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Association of BRCA1 Founder Mutations (185delAG and 5382insC) and TNF-α 308- Polymorphism with Familial Breast Cancer in Iranian Women

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ABSTRACT

Background: Breast cancer is a major cause of cancer-related morbidity and mortality among women worldwide. Germline *BRCA1* mutations and *TNF-α* gene polymorphisms have been associated with hereditary breast cancer risk. This study evaluated the frequency of the *BRCA1* founder mutations (185delAG and 5382insC), their relationship with the *TNF-α* −308 G>A polymorphism, and their associations with clinicopathological features in Iranian women with familial and non-familial breast cancer.

Methods: Eighty-four formalin-fixed paraffin-embedded breast tissue samples were collected from patients treated at Khatam and Imam Khomeini hospitals. *BRCA1* 185delAG and 5382insC mutations were detected using multiplex PCR, while the *TNF-α* −308 G>A polymorphism was analyzed by ARMS-PCR. Histopathological and immunohistochemical characteristics, including mitotic activity, necrosis, pleomorphism, tumor grade, and ER, PR, and TP53 expression, were evaluated. Statistical analyses were performed using Epi Info version 7, with $P < 0.05$ considered significant.

Results: Of the 84 patients, 38 had a family history of breast cancer and 46 did not. Five *BRCA1* founder mutations were detected in the familial group compared with one in the non-familial group. The *TNF-α* −308 GG genotype was also more frequent in familial cases. Compared with non-familial patients, familial cases showed significantly higher mitotic activity, greater pleomorphism, more extensive necrosis, lower ER and PR expression, and higher TP53 positivity. Although no significant association was found between *BRCA1* mutations and the *TNF-α* −308 GG genotype, both markers were independently associated with familial breast cancer.

Conclusion: *BRCA1* founder mutations and the *TNF-α* −308 GG genotype may represent complementary markers for identifying Iranian women at increased risk of familial breast cancer. Combined with clinicopathological features, these markers may improve risk assessment and support earlier diagnosis. However, the findings should be interpreted cautiously because of the limited sample size and require validation in larger multicenter studies.

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INTRODUCTION

Breast cancer (BC) remains the most frequently diagnosed malignancy and the leading cause of cancer-related mortality among women worldwide. According to recent global estimates, more than 2.3 million new cases and approximately 670,000 deaths occurred

in 2022, making breast cancer a major public health challenge (1, 2). Although advances in screening, molecular diagnostics, and targeted therapies have improved survival, hereditary breast cancer continues to account for approximately 5–10% of all breast cancer cases and represents a clinically important subgroup because of its early onset, aggressive biological behavior, and implications for genetic counseling and cancer prevention (3).

Hereditary breast cancer is primarily associated with pathogenic germline variants in **BRCA1** and **BRCA2**, two tumor suppressor genes that play essential roles in homologous recombination-mediated DNA repair and maintenance of genomic stability (4). Loss of BRCA function results in defective DNA damage repair, accumulation of genomic instability, and increased susceptibility to breast and ovarian cancers (5). Current international guidelines therefore recommend comprehensive germline BRCA testing for individuals with suggestive personal or family histories because identification of pathogenic variants directly influences surveillance strategies, prophylactic interventions, therapeutic decision-making, and family counseling (6).

Recent studies have demonstrated that the spectrum and frequency of **BRCA1/BRCA2** pathogenic variants differ substantially across ethnic populations owing to founder effects and population-specific genetic backgrounds (7). In Middle Eastern populations, particularly in Iran, recurrent founder mutations have been reported; however, the distribution of these variants remains heterogeneous among different provinces and ethnic groups. Recent investigations in Iranian cohorts have further emphasized the need for population-specific genetic data to optimize hereditary breast cancer screening and genetic counseling programs (8, 9).

Among the recurrent **BRCA1** founder mutations, **185delAG** and **5382insC** are among the best characterized and have been identified in multiple hereditary breast cancer populations (10, 11). Although these variants account for a proportion of hereditary breast cancers, recent molecular studies have shown that numerous additional pathogenic variants in **BRCA1**, **BRCA2**, and other DNA repair genes contribute to hereditary cancer susceptibility. Consequently, contemporary hereditary breast cancer assessment increasingly relies on multigene sequencing panels rather than targeted mutation analysis alone. Nevertheless, investigation of recurrent founder mutations remains valuable in populations where these variants are relatively prevalent and may provide cost-effective preliminary genetic screening (8, 12).

Besides high-penetrance susceptibility genes, chronic inflammation has emerged as an important contributor to breast carcinogenesis. Tumor necrosis factor-alpha (**TNF-α**) is a multifunctional pro-inflammatory cytokine involved in immune regulation, apoptosis, angiogenesis, tumor proliferation, and metastatic progression. Functional polymorphisms within the promoter region of the **TNF** gene, particularly the **−308 G>A** variant, have been investigated extensively because they may influence cytokine expression and alter the inflammatory tumor microenvironment. However, published studies have produced inconsistent findings, suggesting that the clinical significance of this polymorphism may vary according to ethnicity, genetic background, and study design (6).

In addition to genetic susceptibility, clinicopathological characteristics including hormone receptor status, TP53 expression, tumor grade, mitotic activity, and histological subtype provide valuable prognostic information in hereditary breast cancer (13). BRCA1-associated tumors are more frequently characterized by high histological grade, hormone receptor negativity, increased proliferative activity, and basal-like molecular features. Integrating molecular genetic findings with pathological characteristics may therefore improve risk stratification and contribute to individualized patient management (9).

Although several Iranian studies have investigated **BRCA1** mutations, most focused on limited patient populations or older molecular techniques, and information regarding the combined evaluation of recurrent **BRCA1** founder mutations and **TNF-α −308** polymorphism remains limited. Furthermore, recent molecular evidence indicates considerable genetic heterogeneity among Iranian hereditary breast cancer patients, highlighting the importance of generating updated population-specific data (14).

Therefore, the present study aimed to investigate the association of the two recurrent **BRCA1** founder mutations (**185delAG** and **5382insC**) together with the **TNF-α −308 G>A** polymorphism in Iranian women with familial and non-familial breast cancer and to evaluate their relationship with clinicopathological characteristics. The findings may contribute to improving the understanding of hereditary breast cancer genetics in the Iranian population and provide baseline evidence for future comprehensive genomic Studie.

METHODOLOGY

In this descriptive-analytic study, breast tissue samples were collected from Khatam and Imam Khomeini hospitals, Karaj, Iran and transferred to a molecular lab after histopathological examination. About 4000 FFPT (Formalin Fixed Paraffin Embedded) tissue samples related to patients with breast lesions were examined in the archive of pathology departments. Out of them, 84 samples with breast cancer at different ages were collected. Then, the histopathological characteristics of samples were studied under a microscope and the

diagnosis was confirmed by a pathologist. Finally, samples were classified based on the age of patients and type of lesion.

Five-micron sections were made of the paraffin-embedded samples using by a microtome and then stained using the Hematoxylin-Eosin method. The tumor type was determined based on a standard grading system (Nottingham histological grading) and then confirmed by a pathologist. The immunohistochemistry method was used for identifying the type of estrogen receptor (ER), progesterone receptor (PR), and TP53. Then, samples were stained by the streptavidin-biotin method using the DAKO slides kit (15).

DNA extraction from tissue samples was done using the kit No. DN8115C manufactured by Cinnagen Company, according to the manufacturer's manuals with some modifications. In this step, after deparaffinization, samples were incubated at 52°C for 5 hours under 100 microliters protease buffer and 5 microliters proteinase enzyme. Then, their DNA was extracted according to the manuals of Cinnagen extraction kit.

PCR reaction for β-actin

After DNA extraction, PCR reaction was done using the Cinnagen diagnostic kit (No. PR8252C) in order to verify the presence of the β-actin gene. The formation of the desired fragments in PCR products was also evaluated by electrophoresis on the 1. 8% agarose gel.

Assessment of Multiplex PCR for 185delAG and 5382insC mutations in BRCA1

PCR reaction on 185delAG and 5382insC mutations in BRCA1 was conducted in two separate microtubes (one for normal alleles and the other for mutant alleles) using the following products and specific primers synthesized by Cinnagen Company table 1 (16).

Assessment of ARMS-PCR reaction for the proliferation of polymorphism -308 in TNF-α

PCR reaction on polymorphism -308 in TNF-α was conducted using the Cinnagen diagnostic gene (No. DN8115C) and specific primers synthesized by this company. The sequence of primers used in this reaction has been shown in the following table 2.

STATISTICAL ANALYSIS

Statistical analyses were performed using Epi Info version 7 (CDC, Atlanta, GA, USA). Categorical variables were compared using Pearson's chi-square test or Fisher's exact test when expected cell counts were less than five. Odds ratios (ORs) were calculated to estimate the strength of associations. Because only six patients carried BRCA1 founder mutations, multivariable logistic regression analysis was not performed due to the limited number of events, which would have resulted in unstable estimates and model overfitting. Therefore, the findings should be considered exploratory. Statistical significance was defined as a two-sided *P* value <0.05.

RESULTS

Out of 84 samples studied, 38 samples had at least one affected person among their first-degree relatives and 46 of them did not have such a person (Table 3).

χ^2 test for trend= 31. 39 (P<0.0001)

There is a significant difference between the two

Table 1. Major vaginal community state types and their clinical interpretation.

Primer	Primer sequence	Length (bp)
BRCA1 185delAG	Common forward (P1) 5'-ggttggcagcaatatgtgaa	
	Wild-type reverse (P2) 5'-gctgacttaccagatgggactctc	335bp
	Mutant reverse (P3) 5'-cccaaattaatacactcttgtcgtgacttaccagatgggacagta	354 bp
BRCA1 5382insC	Common forward (P4) 59-gacgggaatccaaattacacag	
	Wild-type reverse (P5) 59-aaagcgagcaagagaatcgca	271bp
	Mutant reverse (P6) 5'-aatcgaagaaaccaccaaagtccttagcgagcaagagaatcacc	295bp

Table 2. The sequence of primers used for PCR reaction on polymorphism -308 in TNF-α

-308G	**ACCCTGGAGGCTGAACCCCGTCTC**
-308A	**ACCCTGGAGGCTGAACCCCGTCTT**
CP	**GCCCCTCCCAGTTCTAGTTCTTC**

Table 3. Separation of samples based on the age of patients

Age	The number of people with a family history (percent) (n=38)	The number of people with no family history (percent) (n=46)	Odds ratio (OR)
21-30	4(52 .10)	1(17 .2)	**1.00**
31-40	7(42 .18)	3(52 .6)	**0.468**
41-50	12 (57 .31)	7(21 .15)	**0.388**
51-60	9 (68 .23)	13(26 .28)	**0.156**
61-70	4 (52 .10)	14 (43 .30)	**0.067**
71-80	2 (26 .5)	8(39 .17)	**0 .053**

groups in terms of age, and the odds ratio for breast cancer among those with a family history is higher than the other group at lower ages.

Histopathology and immunohistochemistry findings

The frequency of ER expression differed significantly between the two groups, with lower ER positivity observed among patients with a family history (Figure 1) Similarly, PR expression was significantly lower in patients with a family history of breast cancer (Figure 2). TP53 positivity was also significantly higher among patients with a family history of breast cancer (Figure 3). Among the 84 samples, the highest frequency was related to ductal carcinoma (82%) which showed no significant difference between the two groups. Out of 38 samples with a family history, 21% showed necrotic lesions and 79% of then lacked such lesions. Which suggests a significant difference between the two groups. The largest tumor size in this study was 2-5 cm with a frequency of 66% and the smallest tumor size was less than 2 cm with a frequency of 25%. In addition, tumors with a size of over 5 cm accounted for 9% of

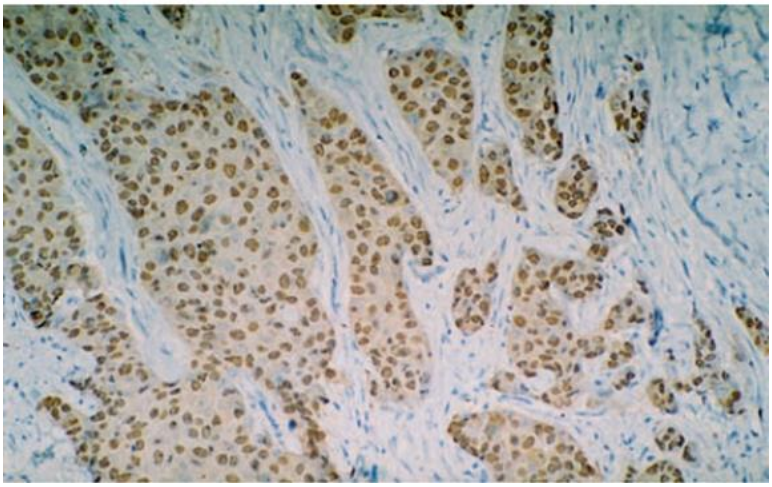

Fig1. Positivity of ER in more than 10% of tumor nucleus in a case of invasive ductal breast cancer (magnification X100)

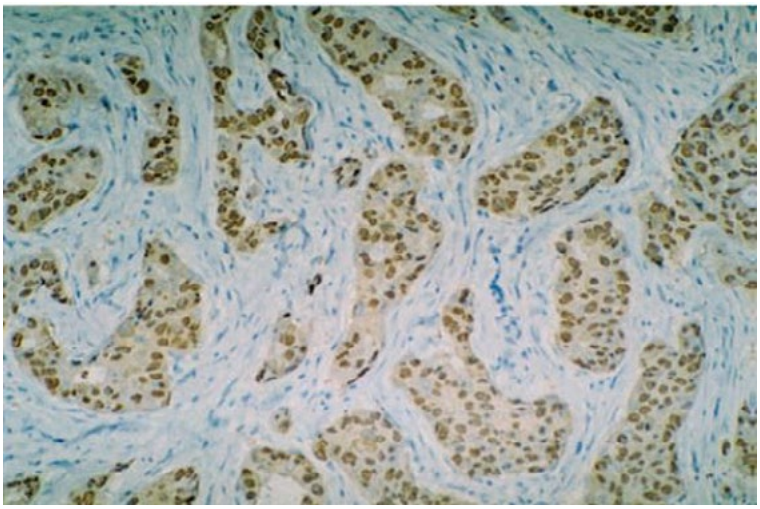

Fig2. Positivity of PR in more than 10% of tumor nucleus in a case of invasive ductal breast cancer (magnification X100)

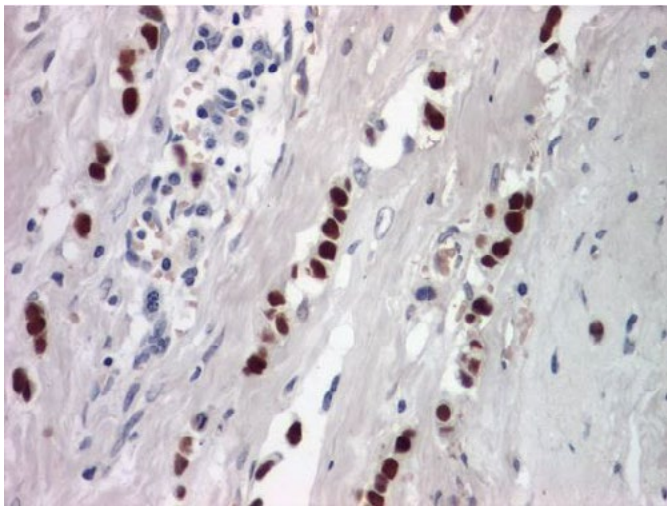

Fig3. Positivity of P53 in more than 10% of tumor nucleus in a case of invasive ductal breast cancer (magnification X100)

all samples. In this regard, no significant difference was found between the two groups. On the other hand, among the 38 samples with a family history, mitotic activity was low in 37% of sample and high in 31% of them, which shows a significant difference between the two groups. In this group, polymorphisms type 1, 3, and 2 had a frequency of 76%, 19%, and 5%, respectively. This indicates a significant difference between the two groups. Among the samples with a family history, the highest and the lowest frequency was related to tumor grade II (47%) and tumor grade I (21%), respectively, which shows no significant difference between the two groups (table 4).

Table 5 presents the results of the frequency of lesions in patients based on ER, PR, and TP53. Statistically, there is a significant difference between the two groups with and without a family history, and those with a family history showed higher negative ER/PR and positive TP53.

PCR to confirm the DNA extraction from tissue samples by β-actin amplification:

After extraction of DNA of from 84 paraffin-embedded tissue sample of breast cancer patients by the standard method, β-actin PCR was performed on all sample to ensure the extraction of DNA from tissue sample. According to the results, the bond was observed in all cases. The length of the desired

Table 4.The frequency of lesions in patients based on tumor grade

Tumor grade	The number of people with a family history (percent) (n=38)	The number of people with no family history (percent) (n=46)	Odds ratio (OR)
I	8(21%)	7(15%)	1
II	18(47%)	30(65%)	0.51
III	12(32%)	9(20%)	1.14
			χ^2 =0. 28(P~0. 6)

Table 5. The frequency of lesions in patients based on the type of ER, PR, and TP53

Types of immunohistochemical markers	The number of people with a family history (percent) (n=38)	The number of people with no family history (percent) (n=46)	Odds ratio (OR)
ER			
+	9(24%)	28(61%)	1
-	29(76%)	18(39%)	4.95
			χ^2=26. 38 (P<0. 00001)
PR			
+	12(32%)	31(67%)	1
-	26(68%)	15(33%)	4.13
			χ^2=23. 00(P<0. 00001)
TP53			
+	24(63%)	13(28%)	1
-	14(37%)	33(72%)	0.22
			χ^2=26. 00(P<0,00001)

fragment for β-actin was 99 bp.

Well M: The molecular marker has been shown as 100 bp and the wells 1 to 8 related to the positive sample of β-actin are visible with the size of 99 bp (figure 4).

Assessment of Multiplex PCR for the identification of 185delAG and 5382insC mutations in BRCA1

The results of PCR showed that 5 mutations (3 5382insC mutations and 2 185delAG mutations) were observed among the 38 samples with a family history, while one mutation of 5382insC type was found among the samples with no family history (figure 5).

Well M: the 100-bp molecular marker- Well 1: the sample containing the mutant allele of 185delAG (354 bp) and the normal allele of 5382insC (271 bp)- Well 2: the negative control sample- Well 3: the sample containing the mutant allele of 5382insC (295 bp) and the normal allele of 185delAG (335 bp)- Wells 4 and 5: the sample containing the normal allele of 5382insC and the mutant allele of 185delAG.

The results of ARMS-PCR for the identification of the polymorphism -308 on TNF-α

After performing PCR on the polymorphism -308 of TNF-α in samples with a family history, genotypes AA, AG, and GG were observed in 8, 14, and 16 cases, respectively. In addition, in samples with no family history, 25, 12, and 9 cases contained genotypes AA, AG, and GG, respectively (figure 6).

Well M: the 100-bp molecular marker- Wells 1, 2, 3, and 4: Samples containing allele G in the polymorphism -308- Wells 5, 6, 7, and 8: the sample containing allele A in the polymorphism -308.

Comparison of the frequency of 185delAG and 5382insC mutations in BRCA1 between the two groups

185delAG and 5382insC mutations in BRCA1 in patients with a family history can increase the risk of breast cancer more than in those with no family history (P<0.002)(table 6).

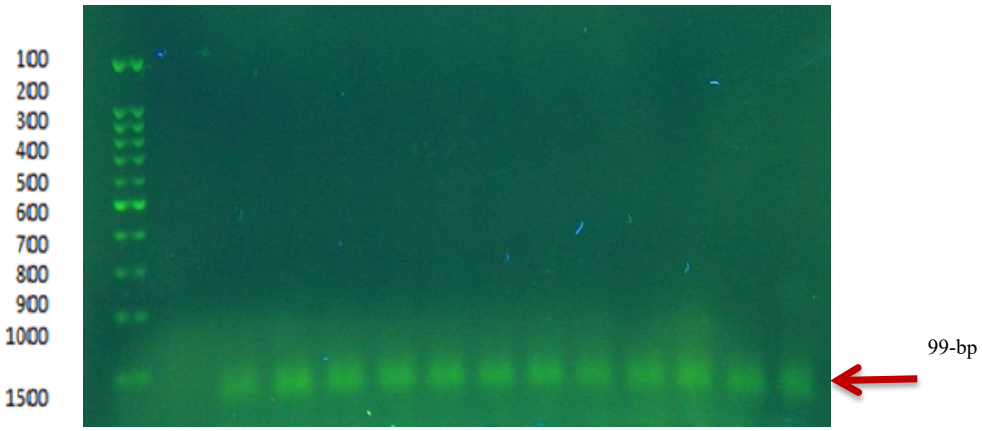

Fig4. β-actin PCR amplification showing the expected 99-bp product. M: 100-bp molecular marker; wells 1–8: positive samples

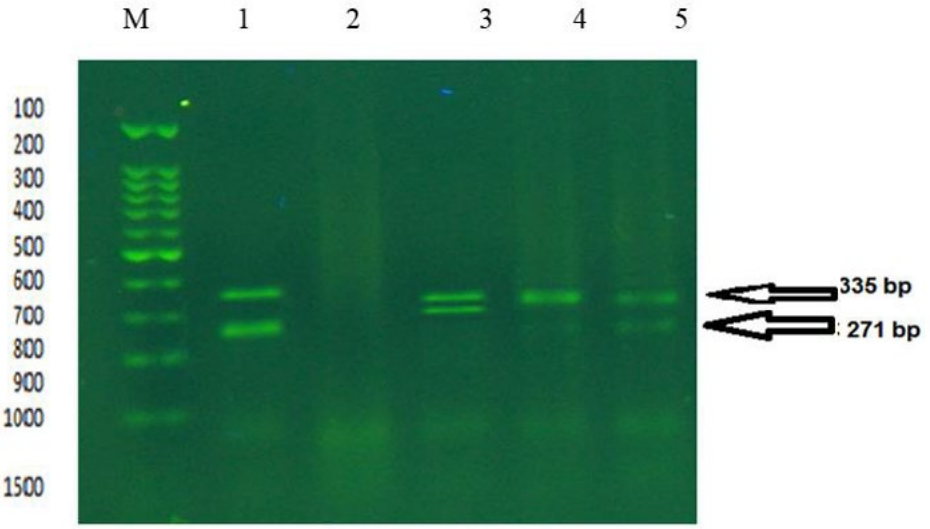

Fig5. Detection of BRCA1 185delAG and 5382insC mutations by PCR analysis. M: 100-bp molecular marker; wells 1–5: representative samples and controls

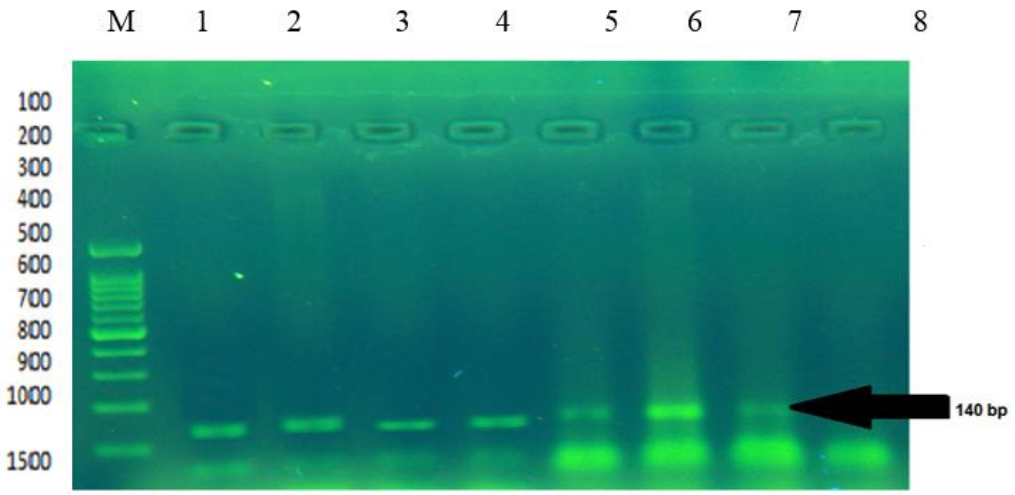

Fig6. The results of PCR for the identification of the polymorphism -308 on TNF-α

Table 6. Comparison of the frequency of 185delAG and 5382insC mutations in BRCA1 between the two groups

Types mutations in BRCA1 gene	The number of people with a family history (percent) (n=38)	The number of people with no family history (percent) (n=46)	Odds ratio (OR)
+	5(13%)	1(2%)	1
_	33(87%)	45(98%)	0.137 χ^2=10. 32(P<0,002)

Chi-square test for Trend

Table 7. Comparison of different types of genotypes in the polymorphism -308 of TNF-α between the two groups

Different types of genotypes in the polymorphism -308 of TNF-α	The number of people with a family history (percent) (n=38)	The number of people with no family history (percent) (n=46)	Odds ratio (OR)
+	5(13%)	1(2%)	1
_	33(87%)	45(98%)	0.137 χ^2=10. 32(P<0,002)

Comparison of different types of genotypes in the polymorphism -308 of TNF-α between the two groups

Genotype GG in the polymorphism -308 of TNF-α can increase the risk of breast cancer in patients with a family history (P≤0.003) (table7).

The relationship of BRCA1 mutations with Genotype GG in the polymorphism -308 of TNF-α

According to the study results, no significant difference was found between the two groups in terms of the relationship of BRCA1 mutations with Genotype GG in the polymorphism -308 of TNF-α. There is no statistical relationship between BRCA1 mutations and Genotype GG in the polymorphism -308 of TNF-α but each alone can increase the risk of breast cancer in people with a family history.

DISCUSSION

The present study investigated the association of two recurrent BRCA1 founder mutations (185delAG and 5382insC) together with the TNF-α -308 G>A polymorphism in Iranian women with familial and non-familial breast cancer. BRCA1 founder mutations were detected more frequently among patients with a positive family history than among those without a family history. Furthermore, familial breast cancer cases exhibited more aggressive clinicopathological characteristics, including higher mitotic activity, increased necrosis, ER/PR negativity, and TP53 positivity. Although these findings support an association between the investigated genetic variants and familial breast cancer, they should be interpreted cautiously because of the limited sample size and the small number of mutation-positive cases (17).

BRCA1 is one of the most extensively studied hereditary breast cancer susceptibility genes and plays a central role in DNA double-strand break repair through homologous recombination. Pathogenic variants in BRCA1 substantially increase the lifetime risk of breast and ovarian cancers and are frequently associated with triple-negative and high-grade breast

tumors. Recent international guidelines from the National Comprehensive Cancer Network (18) and the European Society for Medical Oncology (19) recommend comprehensive BRCA1 and BRCA2 testing using next-generation sequencing together with large genomic rearrangement analysis (MLPA) rather than screening for only recurrent founder mutations. Consequently, the present study, which evaluated only the two common BRCA1 founder mutations (185delAG and 5382insC), likely underestimated the true prevalence of pathogenic BRCA variants in this population.The higher frequency of BRCA1 founder mutations observed among familial breast cancer patients in our study is consistent with previous investigations conducted in Iranian populations. Forghani et al. first demonstrated the presence of recurrent BRCA1 germline mutations among Iranian women with breast cancer (8), whereas Keshavarzi et al. subsequently identified numerous pathogenic BRCA1 and BRCA2 variants using broader molecular approaches. More recently, studies employing next-generation sequencing have revealed considerable genetic heterogeneity among hereditary breast cancer patients, indicating that founder mutations account for only a subset of disease-causing variants. Therefore, our findings are consistent with previous Iranian studies while emphasizing the need for comprehensive genetic testing strategies in clinical practice.

The TNF-α -308 polymorphism has long been investigated as a potential modifier of cancer susceptibility because TNF-α is a key regulator of inflammation, immune responses, angiogenesis, and tumor progression. In the present study, the GG genotype was more frequently observed among patients with familial breast cancer. However, the current evidence regarding the association between TNF-α polymorphisms and breast cancer remains inconsistent. Several recent meta-analyses have suggested that the -308 G>A polymorphism has only a modest or population-dependent association with breast cancer susceptibility, with substantial heterogeneity across ethnic groups. Therefore, our findings should be interpreted as demonstrating an association within this Iranian cohort rather than establishing a causal role of the GG genotype in breast cancer development (20).

Interestingly, patients with familial breast cancer demonstrated more aggressive pathological characteristics, including negative ER and PR expression together with increased TP53 positivity. These observations agree with previous reports indicating that BRCA1-associated tumors frequently display basal-like pathological features, higher histological grade, increased proliferative activity, and hormone receptor negativity. Such clinicopathological characteristics are recognized as hallmarks of hereditary BRCA1-associated breast cancer and may partially explain the poorer prognosis observed in mutation carriers (21).

The TNF-α −308 polymorphism has long been investigated as a potential modifier of cancer susceptibility because TNF-α is a key pro-inflammatory cytokine involved in immune regulation, angiogenesis, and tumor progression. In the present study, the GG genotype was more frequently observed among patients with familial breast cancer. However, the evidence regarding the association between the TNF-α −308 G>A polymorphism and breast cancer susceptibility remains inconsistent. Previous meta-analyses have reported no consistent overall association, while subgroup analyses have suggested that the magnitude and direction of the association may vary according to ethnicity. Substantial differences between populations and study results further suggest that the potential effect of this polymorphism may be population-dependent. Therefore, our findings should be interpreted as an association observed within this Iranian cohort rather than as evidence of a causal role for the GG genotype in breast cancer development (22).

Interestingly, patients with familial breast cancer demonstrated more aggressive pathological characteristics, including negative ER and PR expression together with increased TP53 positivity. These observations agree with previous reports indicating that BRCA1-associated tumors frequently display basal-like pathological features, higher histological grade, increased proliferative activity, and hormone receptor negativity. Such clinicopathological characteristics are recognized as hallmarks of hereditary BRCA1-associated breast cancer and may partially explain the poorer prognosis observed in mutation carriers (23).

Several limitations of this study should be acknowledged. First, the relatively small sample size, particularly the low number of BRCA1 mutation-positive cases, limited the statistical power to detect modest genetic associations and precluded reliable multivariable regression analysis. Therefore, the findings should be considered exploratory rather than definitive. Second, because the study included only patients with breast cancer, comparisons were restricted to familial and non-familial cases rather than patients and healthy controls. Consequently, the observed associations should be interpreted as reflecting familial breast cancer status rather than overall breast cancer susceptibility. Third, only the two recurrent BRCA1 founder mutations (185delAG and 5382insC) were evaluated, whereas comprehensive BRCA1 sequencing, BRCA2 analysis, and multiplex ligation-dependent probe amplification (MLPA) were beyond the scope of the present study. As a result, additional pathogenic variants may have remained undetected. Finally, DNA quality parameters obtained from

FFPE tissues were not systematically documented, representing another methodological limitation.

Despite these limitations, the present study provides valuable population-specific data on the distribution of BRCA1 founder mutations and the TNF-α −308 polymorphism among Iranian women with familial breast cancer. By integrating molecular findings with clinicopathological characteristics, this study contributes additional evidence regarding hereditary breast cancer in an understudied population and provides a foundation for future multicenter investigations incorporating larger cohorts, healthy control groups, comprehensive BRCA1/BRCA2 sequencing, functional validation, and robust multivariable statistical analyses.

CONCLUSION

In this study, BRCA1 founder mutations (185delAG and 5382insC) and the TNF-α -308 GG genotype were observed more frequently among patients with familial breast cancer than among those without a family history. In addition, familial cases were characterized by less favorable clinicopathological features, including higher mitotic activity, increased necrosis, ER/PR negativity, and TP53 positivity.

These findings suggest that the investigated BRCA1 founder mutations and the TNF-α -308 polymorphism may be associated with familial breast cancer in this Iranian cohort. However, given the relatively small sample size, the limited number of mutation-positive cases, the absence of a healthy control group, and the evaluation of only two recurrent BRCA1 founder mutations, the results should be interpreted as exploratory rather than definitive. Furthermore, no causal relationship can be inferred from the present findings.

Larger multicenter studies incorporating healthy controls, comprehensive BRCA1 and BRCA2 sequencing, large genomic rearrangement analysis (MLPA), and multivariable statistical analyses are warranted to validate these observations and to further clarify the potential clinical significance of these genetic markers in hereditary breast cancer risk assessment.

Recommendations

The findings of the present study support the need for larger, multicenter investigations integrating molecular and clinicopathological data to improve the understanding of hereditary breast cancer in the Iranian population. Future studies should evaluate recurrent BRCA1 founder mutations together with comprehensive BRCA1/BRCA2 sequencing, additional susceptibility genes, and inflammatory biomarkers to provide a more complete assessment of hereditary breast cancer risk. Incorporating detailed clinicopathological characteristics, including age at diagnosis, tumor subtype, hormone receptor status, tumor grade, mitotic activity, and other established prognostic factors, may further improve genetic risk stratification and facilitate the identification of clinically relevant molecular signatures. Prospective studies involving younger women and healthy control populations, together with functional analyses of the TNF-α −308 polymorphism, are warranted to validate the present findings and to clarify the potential role of these molecular markers in early risk assessment, personalized screening strategies, and precision oncology.

Authors's Contribution

Z.B. contributed to the study conception and design, data collection, laboratory investigations, data analysis, and interpretation of the results, and drafted the manuscript. M.H. contributed to the study design, supervision of the laboratory investigations, interpretation of the findings, and critical revision of the manuscript. H.R. contributed to the study design, supervision, interpretation of the results, and critical review of the manuscript. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Ethics approval and consent to participate

Not applicable.

Conflict of Interest

The authors declared no conflict of interest.

Consent for publication

Not Applicable.

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