Research Article
Volume 15:4, 2021

Journal of Molecular and Genetic Medicine

ISSN: 1747-0862 Open Access

The Investigation of the Relation of rs7816345, rs17001868 and rs3788577 Polymorphisms with Breast Cancer in the Population of East Azerbaijan

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Abstract

Introduction: Breast cancer is one of the most common types of cancer among women and is the first cause of cancer deaths in women. According to world health statistics, one out of every 8 to 10 women develops breast cancer. According to Iran statistics, out of every 10 to 15 women in our country, one woman has probably breast cancer, so the aim of this study was to investigate the relation between *ADSL* gene rs3788577 polymorphism, rs7816345 polymorphism (near *znf703* gene) and rs17001868 polymorphism associated with *SGSM3* gene with breast cancer in the population of East Azerbaijan.

Methods: In this study, 100 samples from patients with breast cancer and 100 blood samples from healthy individuals were selected as control group. Then, according to the protocol, DNA was extracted from all samples with the DNA extraction kit. Electrophoresis was then carried out to assure the quality of the extracted DNA, and quantified by spectrophotometer. The samples were then PCR-amplified with specific primers and finally "PCR products were treated with the restriction enzyme and electrophoresed on agarose gel". Data were analyzed by SPSS software version 10 using descriptive and chi-square tests and significance level less than 0.05 was considered.

Results: The results of *ADSL* gene rs3788577 polymorphism analysis showed that the percentage of G allele was 14.5% and 18.1% in healthy and diseased individuals, respectively. Examination of these data shows that the G-allele has a 44% increase in diseased people compared to healthy people. The results of *SGSM3* gene polymorphism 17001868 showed that the percentage of T-allele was 15% and 21.5%, respectively. The examination of these results showed that T-allele increased 6.5% in healthy individuals and also rs7816345 polymorphism results showed that the percentage of T-allele in healthy subjects was reported to be 44.5% and 69.5%. Examination of these data shows that the T-allele has an 11% increase in diseased people compared to healthy people.

Discussion: Polymorphism analysis of rs378857 rs7816345 showed that there is probably a relationship between increased G allele (44%) and increased T allele (25%) respectively and the incidence of breast cancer and its prevalence in Azerbaijan population. On the other hand, rs 17001868 polymorphism analysis showed that there is "probably no relation between the T allele increase (by 6.5%) and the incidence of breast cancer.

Conclusion: Given that current methods of treatment for all types of cancers have serious consequences, discovering new ways to diagnose the disease early by identifying specific biomarkers for that type of cancer is essential and can open new therapeutic horizons.

Keywords: *Breast cancer • Polymorphism • rs3788577 • rs7816345 • rs17001868*

Introduction

Cancer is a dynamic process that causes cellular molecular alterations, interfering with its proliferation system by numerous unknown and independent variables. Cancer is responsible for more than 20% of all deaths [1]. Breast cancer, with a 25.5% share among cancers, is the first major cause of cancer deaths and deaths among women worldwide and in Iran as well. So that every three minutes, one woman in the United States gets breast cancer. Over 502,000 women die each year from this type of cancer. Global studies have shown that the number of patients with breast cancer is increasing. West Asia is one of the areas with the highest incidence of cancer. Since Iran is located in this region, the incidence of breast cancer has increased in Iran [2].

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Received 10 March, 2020; **Accepted** 24 May 2021; **Published** 31 May 2021

The Asian National Census Bureau reported that the prevalence of breast cancer in Iran was 21.4% [3]. Newly available methods can only help 60% of breast cancer patients with diagnosis and treatment. If breast cancer is diagnosed at an early stage, more than 90% of patients will be treated and it will reduce their mortality. Early detection of breast cancer is a screening procedure and one of the most important methods of breast cancer screening can be self-examination by a physician. Mammography noted.

Your head swells out of the money supply at the top of your head, with a higher growth rate, higher in the lungs or in the lungs [4]. Tumorigenesis is a complex cancer that is affected by many factors including age, geographic diversity, lifestyle and genetic factors [5]. Available evidence suggests that breast cancer is the result of an interaction between genetic elements and possible environmental factors. Ethnicity also plays an important role in the risk of breast cancer with the lowest incidence in certain groups of Asian women to the highest incidence in Caucasian women.

Polymorphisms are genetic variants whose rare alleles occur in a population with a frequency of at least 1%, regardless of their functional or pathogenetic significance [6,7]. Polymorphisms, or SNPs, are also referred to as individual genetic differences that are associated with the susceptibility to certain diseases.

Research shows that mutations and polymorphisms of genes associated with breast cancer play an important role in the prognosis and prediction of tumor formation, so that the diversity of the ESR1 allele is associated with the risk of breast cancer in whites, with specific clinical features including family history of breast cancer and lymph node metastasis are related, although this effect has sometimes been reported as positive or sometimes negative. At present, little is known about the expression of the ESR1 gene, the rate of mutation, and its allelic diversity in breast cancer among Azerbaijanis, especially those residing in Iran. Rs3788577 *ADSL* Gene-Related Polymorphism one of the polymorphisms associated with breast cancer. The *ADSL* gene is present in the 22q13.1-13.2 gene locus. This gene lasted 6 kb in humans and was fully sequenced by Kmoch in year 6. The coding sequence of this gene consists of 5 bp, which encodes a 5-amino acid protein. Molecular analysis studies of the affected families revealed four distinct mutations in these families. According to the latest update to the human gene mutation database, about 3 point mutations have been identified for this gene. Most of these mutations are heterozygous. Most of these mutations are replacement mutations, of which the most common R426H mutation was identified in all families. The results of GWAS studies also indicate that there are many genetic variants called SNP single nucleotide differences that may be related to breast cancer susceptibility. Examination of these polymorphisms or individual genetic differences in different populations can greatly increase the detection power.

Linkage studies and GWAS over the past years have identified a large number of SNPs associated with breast cancer that have been assigned to specific loci, including the rs7816345 polymorphism near the *ZNF703* gene. The rs7816345 polymorphism is an SNP in chromosome 8 human and is associated with breast size. This polymorphism is located in the chromosomal region of 8p11.23 and is commonly associated with estrogen receptor (ER) -dependent breast cancer with clinical implications. *ZNF703* is the only gene close to this region, possibly an oncogenic stimulus of this hyperactivity (8). *ZNF703* (Zinc finger protein 703) is a new oncogenic breast cancer oncogene and a prognostic marker and therapeutic target in ER positive (estrogen receptor) breast cancer. This gene is located in the chromosomal region of 8p12 *ZNF703* exerts a downregulating effect on the β-TGF signaling pathway. It also cooperates with a form of p53 [8].

Another polymorphism associated with breast cancer is rs17001868 polymorphism

According to GWAS studies, the association of this polymorphism with mammographic density of breast cancer risk has been demonstrated. The rs17001868 polymorphism is located in the 22q.31 gene region of the *SGSM3* gene. The *SGSM3* gene is short for the term 3 Small G protein signaling modulator and is in fact a modulator of small G protein signaling [9]. The G family of proteins or proteins bound to guanosine nucleotide, are proteins that convert guanosine triphosphate GTP to guanosine diphosphate to GDP [10]. The *SGSM3* gene is naturally expressed in immune, neural, muscular, and reproductive and many other tissues [10]. The class of protein gene products is a type of intracellular and membrane protein. Molecular function of this gene is as follows: GTPase17 activation and cell cycle arrest, intracellular transport of a vesicle protein from the plasma membrane to endosomes and then Rap protein signal transduction, Rap signal transduction (16 and regulation of vesicle fusion) [10-14]. The *SGSM3* antibody is most expressed in normal breast tissue, whereas its expression is moderate in breast cancer tissue [6].

Therefore, considering that cancer, as one of the problems of the human society, by threatening human beings in all age groups, it causes great financial, vital, economic, social and familial burden. Among the different types of cancer, breast cancer is one of the most common and leading cause of death in the world and the second most common cancer after lung cancer in the world, and the main cause of cancer deaths in women, because of the link between breast cancer and SNP varies across populations and races. Assessment of the polymorphism complex for each specific population and race seems necessary, and any research on identifying the causes and causes of breast cancer in women can be of great help in the prevention and treatment of breast cancer. Therefore, the present study investigates the relation of rs3788577 polymorphism with *ADSL* polymorphism Vrfysm rs7816345 (near genes *znf703*) and Ply¬Mvrfysm 17001868 rs *SGSM3* gene linked to breast cancer in the population Zrbayjan¬Shrqy to find any relation between this polymorphism and clinical characteristics Mvrfysm¬Ha in Iran.

Research Methodology

The present study was a case-control study to investigate the relation between *ADSL*- related rs3788577 polymorphism, rs7816345 rs7816345 polymorphism (near *znf703* gene) and *SGSM3*-dependent rs 17001868 polymorphism in a population of women with breast cancer. The donor was taken to Tabriz Martyr Madani Hospital between April and May in the Genetic Laboratory of Azad University of Bonab. Blood samples were collected from 3 uninfected women and 3 women with breast cancer with complete consent of health and fertility data. Demographic data of patients referred such as age, sex, metastasis or not, etc. were obtained. From the ethical considerations, consent was obtained from patients and approved. Patients' information remained confidential. After obtaining consent from patients with breast cancer at Shahid Madani Hospital, 100 blood samples were collected and coded in oxalate (anticoagulant) tubes. Specimens prepared by cold chain preservation were transferred to the genetic laboratory of Bonab Azad University for laboratory research and stored at -21°C. Laboratory procedures were first performed for blood samples taken from patients according to the following steps. After the procedure was completed, all procedures for blood samples taken from healthy individuals were repeated.

Genomes were first extracted from blood samples from the target population. To extract DNA, all tubes and heads were sterilized with autoclave. Then DNA extraction was performed according to the protocol instructions. In this study, DNA was extracted from the DNA of the cina clone. Gel-electrophoresis technique was used to ensure the quality of the extracted DNA. Then the extracted DNA was amplified with specific primers for each polymorphism by PCR technique. The primers were designed with Oligo 7 software. The sequences of primers used in this study were as follows:

For PCR, primers F and R were diluted to a ratio of 5.1. An empty 0.5 ml microtube was prepared on ice and poured into 1 µL of F primer and 1 µL of diluted R primer. Then 12.5 µL of Master Mix and 9.5 µL of deionized water were transferred to the same microtubule and its contents were spin slowly for a short time, then 1 µL was transferred into the extracted DNA microtope contents and a short spin slowly spin was done. Finally, microtubes with a final volume of 25 µl were inserted into the PCR machine. After the samples were placed in a thermocycler, the device was adjusted to Table 1. To ensure the quality of the PCR product, the fragment was amplified on agarose gel 1. The% stained with ethidium bromide was electrophoresed (Tables 1-4).

Genotyping

The RFLP method was used to determine the genotype of rs7816345 polymorphism. The PCR product was subjected to TaqI restriction enzyme (Frementas Co.). Post-cut fragments were expected for genotype CC 152-22 and genotype TC174-152-22 and for genotype TT174, respectively. PCR products were treated with Hpa II restriction enzyme (BsiS I) (MSP I). The fragments after enzyme cleavage were for genotype GG18-59-141, for GA18-59-177-141 and for AA77-141 genotype, respectively. Waiting in order to observe and evaluate the rs17001868 polymorphism in the studied samples, the procedure was pre-treated and treated with SSPI enzyme, for AA genotype 23-135 for CC 158 and for AC genotype 15-135-15.

First, 10 microliters of the PCR product of one sample was poured into the microtube then 18 microliters of deionized water was added. It was also added 2 µL of buffer and 2 µL of restriction enzyme. It was then gently mixed with pipetting and the microtope lid was tightly closed and paraffin-embedded. These steps were repeated for other samples. Finally, the microtubes were incubated in bin Marie at 65°C for 16h. To investigate the effect of this enzyme, enzyme-treated products were observed by gel electrophoresis and gel staining.

Agarose gel was incubated in ethidium bromide solution for 20 minutes to see staining. Finally, the gel was transferred to the Trans Illuminator and bands

Table 1. Sequences of primers used in the study (rs7816345 polymorphism).

Primer name	Primer sequence	Length
Forward	**'3** -TAGGAATATTTTGGGTTGTA**-'5**	**20**
Reverse	**'3**-AATAAGGTGTGGAAGTTGTAA**-'5**	**21**

Table 2. Sequences of primers used in the study (*ADSL* gene rs3788577 polymorphism).

Primer name	Primer sequence	Length
Forward	**'3** -AAGAGGAAAGGAATAAAAA**-'5**	**19**
Reverse	**'3**-GAGAAAGAGGAATGATGAGAT**-'5**	**21**

Table 3. Sequences of primers used in the study (*SGSM3* gene rs17001686 polymorphism).

Forward Primer - 1	ATAAATGGAAGAACTGGTGGAATAT
Reverse primer - 2	TCATGATGTGAAATGAGAGAATAAGA

Table 4. Time and temperature schedule of the PCR Device.

Number of cycles	Time	Temperature (°C)	Stage
1	10 min	95	Primary denaturation
34	1 min	95	Denaturation
	1 min	*	Primer connecting
	1 min	74	Elongation
1	5 min	74	Final elongation

containing cut DNA fragments were observed and photographed. At the end, all data were analyzed by SPSS version 21 using descriptive and chi- square tests and significance level less than 0.05 was considered significant.

Findings

Patients' demographic data were obtained from the hospital, including information such as patient age, patient sex, metastasis or non-metastatic, bilateral or unilateral, cancer, pregnancy and delivery records, lactation history, disease progression. In terms of gender, 2 blood samples from female patients with breast cancer and 3 healthy blood samples were selected as the control group. The other factors mentioned above were not included in the results due to disapproval from Tabriz University of Medical Sciences. Chi-square test was performed on the data of frequency of genotypes (Table 5).

The results of chi-square test showed that the significant values in rs7816345 and rs3788577 were equal to zero. Therefore, it can be generally said that there is a significant difference between the frequency of genotypes between the healthy group and the patient group. ($P < 0.05$) while the results showed that in rs17001868 between healthy and diseased individuals, CC genotype had the highest and AC genotype had the least frequency and the significant value (P) was 0.45. The results showed that there was no significant difference ($P > 0.05$) between genotype and patient group in frequency of genotypes at rs17001868.

The results also showed that among healthy people, rs3788577 had the highest AA genotype and the lowest GG genotype, and the sick GG genotype had the highest frequency and the lowest AA genotype. The frequency of AA, GG and AG genotypes was significantly different in healthy and diseased individuals ($P < 0.05$).

Results and Discussion

Frequency study of alleles in the target population

After obtaining the genotypes and their frequency, allele frequencies and percentages were calculated based on Hardy-Weinberg principle (Table 6).

The results show that at rs7816345 the T allele was most frequent in patients and showed a 25% increase in healthy individuals. The C allele was also more common in healthy subjects and showed a 25% increase in patients. These comparisons indicate that there may be a relationship between increased T allele and breast cancer. The results also showed that the rs3788577 G allele had the highest frequency in patients and a 44% increase in healthy subjects. The A allele was also more common in healthy subjects and showed a 44% increase compared to the diseased individuals, which suggests that there may be a link between increased G allele and breast cancer. On the other hand, analysis of rs 17001868 polymorphism in *SGSM3* gene showed that there is probably no relationship between T allele increase (6.5%) and breast cancer incidence.

Breast cancer is one of the most common types of cancer that causes many deaths each year among men and women, and despite many advances in early diagnosis and appropriate treatment, still remains the leading cause of death cancer among women [12]. Although newer approaches to breast cancer are being introduced every day, the disease still puts many at risk. More attention may be paid to the molecular structure and biological basis of the disease, but it may be possible to obtain more information on the development and pathogenicity of this fatal disease by further knowledge of how it occurs at the cell surface [13].

In general, cancer can be considered as a heterogeneous disease, in addition to numerous environmental factors, genetic alterations such as genetic polymorphisms can also be contributing factors to the risk of cancer [14,15]. The findings suggest that single nucleotide polymorphisms (SNPs), which, as genetic variation determines phenotypic variation among individuals, are involved in susceptibility to cancers and disease progression. Study of DNA polymorphisms in human genetics and chromosomal location of genes related to hereditary diseases in the context of abnormalities caused by multiple natural and genetic factors such as heart disease, cancer, diabetes, depression, etc. Harmful factors as a risk factor that increase the risk of these diseases can be fruitful [16].

Unfortunately, the disease is often diagnosed at its advanced stages, leading to a poor prognosis. Although a variety of screening methods are available for early detection, their diagnostic value is limited due to a lack of sensitivity, high cost, or inconvenience to the patient. Therefore, identifying early diagnostic biomarkers before the disease progresses and even informing the healthy individual of their potential for breast cancer can be very helpful.

Table 5. Chi-square test results to compare the frequency of two groups of patient and healthy according to genotypic variable classes.

Variables		Types	Group		Chi square	P-value
			Healthy	Diseased		
Rs7816345		TT	39	61		
polymorphism	Genotype	CC	50	22	17/015	0
(near znf703 gene)		TC	11	17		
Rs17001868		AA	12	18		
polymorphism	Genotype	CC	82	75	1/5	0.45
(related to SGSM3 gene)		AC	6	7		
Rs3788577		AA	77	24		
polymorphism	Genotype	GG	6	41	60/106	0
(related to ADSL gene)		AG	17	35		

Table 6. Percentage of alleles studied and their percentage difference in healthy and diseased subjects.

Variables	Allele name	Allele percentage in diseased subjects	Allele percentage in healthy subjects	Difference percentage in diseased and healthy subjects
Rs7816345 polymorphism	T	69/5%	44/5%	25%
	C	30/5%	55/5%	25%
Rs17001868 polymorphism (related to SGSM3 gene)	A	21/5%	15%	6/5%
	C	78/5%	85%	6/5%
Rs3788577 polymorphism (related to ADSL gene)	A	41/5%	85/5%	44%
	G	58/5%	14/5%	44%

Therefore, one of the variables studied in this study was the relation of rs3788577 single nucleotide polymorphism with *ADSL* gene, with breast cancer occurrence in East Azerbaijan population. In the present study, the frequency of single nucleotide A/G polymorphism was investigated. The results showed that in healthy individuals the frequency of genotypes were AA=77%, GG=6% and AG=17%, and in healthy individuals the frequency of genotypes were AA=24%, GG=41% and AG=35% was calculated. The percentage of A allele in healthy and diseased individuals was 85.5% dna 41.5%, ysevstcepser, dna the vsytsncdes of G allele in healthy and diseased individuals was 14.5% and 58.5%, respectively. Examination of these data shows that the G allele has a 44% increase in diseased people compared to healthy people, and the A allele shows a 44% decrease in diseased people compared to healthy people. This indicates an increase in the A allele (up to 44%) and the incidence of breast cancer.

A protein encoded by the *ADSL* gene belongs to the Lyase 1 family. This enzyme is involved in purine metabolism and catalyzes two types of non-consecutive reactions in the purine biosynthesis pathway. Mutations in this gene are associated with adenylucoxinase deficiency, which is an abnormality with symptoms of psychological retardation, epilepsy or autistic features [17]. The relation of rs3788577 single nucleotide polymorphism with *ADSL* gene with breast cancer has not been studied at home and abroad. Unfortunately, or fortunately, very few studies have been done on the polymorphism of this gene in the world and more studies have been done on animals such as chickens and pigs.

Genetic polymorphisms can be associated not only with the occurrence of diseases but also with the occurrence of some non-disease-related features. In a study by Zhang et al. on the relation of *ADSL* and LPL polymorphisms with meat quality in chickens, they concluded that the polymorphisms of these genes could be affected by differences in meat quality in breeds. Different chickens are related [18]. In a similar study by Lim et al., They concluded that the single nucleotide polymorphism of the *ADSL* gene affects the quality and efficiency of Korean beef [19]. These two recent studies may be related to this study in terms of phenotype association with *ADSL* polymorphism, which is the gene studied in this study. Masvinkle also reported in 1997 d TaA a mutation in an *ADSL*D gene in a newborn with *ADSL*D [20].

GWAS is one of the best methods for identifying genetic factors that predispose to complex and multifactorial diseases such as breast cancer, in which the prevalence and frequency of a specific allele in patients is compared to healthy controls (control group). It takes. These types of studies show polymorphisms of different genes as genetic risk factors for association with a particular type of disease in populations [21]. But one of the important genes that has a strong association with breast cancer is *ZNF703*, which is located in the chromosomal region 8p12. The importance of this gene in our study is that the polymorphism studied in our study (rs7816345) is close to this gene. The results of the present study show that the T allele shows a 25% increase in diseased individuals compared to healthy individuals, and the C allele shows a 25% decrease in diseased individuals compared to healthy individuals. These findings are significant, and the results indicate a possible association between an increased T allele (up to 25%) and the incidence of breast cancer. The relationship between the expression of this gene and the incidence of luminal B breast cancer was investigated by Sircolumb et al. The results of this study showed that increased expression of *ZNF703* occurs in luminal B tumors, and the results showed that it plays a role in regulating the population of luminal B stem cells through transcriptional control of cellular processes [5].

Another study of the association between polymorphism and breast cancer is the study of Hong et al., Whose results showed that the distribution of IL-1α gene polymorphism (rs3783553/- rs378) was significantly different between patients and groups. The evidence is different and correlated with age, age of menarche, and geographical differentiation. "They also evaluated the potential association between overexpression polymorphism (rs 3783553) and breast cancer risk and showed the frequency of ins/ins (ttca/ttca) and our ins allele (ttca) were significantly different between the control and patient groups, and in another study by Holland et al. AHS 307FNZ gene was shown to be common in the development of Luminal B cancer and regulates basal and luminal precursors in human breast epithelium [22,23]. *ZNF703* gene activity as an oncogene in gastric cancer progression also specified [24]. rs7816345 is located in the 8p12 region, which is commonly present in high-grade luminal B cancers that contain estrogen receptors (ER) and have poor clinical outcomes [25]. *ZNF703* is regulated by estrogen and is a cofactor for the nuclear suppressor complex that plays an important role in regulating ER activity. It is

also involved in the regulation of cell proliferation cells and its overexpression leads to increased breast cancer stem cells [5,23]. Interestingly, *ZNF703* exerts a downstream effect on the TGF beta signaling pathway and also cooperates with a form of p53 [23,26].

A 2012 study by Ericsson and colleagues on the effect of genetic variation on breast size and its association with breast cancer risk in European women revealed that rs7816345 polymorphisms near *ZNF703*, rs4849887 and rs17625845 flanking INHBB, rs12173570 near ESR1, rs7089814 at ZNF365, rs12371778 near PTHLH, and rs62314947 near AREG, of which the three polymorphisms (*ZNF703*, INHBB, AREG) were most associated with breast density and cancer risk [8].

This study showed similar results with our study in terms of relation between rs7816345 polymorphism and breast cancer.

Another study was conducted in 2014 by Sawyer and colleagues with relation to the genetic susceptibility of immobilized lobular breast cancer. The study showed that invasive lobular carcinoma (ILC) accounts for 10 to 15 percent of all breast cancers. Genomic studies in this study have identified more than 75 common breast cancer polymorphisms, most of which include ductal cancer (IDC). Important polymorphisms for (ILC) include rs11249433/1p11, rs2981579/10q26/FGFR2 and rs10995190/10q21/ZNF365 and for IDC include 5 p12/rs10941679; rs2588809 /41q41/414DTa, rs6472903/8q21 and rs1550623/2q31/CDCA7 [27]. This study demonstrates the relation between polymorphism and breast cancer, which was also identified in our study. In the present study, the probability of relation between rs7816345 polymorphism and breast cancer was determined. Therefore, the aforementioned polymorphism can be suggested with closer examination as a marker to identify the potential of breast cancer in different populations.

Another polymorphism examined in the present study is the *SGSM3* gene rs17001868 polymorphism. The results of this study showed that in rs17001868 between healthy and diseased individuals, CC genotype had the highest and AC genotype had the least frequency and there was no significant difference between genotypes between healthy and patient group. In fact, the results indicate that there is no relation between the T allele increase (6.5%) and the incidence of breast cancer.

Tan Tan and colleagues (1999) examined the relation between the genetic diversity of ESR1 and *SGSM3* genes with the susceptibility of breast cancer in the Chinese female population to the statistical population of 3 breast cancer patients and 4 controls in 2016. The expression level of *SGSM3* and ESR1 genes was significantly lower in breast tumor compared to healthy breast tissue (0.8 vs 0.8, $P < 0.001$). In addition, rs17001868 may be a predictive type of function that can affect *SGSM3* expression in patients with BC. This means that the presence of the rs17001868 polymorphism in the *SGSM3* gene may be associated with breast cancer [28]. A 2015 study by Jenifer Ston and colleagues about the relation between breast cancer prevalence and mammographic density with high risk prediction. In a study conducted among four women, they found that dense breast tissue regions have been linked to the rs17001868 polymorphism in the *SGSM3* gene and the risk of breast cancer [29].

Also in a study conducted by Shivaani Mariapun on lifestyle and genetic factors of mammography density in Malaysian women in year 2, they found that the rs 17001868 vrerpryvheep in *SGSM3* gene is associated with dense breast tissue in findings. Mammography is related. He believes polymorphisms (rs10034692, rs2046210, rs10484919, rs7816345, rs703556, rs7289126, rs17001868, rs4849887, rs10941679, rs17817449, rs1781244, rs62314, rs62314 will increase [30].

In a two-year study in 2015, Rudolph and colleagues investigated a comprehensive evaluation of the interplay between genetic variation and the use of hormone therapy in menopause on mammography density in four postmenopausal women and concluded that potential interactions in mammography density between current use of hormone therapy in menopause and the rs 17001868 polymorphism in the *SGSM3* gene is also recognized. 23-rs7816345, LSP1-rs3817198, IGF1-rs703556, 12q24- rs1265507, TMEM184B-rs7289126) are also associated with mammographic density [31].

In a conducted study by Marques and colleagues in October 2017 on the relation of insertion deletion polymorphisms with colorectal cancer risk, they concluded that *SGSM3* gene polymorphisms are associated with an increased risk of colorectal cancer [32]. In a study carried out by Lindstrom and colleagues in 2014, the relation between different gene loci including *SGSM3* gene with breast cancer and mammography density was investigated. They concluded that the *SGSM3* gene- related rs17001868 polymorphism had a direct relationship with mammography density and incidence of breast cancer, which was not consistent with the results of the present study [9].

Conclusion

All the aforementioned studies and the results of our study show that the presence of different polymorphisms can contribute to the development of susceptibility to diseases such as breast cancer, depending on the race and geographical position. Depending, the discovery of this relationship requires further studies. The types of polymorphisms that cause genetic variation that determine phenotypic variation among individuals appear to be involved in susceptibility to disease and disease progression. Given that gene polymorphisms are one of the risk factors for breast cancer and because these gene polymorphisms show different distribution in different geographical communities and regions, therefore, the study candidate gene variants in different populations are needed to find out their association with breast cancer, and given that current methods of treating various cancers have serious consequences, discovering new methods for early detection. The disease can open new therapeutic horizons by identifying specific biomarkers for that type of cancer.

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How to cite this article: Pour, Parisa Malek. "The Investigation of the Relation of rs7816345, rs17001868 and rs3788577 Polymorphisms with Breast Cancer in the Population of East Azerbaijan." J Mol Genet Med 15 (2021): 491.