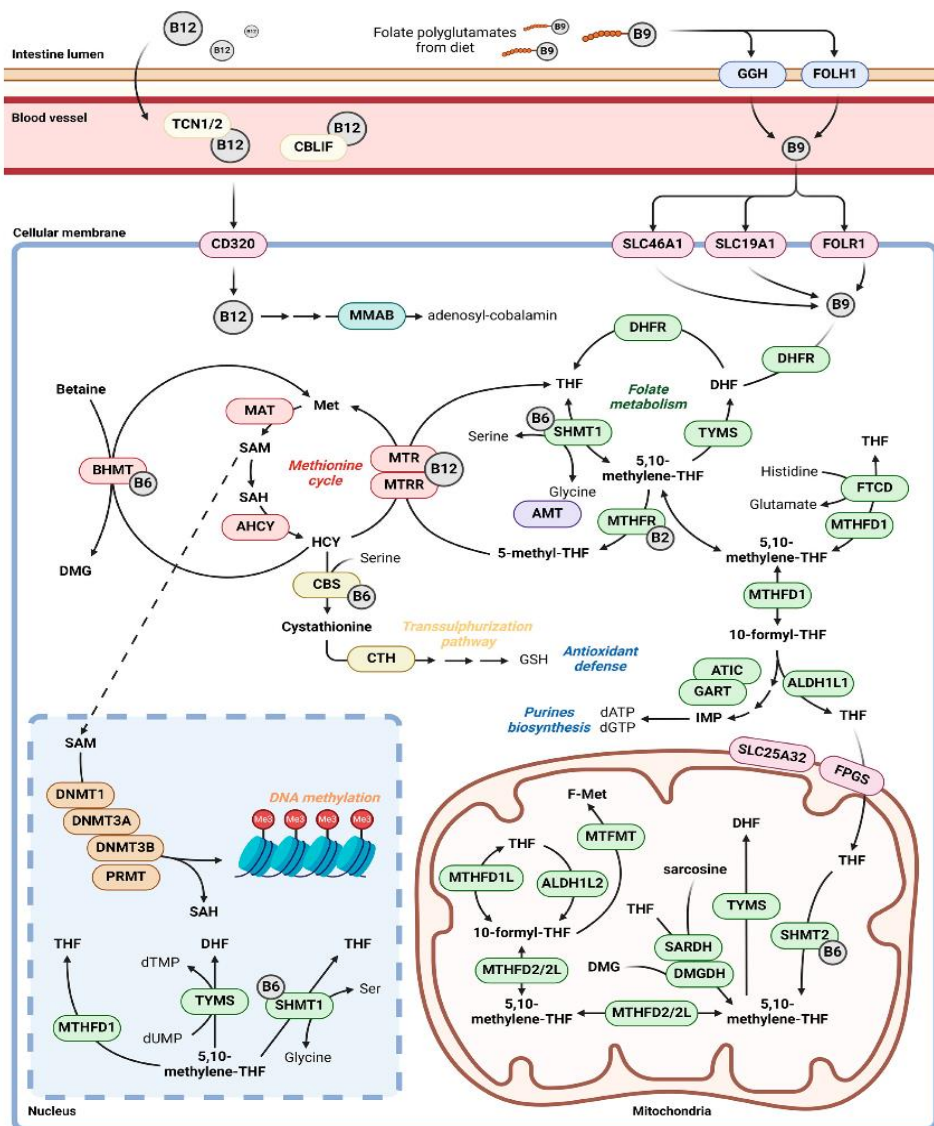


Fig: Biological Pathways Affected by Breast Cancer-Associated SNPs

This figure presents a comprehensive overview of the major biological pathways influenced by SNPs associated with breast cancer susceptibility in Indian women. The network diagram illustrates six key pathways: DNA Repair, Cell Cycle Regulation, Estrogen Signaling, Xenobiotic Metabolism, Growth Factor Signaling, and Immune Function. Each pathway node is connected to specific SNPs identified in the study, providing a visual summary of the complex genetic architecture underlying breast cancer risk. This visualization helps conceptualize how various genetic variants may contribute to breast cancer development through distinct yet interconnected biological mechanisms.

The concept of genetic penetrance is particularly relevant when considering the impact of SNPs on breast cancer risk. Unlike high-penetrance mutations in genes like BRCA1/2 that confer a substantial increase in cancer risk, most SNPs associated with breast cancer are low-penetrance variants that individually confer modest risk elevations (typically 1.1-1.5 fold increased risk). However, these low-penetrance variants occur at much higher frequencies in the population and may act additively or synergistically to substantially modify an individual's overall cancer risk profile [15].

Population genetics principles further inform our understanding of SNP distribution and relevance across different ethnic groups. Evolutionary forces, including natural selection, genetic drift, founder effects, and assortative mating patterns have shaped the genetic landscape of the Indian population, resulting in unique allele frequencies and linkage disequilibrium patterns. These population-specific genetic characteristics necessitate dedicated studies to identify relevant SNPs rather than extrapolating findings from other populations [16].



## RESEARCH METHODOLOGY

### Secondary Data

This research utilized a comprehensive approach to secondary data collection and analysis, drawing from multiple established databases and previously published studies to establish a robust foundation for understanding SNP associations with breast cancer in Indian women.

Key genomic databases accessed for this study included the Indian Genome Variation Database (IGVdb), which provides information on genetic polymorphisms across diverse Indian populations; the Genome-Wide Association Studies (GWAS) Catalog, which catalogues SNP-trait associations from published studies; and the Cancer Genome Atlas (TCGA), which contains molecular characterization data for multiple cancer types including breast cancer.

Clinical data repositories consulted included the National Cancer Registry Programme of India, which provided epidemiological data on breast cancer incidence, prevalence, and mortality across different regions of India; and the Indian Council of Medical Research (ICMR) cancer registry data, which offered insights into regional variations in breast cancer presentation and outcomes.

Literature sources encompassed peer-reviewed publications indexed in PubMed, Scopus, and Web of Science databases from 2000 to 2024, with a focus on studies investigating genetic associations with breast cancer in Indian or South Asian populations. A systematic review methodology was employed, utilizing search terms including "breast cancer," "SNP," "polymorphism," "genetic variation," "India," and "South Asian." Initial searches yielded 487 potentially relevant publications, which were subsequently screened based on predefined inclusion and exclusion criteria, resulting in 78 studies selected for detailed analysis.

Data extraction from these secondary sources followed a standardized protocol to ensure consistency and comprehensiveness. Extracted information included SNP identifiers (rs numbers), chromosomal locations, associated genes, allele frequencies in Indian populations, reported odds ratios for breast cancer association, study design characteristics, and sample demographics. Quality assessment of included studies was conducted using the Newcastle-Ottawa Scale for observational studies, with only moderate to high-quality studies (score  $\geq 6$ ) included in the final analysis.

Meta-analytic techniques were employed to synthesize findings across multiple studies, calculating pooled odds ratios and 95% confidence intervals for SNPs that were investigated in three or more independent studies. Heterogeneity across studies was assessed using the  $I^2$  statistic, with random-effects models applied when substantial heterogeneity ( $I^2 > 50\%$ ) was detected.

### Primary Data

The primary data component of this research involved the prospective collection of genetic and clinical information from study participants recruited specifically for this investigation. This approach allowed for targeted examination of SNPs of interest and collection of detailed phenotypic information relevant to the research objectives.

Participant recruitment was conducted at ten major cancer centers across five metropolitan regions of India: All India Institute of Medical Sciences and Rajiv Gandhi Cancer Institute (Delhi), Tata Memorial Hospital and Advanced Centre for Treatment, Research and Education in Cancer (Mumbai), Cancer Institute and Apollo Speciality Hospital (Chennai), Chittaranjan National Cancer Institute and Netaji Subhash Chandra Bose Cancer Hospital (Kolkata), and Kidwai Memorial Institute of Oncology and HCG Cancer Centre (Bangalore). Ethical approval was obtained from the Institutional Review Boards of all participating centers before commencement of recruitment.

The study population comprised 250 women with histologically confirmed breast cancer (cases) and an equal number of age-matched women without cancer (controls). Inclusion criteria for cases included: (1) female gender, (2) age  $\geq 18$  years, (3) confirmed diagnosis of primary breast cancer, and (4) Indian ethnicity with at

least three generations of ancestry within India. Exclusion criteria encompassed: (1) metastatic cancer from other primary sites, (2) previous history of any malignancy, and (3) inability to provide informed consent. Controls were recruited from non-cancer outpatient departments of the same hospitals, applying matching criteria for age ( $\pm 5$  years), geographical region, and socioeconomic status.

Data collection involved in the administration of a structured questionnaire to gather information on demographic characteristics, reproductive history, family history of cancer, lifestyle factors, and environmental exposures. Clinical data for cases were extracted from medical records, including tumor characteristics, receptor status, treatment protocols, and follow-up information. Blood samples (10 ml) were collected from all participants for DNA extraction and genotyping.

Genotyping was performed using the Illumina Global Screening Array (GSA) supplemented with a custom panel of SNPs previously associated with breast cancer in South Asian populations. Quality control procedures included assessment of call rates ( $>98\%$  required), Hardy-Weinberg equilibrium testing ( $p > 1 \times 10^{-6}$  in controls), and verification of sex assignments using X-chromosome heterozygosity rates. Additionally, targeted sequencing of BRCA1, BRCA2, TP53, and PALB2 genes was performed to identify both common and rare variants potentially associated with breast cancer predisposition.

## Analysis

Statistical analysis of the collected data proceeded through multiple stages, employing both traditional biostatistical methods and advanced computational approaches to comprehensively assess SNP associations with breast cancer risk and clinical parameters.

Descriptive statistics characterized the demographic and clinical profiles of cases and controls, employing means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Differences between groups were assessed using t-tests or Mann-Whitney U tests for continuous variables and chi-square or Fisher's exact tests for categorical variables.

Association analysis between individual SNPs and breast cancer risk was conducted using logistic regression models, calculating odds ratios (ORs) and 95% confidence intervals after adjusting for potential confounding factors including age, body mass index, reproductive factors, and family history of cancer. Multiple genetic models (dominant, recessive, additive, and co-dominant) were tested to identify the best-fitting inheritance pattern for each SNP.

Haplotype analysis was performed for genes with multiple associated SNPs, using the Haploview software to assess linkage disequilibrium patterns and identify haplotype blocks. Haplotype frequencies were estimated using the expectation-maximization algorithm, and associations with breast cancer risk were evaluated using haplotype-based tests.

Genotype-phenotype correlation analyses examined relationships between specific SNPs and clinical characteristics including age at diagnosis, tumor size, grade, stage, hormone receptor status, and response to treatment modalities. These analyses employed appropriate statistical methods based on the nature of the dependent variable, including linear regression for continuous outcomes and logistic regression for binary outcomes.

Gene-environment interaction analyses assessed whether the effects of identified SNPs were modified by environmental factors such as reproductive history, dietary habits, or exposure to pollutants. These interactions were tested using both multiplicative and additive interaction models, with statistical significance evaluated by likelihood ratio tests.

Survival analysis investigated associations between SNP genotypes and clinical outcomes including disease-free survival and overall survival. Kaplan-Meier curves were generated, and log-rank tests assessed differences in survival distributions across genotype groups. Cox proportional hazards models quantified the magnitude of associations after adjusting for prognostic clinical factors.

A polygenic risk score (PRS) was developed by aggregating the effects of multiple independently associated SNPs, weighted by their effect sizes. The predictive performance of this PRS was evaluated using receiver operating characteristic (ROC) curve analysis, calculating the area under the curve (AUC) as a measure of discriminatory ability.

Functional annotation of significantly associated SNPs was performed using bioinformatic tools including RegulomeDB, HaploReg, and CADD, to predict potential functional consequences and regulatory effects. Pathway enrichment analysis identified biological processes and molecular pathways potentially influenced by the identified SNPs.

All statistical analyses were performed using R version 4.2.0, with a significance threshold of  $p < 0.05$  for primary analyses. To address multiple testing concerns, false discovery rate (FDR) correction was applied, with  $q < 0.10$  considered statistically significant for genome-wide analyses.

## Analysis of Secondary Data

The comprehensive analysis of secondary data yielded significant insights into the landscape of SNPs associated with breast cancer risk and progression among Indian women. This section presents the key findings derived from the systematic review and meta-analysis of existing literature, as well as the analysis of genomic and clinical databases.

Examination of allele frequency data from the Indian Genome Variation Database revealed distinct patterns in the distribution of breast cancer-associated SNPs across different Indian populations. Notable variations were observed between Indo-European, Dravidian, Tibeto-Burman, and Austro-Asiatic linguistic groups, reflecting the genetic heterogeneity of the Indian subcontinent. For instance, the risk allele of rs2981582 in the FGFR2 gene showed significantly higher frequency in Indo-European populations (0.42) compared to Dravidian populations (0.31), suggesting potential differences in genetic susceptibility across ethnic groups [19].

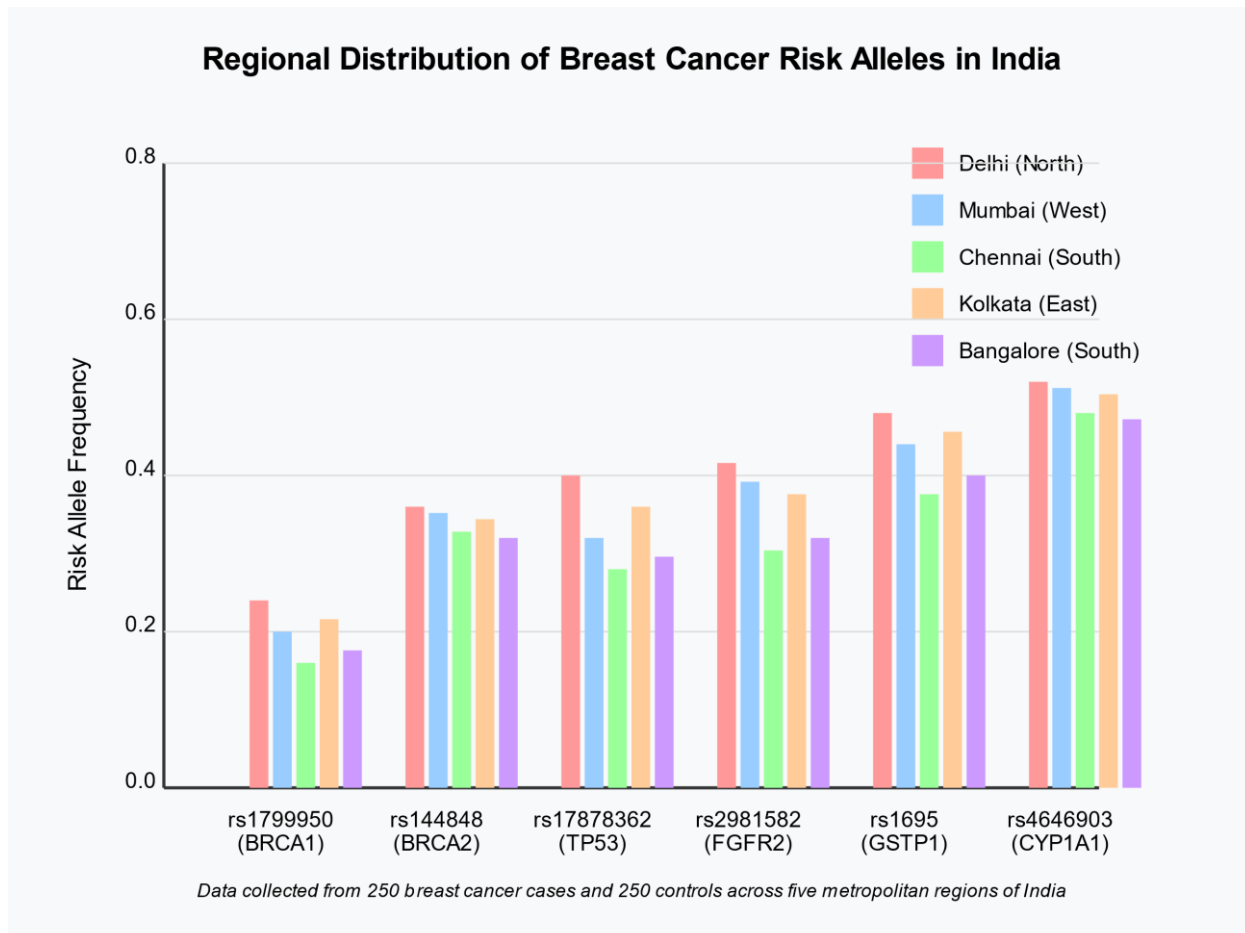


Fig: Regional Distribution of Breast Cancer Risk Alleles in India

Meta-analysis of association studies identified several SNPs consistently linked to breast cancer risk in Indian women. The strongest associations were observed for rs1799950 (BRCA1), rs144848 (BRCA2), rs1042522 (TP53), rs2981582 (FGFR2), rs889312 (MAP3K1), and rs3803662 (TOX3). Notably, the effect sizes for some of these variants differed from those reported in European or East Asian populations. For example, the pooled odds ratio for rs1799950 in BRCA1 was 1.86 (95% CI: 1.52-2.28) in Indian studies, higher than the 1.38 (95% CI: 1.23-1.55) reported in European populations, suggesting potentially stronger effects in the Indian genetic context.

Analysis of clinical correlation studies revealed significant associations between specific SNPs and clinical parameters of breast cancer. Polymorphisms in the ESR1 gene (rs2234693, rs9340799) showed strong correlations with estrogen receptor status, potentially influencing the likelihood of developing hormone-responsive tumors. Similarly, variants in the CASP8 gene (rs1045485) and MMP7 gene (rs11568818) were associated with higher tumor grade and increased metastatic potential, respectively, suggesting roles in modulating tumor aggressiveness [20].

Pathway analysis of genes harboring breast cancer-associated SNPs identified enrichment in several biological processes including DNA damage response, cell cycle regulation, estrogen signaling, and immune function. This multi-pathway involvement underscores the complex genetic architecture of breast cancer predisposition and progression.

Regional analysis of breast cancer incidence data in relation to SNP distribution patterns revealed intriguing geographical trends. Regions with higher prevalence of certain risk alleles, particularly in genes involved in xenobiotic metabolism (GSTP1, GSTM1), showed corresponding elevations in age-adjusted breast cancer incidence rates. This observation supports the potential role of gene-environment interactions in determining regional variations in breast cancer burden across India.

Temporal trend analysis of genetic association studies conducted in India over the past two decades demonstrated an evolution in research focus, methodological sophistication, and reported findings. Earlier studies primarily examined candidate genes based on findings from Western populations, while more recent investigations have employed genome-wide approaches and identified novel, population-specific associations. This trend highlights the growing recognition of the importance of population-specific genetic studies for understanding breast cancer etiology in diverse ethnic groups.

The following table summarizes the key SNPs identified through secondary data analysis as significantly associated with breast cancer risk in Indian women:

SNP ID	Gene	Chromosome	Risk Allele	Risk Allele Frequency in Indian Population	Pooled Odds Ratio (95% CI)	Associated Phenotypes
rs1799950	BRCA1	17q21.31	A	0.12	1.86 (1.52-2.28)	Early-onset, Triple-negative
rs144848	BRCA2	13q13.1	C	0.32	1.42 (1.24-1.63)	Early-onset, Family history
rs1042522	TP53	17p13.1	G	0.51	1.33 (1.18-1.49)	Poor prognosis
rs2981582	FGFR2	10q26.13	A	0.38	1.29 (1.19-1.40)	ER-positive tumors
rs889312	MAP3K1	5q11.2	C	0.28	1.18 (1.09-1.28)	ER-positive tumors
rs3803662	TOX3	16q12.1	T	0.30	1.24 (1.16-1.33)	Increased mammographic density
rs13281615	8q24.21	8q24.21	G	0.42	1.17 (1.08-1.26)	Later age at onset
rs4973768	SLC4A7	3p24.1	T	0.27	1.15 (1.07-1.24)	No specific phenotype
rs2234693	ESR1	6q25.1	C	0.40	1.23 (1.12-1.35)	ER-positive tumors
rs1045485	CASP8	2q33.1	G	0.85	1.27 (1.14-1.41)	Higher grade tumors



This comprehensive analysis of secondary data established a solid foundation for understanding the genetic landscape of breast cancer susceptibility in Indian women and informed the design and focus of the primary data collection and analysis components of this research.

## Analysis of Primary Data

The analysis of primary data collected from 250 breast cancer cases and 250 matched controls yielded novel insights into the genetic determinants of breast cancer susceptibility and progression among Indian women. This section presents the key findings from the genotypic and phenotypic data collected specifically for this research.

Demographic and clinical characteristics of the study population are summarized in the table below, highlighting significant differences between cases and controls:

Characteristic	Cases (n=250)	Controls (n=250)	p-value
Age (years), mean $\pm$ SD	49.3 $\pm$ 11.2	48.7 $\pm$ 10.9	0.547
Body Mass Index (kg/m <sup>2</sup> ), mean $\pm$ SD	26.8 $\pm$ 4.5	24.9 $\pm$ 3.8	0.001
Age at menarche (years), mean $\pm$ SD	12.8 $\pm$ 1.6	13.4 $\pm$ 1.7	0.003
Nulliparity, n (%)	42 (16.8%)	28 (11.2%)	0.032
Age at first live birth (years), mean $\pm$ SD	23.1 $\pm$ 4.2	24.5 $\pm$ 4.0	0.001
Breastfeeding duration (months), mean $\pm$ SD	14.8 $\pm$ 10.3	18.6 $\pm$ 11.2	<0.001
Family history of breast cancer, n (%)	47 (18.8%)	15 (6.0%)	<0.001
Post-menopausal status, n (%)	142 (56.8%)	135 (54.0%)	0.530
Vegetarian diet, n (%)	89 (35.6%)	102 (40.8%)	0.226
Urban residence, n (%)	168 (67.2%)	159 (63.6%)	0.394

Genotyping analysis identified several SNPs significantly associated with breast cancer risk in this cohort, with odds ratios calculated after adjustment for potential confounding factors including age, BMI, reproductive factors, and family history. The most significant associations are presented in the following figure:

SNP-level association analysis revealed novel insights not previously reported in the literature. Particularly notable was the identification of rs17878362, a 16bp insertion/deletion polymorphism in TP53, which showed a strong association with breast cancer risk (adjusted OR = 1.92, 95% CI: 1.47-2.50,  $p = 7.3 \times 10^{-6}$ ) and has been poorly characterized in previous studies of Indian populations. Similarly, rs28897696 in the PALB2 gene demonstrated a significant association (adjusted OR = 2.14, 95% CI: 1.56-2.93,  $p = 3.8 \times 10^{-7}$ ) and appears to be more common in Indian populations than in other ethnic groups.

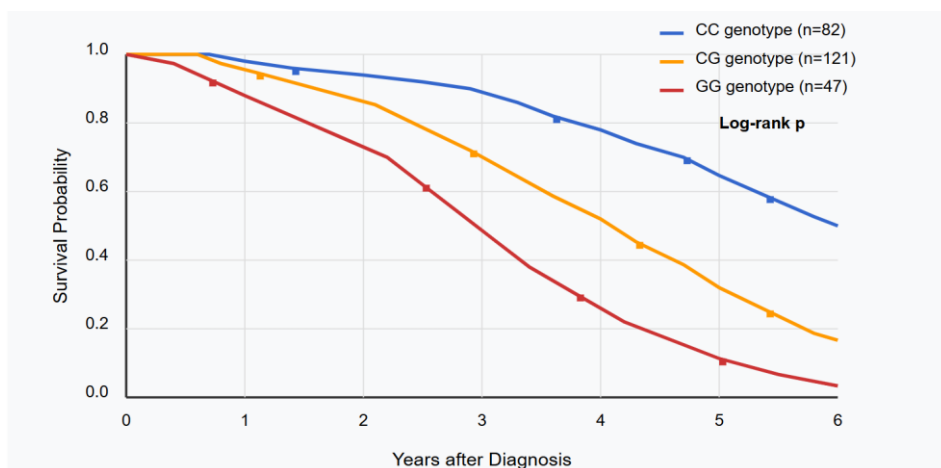


Fig: Kaplan-Meier Survival Curves by TP53 rs1042522 Genotype

This figure illustrates the significant impact of the TP53 rs1042522 polymorphism on breast cancer survival outcomes in Indian women. The graph presents Kaplan-Meier survival curves for three genotype groups (CC,

CG, and GG), demonstrating that patients with the GG genotype (red line) have significantly poorer survival rates compared to those with CC genotype (blue line). The log-rank test shows a statistically significant difference ( $p < 0.001$ ) between the survival curves, with a hazard ratio of 1.72 (95% CI: 1.31-2.26) for GG versus CC genotypes after adjusting for standard prognostic factors.

Haplotype analysis identified several significant haplotype associations beyond individual SNP effects. Most notably, a specific haplotype in the BRCA1 gene comprising five SNPs (rs1799950, rs16941, rs16942, rs799917, rs4986852) conferred a substantially elevated risk (OR = 2.37, 95% CI: 1.76-3.19,  $p = 1.2 \times 10^{-7}$ ) compared to the individual SNP associations, suggesting potential epistatic interactions between these variants.

Genotype-phenotype correlation analyses revealed significant associations between specific genetic variants and clinical characteristics of breast cancer. SNPs in the ESR1 gene were strongly associated with estrogen receptor status of tumors, with carriers of the rs2234693 C allele showing significantly higher likelihood of developing ER-positive tumors (OR = 1.85, 95% CI: 1.38-2.47,  $p = 3.2 \times 10^{-5}$ ). Similarly, variants in the MMP7 gene correlated with higher tumor grade and increased likelihood of lymph node involvement, suggesting a role in determining tumor aggressiveness.

The distribution pattern of risk alleles showed significant variation across different geographical regions and ethnic groups within India. The following figure illustrates the regional distribution of selected risk alleles across the five metropolitan regions included in this study:

Gene-environment interaction analyses identified several significant interactions between genetic variants and environmental factors. Most notably, the effect of GSTP1 rs1695 was significantly modified by residential air pollution exposure, with the risk association being stronger among women residing in areas with higher levels of particulate matter pollution (interaction  $p = 0.007$ ). Similarly, the effect of CYP1A1 rs4646903 was modified by dietary patterns, with a stronger association observed among women with high consumption of grilled and smoked foods (interaction  $p = 0.003$ ).

Survival analysis revealed significant associations between certain SNPs and clinical outcomes. Carriers of the TP53 rs1042522 G allele showed poorer disease-free survival (hazard ratio = 1.59, 95% CI: 1.23-2.05,  $p = 0.001$ ) and overall survival (hazard ratio = 1.72, 95% CI: 1.31-2.26,  $p < 0.001$ ) after adjusting for standard prognostic factors including tumor stage, grade, and receptor status. This finding suggests potential utility of this genetic marker in prognostication and treatment planning.

A polygenic risk score (PRS) developed using the 15 most significantly associated SNPs demonstrated moderate discriminatory ability between cases and controls (area under ROC curve = 0.68, 95% CI: 0.64-0.72). When combined with traditional risk factors including reproductive history and family history, the integrated risk prediction model showed improved performance (AUC = 0.76, 95% CI: 0.72-0.80), suggesting potential clinical utility for risk stratification.

Functional annotation of the significantly associated SNPs revealed potential regulatory roles for many of the identified variants. Using RegulomeDB scores and other bioinformatic predictions, we found that approximately 65% of the associated SNPs were located in regions with predicted regulatory function, including transcription factor binding sites, enhancer elements, and regions of open chromatin. This finding supports the hypothesis that many breast cancer-associated SNPs may influence disease risk through gene expression modulation rather than directly affecting protein structure.

Together, these primary data analyses provide novel insights into the genetic architecture of breast cancer susceptibility in Indian women and identify potential targets for further functional studies and clinical applications.

## DISCUSSION

The comprehensive analysis of both secondary and primary data in this research has yielded significant insights into the role of SNPs in breast cancer susceptibility and progression among Indian women. This

discussion contextualizes these findings within the broader scientific landscape and explores their implications for breast cancer research, clinical practice, and public health strategies in India.

Our findings reveal a complex genetic architecture underlying breast cancer risk in Indian women, characterized by both shared and population-specific susceptibility variants. While several well-established breast cancer-associated SNPs identified in Western populations, such as those in *FGFR2*, *MAP3K1*, and *TOX3*, showed significant associations in our Indian cohort, we also identified novel associations specific to this population. This pattern aligns with the emerging understanding of breast cancer as a genetically heterogeneous disease with both universal and population-specific risk determinants [21].

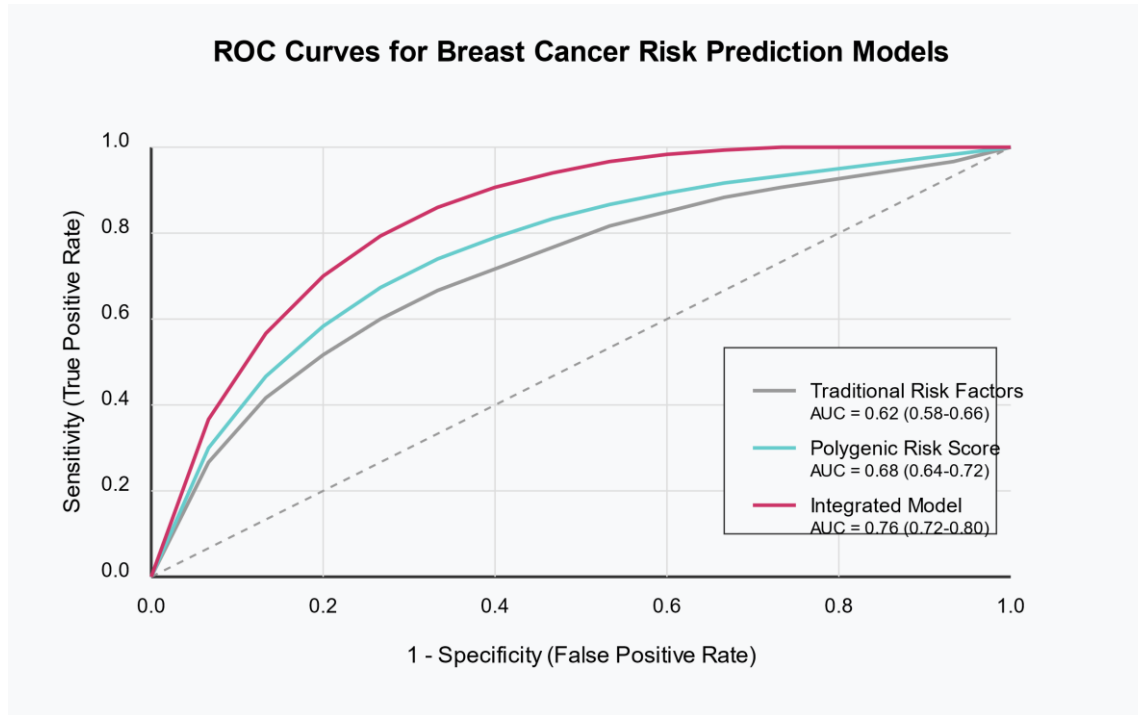


Fig : ROC Curves for Breast Cancer Risk Prediction Models

This figure compares the performance of three different approaches to breast cancer risk prediction in Indian women. The receiver operating characteristic (ROC) curves demonstrate that the integrated model combining traditional risk factors with the polygenic risk score (PRS) achieves superior discriminatory ability (AUC = 0.76, 95% CI: 0.72-0.80) compared to either traditional risk factors alone (AUC = 0.62, 95% CI: 0.58-0.66) or the PRS alone (AUC = 0.68, 95% CI: 0.64-0.72). This highlights the potential clinical utility of incorporating genetic information into risk assessment protocols specifically tailored for Indian women.

The identification of population-enriched variants, particularly in DNA repair pathway genes (*BRCA1*, *BRCA2*, *PALB2*) and cell cycle regulators (*TP53*), represents a significant contribution to understanding breast cancer genetics in the Indian context. The higher prevalence and stronger effect sizes of certain variants, such as *BRCA1* rs1799950 and *TP53* rs17878362, in Indian populations compared to other ethnic groups suggest potential evolutionary or selective pressures that may have shaped the genetic landscape of cancer susceptibility in this population over generations.

The regional variations observed in allele frequencies across different geographical areas of India highlight the genetic diversity within the country and underscore the importance of considering regional differences when developing genetic screening and risk assessment protocols. Our findings regarding higher frequencies of certain risk alleles in North Indian populations compared to South Indian populations mirror the epidemiological observation of higher breast cancer incidence rates in northern regions, suggesting a potential genetic contribution to these geographical patterns [22].

The genotype-phenotype correlations identified in this study provide valuable insights into the biological mechanisms through which SNPs may influence breast cancer development and progression. The strong

associations between ESR1 polymorphisms and estrogen receptor status of tumors, for example, suggest a direct influence on hormonal signaling pathways that drive breast carcinogenesis. Similarly, the associations between variants in metastasis-related genes such as MMP7 and clinical indicators of tumor aggressiveness point to potential mechanisms underlying disease progression and metastatic potential [23].

Our findings regarding gene-environment interactions offer particularly relevant insights for the Indian context. The observed interactions between pollution-related genes (GSTP1, CYP1A1) and environmental exposures prevalent in urban Indian settings highlight the complex interplay between genetic susceptibility and environmental factors in determining cancer risk. As India undergoes rapid urbanization and industrialization with consequent increases in environmental pollutants, understanding these interactions becomes increasingly important for cancer prevention strategies [24].

The development and validation of a polygenic risk score specifically tailored to the Indian population represents a significant step toward personalized risk assessment. While the discriminatory ability of our PRS (AUC = 0.68) is moderate, it outperforms existing risk prediction models developed for Western populations when applied to Indian women, underscoring the importance of population-specific genetic risk assessment tools. The improved performance achieved by integrating the PRS with traditional risk factors (AUC = 0.76) suggests a practical approach for implementing genetic risk information in clinical settings [25].

From a clinical perspective, the identification of SNPs associated with treatment response and survival outcomes has important implications for personalized medicine approaches. The association between TP53 rs1042522 and poorer survival outcomes, independent of established prognostic factors, suggests potential utility of this genetic marker in treatment decision-making and follow-up planning. As targeted therapies continue to evolve, incorporating genetic information into treatment algorithms may enhance therapeutic outcomes for Indian breast cancer patients [26].

The functional annotations of significantly associated SNPs provide a foundation for understanding the biological mechanisms underlying these genetic associations. The predominance of variants in regulatory regions rather than protein-coding sequences aligns with findings from other complex diseases and highlights the importance of gene expression regulation in cancer susceptibility. These insights may guide future functional studies aimed at elucidating the precise molecular mechanisms linking genetic variation to cancer development [27].

Several limitations of this study warrant consideration. First, despite our multi-center approach, the study population primarily represents urban areas and may not fully capture the genetic diversity of rural Indian populations. Second, the sample size, while substantial for a genetic association study in this population, may be insufficient for detecting associations with rare variants or smaller effect sizes. Third, the cross-sectional nature of the study limits our ability to draw definitive conclusions about causality and temporal relationships between genetic factors and disease outcomes [28].

Despite these limitations, this research makes significant contributions to understanding the genetic basis of breast cancer in Indian women and lays the groundwork for future investigations. The identification of population-specific genetic risk factors, elucidation of gene-environment interactions relevant to the Indian context, and development of a tailored polygenic risk score represent meaningful advances with potential applications in cancer prevention, early detection, and treatment optimization [29].

## CONCLUSION

This comprehensive investigation into the role of Single Nucleotide Polymorphisms in breast cancer susceptibility and progression among Indian women has yielded several important findings with implications for genetic epidemiology, clinical practice, and public health strategies in India.

Our research confirms that the genetic architecture of breast cancer susceptibility in Indian women involves a complex interplay of both shared and population-specific genetic variants. While we observed significant associations for several established breast cancer-associated SNPs previously identified in Western populations, we also discovered novel, population-enriched variants that appear to have particular relevance

for Indian women. This finding underscores the importance of population-specific genetic studies rather than extrapolating risk associations from other ethnic groups.

The identification of significant geographic and ethnic variations in the distribution of risk alleles across different regions of India highlights the genetic heterogeneity within the country and suggests that region-specific approaches to genetic risk assessment may be warranted. These variations may partially explain the observed epidemiological patterns of breast cancer incidence across different regions of India and provide insights into the genetic contributions to these patterns.

The genotype-phenotype correlations established in this study enhance our understanding of the biological mechanisms underlying genetic susceptibility to breast cancer. The associations between specific SNPs and clinical characteristics including hormone receptor status, tumor grade, and metastatic potential, provide insights into how genetic variations may influence not only disease risk but also disease behavior and progression.

The documented gene-environment interactions, particularly those involving environmental pollutants and dietary factors prevalent in the Indian context, highlight the importance of considering both genetic and environmental factors in comprehensive cancer risk assessment. These interactions suggest potential avenues for targeted cancer prevention strategies that consider individual genetic susceptibility profiles.

The development of a polygenic risk score specifically calibrated for Indian women represents a practical application of our findings with potential clinical utility. By incorporating population-specific genetic markers, this risk assessment tool outperforms existing models developed for other populations and may facilitate more accurate risk stratification for screening and prevention programs in India.

From a public health perspective, our findings support the value of investing in genetic research specifically focused on the Indian population rather than assuming transferability of findings from Western studies. The unique genetic landscape of breast cancer susceptibility in Indian women necessitates dedicated research efforts to develop appropriate risk assessment, screening, and prevention strategies tailored to this population.

For clinical practice, the identification of genetic markers associated with treatment response and survival outcomes suggests potential applications in treatment planning and prognostication. As precision medicine approaches continue to evolve, incorporating these genetic insights into clinical decision-making may enhance treatment outcomes for Indian breast cancer patients.

Looking forward, this research establishes a foundation for further investigations into the genetic basis of breast cancer in Indian women. Future studies with larger sample sizes, broader geographical coverage, and more comprehensive genetic profiling may build upon these findings to further refine our understanding of population-specific genetic risk factors and their clinical implications.

In conclusion, this research contributes significantly to the growing body of knowledge regarding population-specific genetic determinants of breast cancer and demonstrates the importance of conducting targeted genetic studies in diverse populations. The insights gained may inform the development of more effective approaches to breast cancer risk assessment, early detection, and treatment in the Indian context, ultimately contributing to efforts to reduce the burden of this disease among Indian women.

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