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RESEARCH

Association of *ESR1*, *HER1*, and *HER2* Polymorphisms with Breast Cancer Risk in the KP Population, A Case-Control Study

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Abstract

Breast cancer is a complex disease characterized by the uncontrolled growth of breast cells. Genetic variants in *ESR1*, *HER1*, and *HER2* have been associated with breast cancer risk across different populations, with varying results. This study aimed to validate the association of *ESR1* (rs2234693 and rs2046210), *HER1* (rs11543848), and *HER2* (rs1136201) variants with breast cancer risk in the KP population of Pakistan using a larger dataset. The study cohort included 528 patients with BC and 530 healthy controls. Blood samples were collected, and DNA was extracted using a non-enzymatic method. Genotyping was performed using the T-ARMS-PCR protocol. Our results for *ESR1* (rs2234693) indicated a non-significant association between the mutant C allele ($P=0.102$), TC ($P=0.1002$), and CC genotype ($P=0.398$) and breast cancer risk. In contrast, *ESR1* and rs2046210 showed a significant association with the mutant A allele ($P=0.001$), GA ($P=0.001$), and AA genotype ($P=0.001$), indicating an increased risk. *HER1* and rs11543848 showed an increased risk of breast cancer, with the mutant allele A ($P=0.001$), GA ($P=0.001$), and AA genotype ($P=0.001$). Similarly, alleles G ($P=0.004$), AG ($P=0.001$), and GG genotype ($P=0.003$) of *HER2* (rs1136201) were associated with higher breast cancer risk. Furthermore, *ESR1* (rs2234693) was significantly associated with PR status, while both *HER1* (rs11543848) and *HER2* (rs1136201) were considerably associated with HER2 receptor status. In conclusion, this study explored the association of the selected variants of *ESR1*, *HER1*, and *HER2* with breast cancer risk in the KP population using a larger data set, providing valuable insights into the genetic factors contributing to breast cancer risk and corresponding value added to breast cancer management.

Keywords Breast cancer · Genetic variation · *ESR1* · *HER1* · *HER2* · Risk association

Introduction

Breast cancer is a type of cancer that originates in the cells of the breast [1]. It usually begins as a small confined tumor that can spread to other parts of the body if not treated early [2]. It encompasses various types of carcinomas including ductal and lobular carcinomas. Common symptoms of breast cancer include a lump or mass of the tumor in the breast area, changes in breast size or shape, skin changes (dimpling), nipple changes (inversion or discharge), and persistent breast discomfort [3, 4].

According to Globocan Cancer Data Statistics 2022, breast cancer is the second most diagnosed cancer worldwide, accounting for one in every four cancer cases and one in every six cancer deaths. The registered number of breast cancer statistics in global cancer data for 2022 is around 2,308,897 cases and 656,84 mortalities worldwide [5]. Several risk factors contribute to the development of breast cancer, including environmental factors, hormonal influences, genetic factors, and lifestyle choices (alcohol consumption, obesity, and lack of physical activity) [6].

Genetic mutations play a crucial role in the etiology of breast cancer. Some common genetic mutations associated

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with breast cancer include *BRCA1*, *BRCA2*, *TP53*, *PALB2*, and *ATM* [7]. Alongside these extensively studied genes, recent studies have associated genetic mutations within *ESR1*, *HER1*, and *HER2* genes in breast cancer [8].

The estrogen receptor1 (*ESR1*) gene encodes estrogen receptor α (ERα), a key protein expressed in most breast cancers and serves as an important biomarker in tumors [9]. ERα regulates breast cancer risk by affecting estrogen metabolic pathways, and is essential for normal breast epithelial growth and differentiation. Variations in *ESR1*, particularly single nucleotide polymorphisms (SNPs), have been studied exclusively to understand their association with breast cancer [10]. The two most studied polymorphisms in the *ESR1* gene are rs2234693 and rs2046210 [11, 12].

The rs2234693 polymorphism, located in intron one, is a well-characterized SNP associated with an increased risk of breast cancer and other estrogen-related diseases [13]. This variant may affect breast cancer risk by altering transcription factor-binding sites and affecting alternative splicing of the *ESR1* gene, thereby altering gene expression [14]. *ESR1* and rs2046210 are located at the 6q25.1 locus on chromosome 6, approximately 29 kb upstream of *ESR1* [15]. Its proximity suggests a potential role in modulating *ESR1* expression, possibly influencing the proliferation of breast epithelial cells, and contributing to breast tumorigenesis [16].

HER1, also known as ErbB1 or EGFR, is a transmembrane receptor protein involved in important cellular processes such as cell division, growth promotion, apoptosis inhibition, and angiogenesis stimulation [17]. Activation occurs when ligands, such as transforming growth factor alpha (TGF alpha), bind to its extracellular domain, leading to autophosphorylation of tyrosine kinase residues in the intracellular domain. This activation initiates a cascade of downstream signals, including the MAPK and PI3K pathways, which regulate cell proliferation and survival [18]. SNP rs11543848, also known as *HER*1 R497K, involves a single nucleotide substitution (142285G>A) at codon 521 of the extracellular subdomain IV of the EGFR gene, leading to an arginine (R) to lysine (K) change [19]. This genetic variation may affect EGFR-mediated signaling pathways, which may further affect cancer susceptibility and treatment responses, including implications for breast cancer research [20].

HER2 is a proto-oncogene located on chromosome 17q12 that encodes a 185 kDa transmembrane glycoprotein involved in regulating cell growth and differentiation [21]. Unlike other members of this family, *HER2* is constitutively active and independent of ligand binding [22]. Dimerization of *HER3* or *HER4* triggers transphosphorylation of the intracellular tyrosine kinase domain, thereby initiating pathways such as MAPK and PI3K [23]. Overexpression or amplification of *HER2* occurs in 20–25% of breast cancers, correlating with aggressive tumor behavior, increased metastasis, and therapy insensitivity [24]. The rs1136201 SNP, known as I655V, causes a valine-to-isoleucine substitution in the transmembrane domain of the *HER2* protein [25]. This polymorphism in the transmembrane region of *HER2* is associated with a higher risk of breast cancer [26]. This amino acid change promotes enhanced dimerization, tyrosine kinase activity, and autophosphorylation, thereby initiating cell transformation [21].

This study aimed to investigate the association of *ESR1* (rs2234693 and rs2046210), *HER1* (rs11543848), and *HER2* (rs1136201) polymorphisms with breast cancer risk in the Pashtun population. Previous studies have identified genetic markers for this demographic [27, 28]. However, the purpose of this research was to provide strong validation and deep insight through a comprehensive analysis of larger datasets.

Materials and Methods

The study was conducted from January to December 2023 at the Institute of Biotechnology and Genetic Engineering (IBGE), University of Agriculture, Peshawar, Pakistan. The study cohort included 528 patients with breast cancer and 530 age- and sex-matched healthy controls. Patients with breast cancer were enrolled at the Institute of Radiology and Nuclear Medicine (IRNUM) Hospital in Peshawar. Ethical approval for the study was obtained from the IBGE and IRNUM Hospital Peshawar. Informed written consent was obtained from all participants after explaining the study objectives.

Inclusion Exclusion Criteria and Blood Collection

Blood samples were collected from patients with breast cancer based on the inclusion and exclusion criteria. Patients with other significant comorbidities, such as diabetes or other chronic conditions that could potentially affect the study outcomes, were excluded from the study. Additionally, individuals who did not meet the age- and gender-matching criteria with the breast cancer patient group were also excluded from the health control group. Furthermore, demographic and clinicopathological data alongside a 3mL blood sample, were collected from breast cancer patients.

DNA Extraction, Genotyping and Gel Electrophoresis

DNA extraction was performed using non-enzymatic or salting-out method [29–31]. Genotyping was performed by T-ARMS PCR. Specific sequenced matched primers

Table 1 Specific primer sequences for genotyping

Genes	Primers	Sequence 5'-3'
***ESR1*, rs2234693**	Forward Outer	CTGATATCCAGGGTTATGTGG
	Reverse Outer	TAACCTTGAGGGGAAATTGT
	Forward Inner	GAGTTCCAAATGTCCCAGCC
	Reverse Inner	ACAGAGACAAAGCATAAA ACA
***ESR1*, rs2046210**	Forward outer	CCAAATCACATCTGGAATCC
	Reverse Outer	GGCACTCAACATCCATTTCTC
	Forward Inner	ACATACATACAGTCACATACA
	Reverse Inner	TCTTTTATTTCAGGTAGATGC
***HER1*, rs11543848**	Forward Outer	TTGTCCTTCCAGTCACGGT CG
	Reverse Outer	TCAAACAGAATGCCTGTAA AGCT
	Forward Inner	GGGGCCCGGAGCCCAA
	Reverse Inner	GGCAAGAGACGCAGTCCC
***HER2*, rs1136201**	Forward Outer	GAGCCAAGGCAGGTTTTA GAG
	Reverse Outer	TCTGCGCCTGGTTGGG
	Forward Inner	GCCCTCTGACGTCCATC
	Reverse Inner	GCCAACCACCGCAGAGAT

Table 2 The optimized condition for PCR reaction

SNPs	Denaturation	Annealing Tm	Extension	Cycles
HER1	95ºC/5 min,	Wild 65ºC/30 sec	72ºC/1 min	38
rs11543848	94ºC/30 sec	Mutant 61 ºC/30 sec	72ºC/10 min	
HER2	95ºC/5 min,	Wild 57ºC/30 sec	72ºC/1 min,	38
rs1136201	94ºC/ 30 s	Mutant 57ºC/30 sec	72ºC/10 min	
ESR1	95ºC/5 min,	Wild 58ºC/30 sec	72ºC/1 min,	38
rs2234693	94ºC/ 30 s	Mutant 58ºC/30 sec	72ºC/10 min	
ESR1	95ºC/5 min,	Wild 58ºC/30 sec	72ºC/1 min,	38
rs2046210	94ºC/30 sec	Mutant 58ºC/30 sec	72ºC/10 min	

were designed using the NCBI primer BLAST software (Table 1). The inner and outer primers were designed in two sets (reverse and forward each) to detect heterozygous and homozygous dominant and recessive alleles, respectively. The conditions used for the genotyping are presented in Table 2. The PCR results were confirmed by 1.5% gel electrophoresis.

Statistical Analysis

The collected data were analyzed statistically using the MedCalc odd ratio calculator and Statistical Package for Social Sciences (SPSS) version 25 to assess the association between polymorphisms and breast cancer risk. Statistical significance was set at $P<0.05$. Clinicopathological and genetic variant associations were determined using the chi-squared test. Odds ratios and 95% confidence intervals (CI) were calculated to determine risk factors associated with the selected polymorphisms.

Results

Association of *ESR1* (rs2234693 and rs2046210), *HER1* (rs11543848) and *HER2* (rs1136201) Polymorphism with Breast Cancer Patients

Genotyping was performed for 528 patients with breast cancer and 530 healthy controls using T-ARMS-PCR, followed by gel electrophoresis (Fig. 1). Genotyping results were statistically analyzed, which yielded the following results (Table 3). The *ESR1* (rs2234693) analysis indicated that risk allele C (OR = 1.18,95% CI = 0.967– 1.445, $P=0.102$) and both heterozygous TC (OR = 1.23, 95% CI = 0.9597– 1.5986, $P=0.1002$) and homozygous CC genotype (OR = 1.26, 95% CI = 0.7355– 2.1645, $P=0.398$) indicated a higher risk but non-significant association with breast cancer. The risk allele A (OR = 1.55, 95% CI = 1.3085– 1.8481, $P=0.001$) of rs2046210 and both heterozygous GA (OR = 2.33, 95% CI = 1.7423– 3.1239, $P=0.001$) and homozygous AA genotypes (OR = 2.62, 95% CI = 1.7703– 3.8989, $P=0.001$) were significantly associated with breast cancer. Moreover, both the selected SNPs of *HER1* and *HER2* were significantly associated with breast cancer patients. The risk allele A (OR = 1.65, 95% CI = 1.3951– 1.9702, $P=0.001$) of HER 1 (11543848) and both the heterozygous GA (OR = 3.31, 95% CI = 2.4323– 4.5272, $P=0.001$) and homozygous AA (OR = 3.19, 95% CI = 2.1208– 4.8152, $P=0.001$) genotypes showed a higher risk and significant association. The analysis for *HER2* (rs1136201) indicated that the risk allele G (OR = 1.37, 95% CI = 1.1498– 1.6361, $P=0.004$) and both heterozygous AG (OR = 2.00, 95% CI = 1.5208– 2.6411, $P=0.001$) and homozygous GG (OR = 1.96, 95% CI = 1.2424– 3.1220, $P=0.003$) genotypes were significantly associated with breast cancer.

Association of *ESR1* (rs2234693 and rs2046210), *HER1* (rs11543848) and *HER2* (rs1136201) Polymorphisms with Receptor Status of Breast Cancer

The association of the selected SNPs with receptor status was statistically determined using SPSS and MedCalc, an odd ratio calculator. The results indicated a significant association between *ESR1* (rs2234693) polymorphism and PR

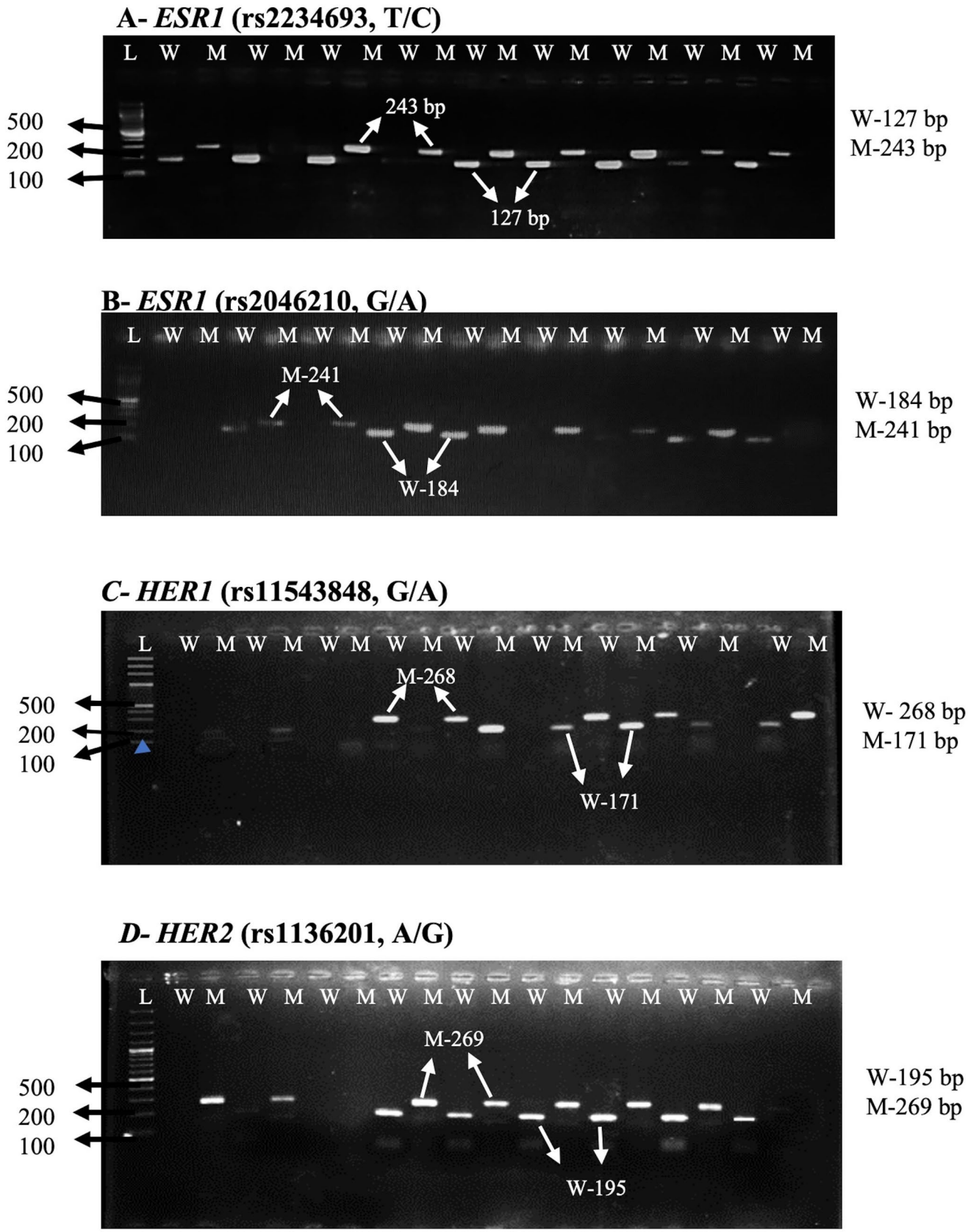

Fig. 1 Representative gel pictures of the *ESR1* (**a**, **b**) *HER1* (**c**), and *HER2* (**d**). L represents DNA ladder, M- mutant allele, and W- wild allele

Table 3 Association of ESR1 (rs2234693 and 2046210), HER1 (rs11543848) and HER2 (rs1136201) with breast cancer patients and healthy controls

SNP	Healthy Controls	Patients	Odd Ratios	CI	*P* value
rs2234693					
T	825	790			
C	235	266	1.18	0.967 to 1.445	**0.1025**
Genotypes					
TT	322	293			
TC	181	204	1.23	0.9597 to 1.5986	**0.1002**
CC	27	31	1.26	0.7355 to 2.1645	**0.3984**
HWE	0.971	0.846			
rs2046210					
G	648	531			
A	412	525	1.55	1.3085 to 1.8481	**0.0001**
Genotypes					
GG	187	98			
GA	274	335	2.33	1.7423 to 3.1239	**0.0001**
AA	69	95	2.62	1.7703 to 3.8989	**0.0001**
HWE	0.129	0.001			
rs11543848					
G	646	512			
A	414	544	1.65	1.3951 to 1.9702	**0.0001**
Genotypes					
GG	187	75			
GA	272	362	3.31	2.4323 to 4.5272	**0.0001**
AA	71	91	3.19	2.1208 to 4.8152	**0.0001**
HWE	0.198	0.001			
rs1136201					
A	690	591			
G	370	465	1.37	1.1498 to 1.6361	**0.004**
Genotypes					
AA	196	115			
AG	307	361	2.00	1.5208 to 2.6411	**0.0001**
GG	45	52	1.96	1.2424 to 3.1220	**0.003**
HWE	0.001	0.001			

Status ($P=0.001$). Similarly, both *HER1* (rs11543848) and *HER2* (rs1136201) variants are significantly associated with HER2 receptors in patients with breast cancer. Moreover, all selected variants showed a non-significant ($P<0.05$) association with ER and TNBC.

ESR1 rs2234693						ESR1 rs2046210				
HER2 subtype	**TT**	TC	CC	OR	P Value	GG	GA	AA	OR	P Value
Negative	216	132	24	0.70	0.06	74	230	68	0.73	0.22
Positive	77	72	7	1.42	0.06	24	105	27	1.36	0.22
PR Status										
Negative	169	20	15	0.25	0.001	54	194	56	0.72	0.14
Positive	124	84	16	3.89	0.001	44	141	139	1.37	0.14
ER Status										
Negative	160	131	18	1.34	0.10	51	208	50	1.38	0.14
Positive	133	73	13	0.74	0.10	47	127	45	0.72	0.14
TNBC										
Negative	220	158	23	1.11	0.60	73	254	74	1.10	0.70
Positive	73	46	8	0.89	0.60	25	81	21	0.90	0.70
***HER1*(rs11543848)**						***HER2*(rs1136201)**				
HER2	GG	GA	AA			AA	AG	GG		
Negative	20	257	63	2.78	0.001	72	265	35	1.58	0.03
Positive	23	105	28	0.35	0.001	43	96	17	0.63	0.03
PR Status										
Negative	41	215	48	1.14	0.58	72	196	36	0.76	0.21
Positive	34	147	43	0.87	0.58	43	165	16	1.30	0.21
ER Status										
Negative	43	211	55	1.05	0.82	73	203	33	0.76	0.22
Positive	32	151	36		0.82	42	158	19	1.30	0.22
TNBC										
Negative	56	273	72	1.08	0.77	94	269	38	0.64	0.10
Positive	19	89	19	0.92	0.77	21	92	14	1.54	0.10

Discussion

Breast cancer is a complex multifactorial disease with mechanisms that have not been fully explored [32]. Genome-wide association studies (GWAS) have demonstrated that both genetic and environmental factors contribute to breast cancer pathogenesis [33]. Additionally, specific nucleotide polymorphisms within susceptibility genes may play a significant role in breast cancer development [34]. Numerous clinical studies have investigated SNPs within *ESR1*, *HER1*, and *HER2* with contradictory results across several populations [19, 35, 36]. This study aimed to explore the role of *ESR1* (rs2234693 and rs2046210), *HER1* (rs11543848), and *HER2* (rs1136201) polymorphisms in breast cancer risk in the Pashtun population using a larger dataset. The study cohort included 528 patients with BC and 530 healthy controls. The research methodology included DNA extraction using a non-enzymatic method and genotyping using ARMS-PCR. The results were statistically analyzed.

The analyzed results indicated a non-significant association between *ESR1* (rs2234693) risk allele C ($P=0.102$) and both heterozygous TC ($P=0.1002$) and homozygous CC ($P=0.398$). Additionally, *ESR1* (rs2234693) was significantly associated with the PR status in breast cancer. In contrast, *ESR1* (rs2046210) risk allele A ($P=0.001$) and both heterozygous GA ($P=0.001$) and homozygous AA ($P=0.001$) were significantly associated with breast cancer risk. Moreover, *ESR1* (rs2046210) failed to exhibit a significant association with the receptor status of breast cancer. Our results are consistent with those of a previous study conducted in Mexican [37] and Chinese [38] populations, where rs2234693 did not show any association with breast

cancer risk. Conversely, a study on an Iranian population showed a significant association between rs2234693 and breast cancer risk [39]. Furthermore, for *ESR1* (rs2046210), previous studies in Chinese [40, 41] and Vietnamese populations [42] also demonstrated a risk association with breast cancer, supporting our results. Additionally, another study conducted in the Pashtun population also aligns with our results, further confirming our results. However, the results diverged in terms of receptor status, where rs2046210 was significantly associated with TNBC, whereas rs2234693 was significantly associated with ER status [27].

Moreover, both the selected SNPs of *HER1* and *HER2* were significantly associated with breast cancer risk. For *HER1* (11543848), the risk allele A ($P=0.001$), heterozygous GA ($P=0.001$), and homozygous AA ($P=0.001$) genotypes indicated a higher risk and a significant association. For *HER2* (rs1136201), the risk allele G ($P=0.004$), heterozygous AG ($P=0.001$), and homozygous GG ($P=0.003$) genotypes were significantly associated with breast cancer. Furthermore, both the selected variants exhibited a significant association with HER2 receptor status. A previous study conducted in the Egyptian population supported our results, where both *HER1* (11543848) and *HER2* (rs1136201) polymorphisms were significantly associated with breast cancer [43]. In contrast, a study of Tunisian patients found no significant association between *HER1* (11543848) and breast cancer risk [44]. Furthermore, the research study conducted in the Pashtun population also supported our results, except for both homozygous mutant genotypes, which indicated a non-significant association with breast cancer risk [28].

Conclusion

In conclusion, this study confirmed the role of *ESR1* (rs2234693 and rs2046210), *HER1* (rs11543848), and *HER2* (rs1136201) in breast cancer risk in the Pashtun population using a larger dataset. Despite the utilization of larger datasets, it is necessary to acknowledge certain limitations inherent to this study. This study focused on only a few SNPs within the entire gene, which may not fully capture the genetic variability that could contribute to breast cancer risk. Future studies should further consider whole-gene sequencing to explore other potential SNPs within the same or other associated genes.

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Author Contributions NUK, HK did the experimental work and wrote the first draft. ARA and TC did the formal analysis and critically reviewed the final manuscript.

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Data Availability The manuscript includes all the necessary data; related data may be provided on request from the corresponding author.

Declarations

Ethical Approval and Consent to Participate Ethical approval was obtained from the Institute of Biotechnology and Genetic Engineering (IBGE), University of Agriculture, Peshawar, Pakistan. Written informed consent was obtained from all participants after the aim of the study was explained to them.

Consent for Publication All the authors have read and approved the article for publication.

Competing Interests The authors declare no competing interests.

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