European Review for Medical and Pharmacological Sciences 2023; 27: 3088-3095

SOD1 gene variants rs4817415, rs2070424, and rs1041740 and their association with breast cancer risk

M.P. GALLEGOS-ARREOLA[1], M.G. MÁRQUEZ-ROSALES[1], B.C. GÓMEZ-MEDA[2], G.M. ZÚÑIGA-GONZÁLEZ[3], A.M. PUEBLA-PÉREZ[4], A.L. ZAMORA-PÉREZ[5], J.I. DELGADO-SAUCEDO[4], L.E. FIGUERA[1,6]

[1]División de Genética, Centro de Investigación Biomédica de Occidente (CIBO), Centro Médico Nacional de Occidente (CMNO), Instituto Mexicano del Seguro Social (IMSS), Guadalajara, Jalisco, México
[2]Departamento de Biología Molecular y Genómica, Instituto de Genética Humana "Dr. Enrique Corona Rivera", Centro Universitario de Ciencias de la Salud (CUCS), Universidad de Guadalajara (UdeG), Guadalajara, Jalisco, México
[3]División de Medicina Molecular, CIBO, CMNO, IMSS, Guadalajara, Jalisco, México
[4]Laboratorio de Inmunofarmacología, Centro Universitario de Ciencias Exactas e Ingenierías, CUCS, UdeG, Guadalajara, Jalisco, México
[5]Departamento de Clínicas Odontológicas Integrales, Instituto de Investigación en Odontología, CUCS, UdeG, Guadalajara, Jalisco, México
[6]Doctorado en Genética Humana, CUCS, UdeG, Guadalajara, Jalisco, México

Abstract. – OBJECTIVE: The aim of this investigation was to determine the frequency and association of the variants rs4817415, rs2070424, and rs1041740 of the *SOD1* gene in healthy women and breast cancer (BC) patients.

PATIENTS AND METHODS: Genomic DNA samples from 146 healthy women and 130 patients with BC were analyzed.

RESULTS: GG genotype (OR 2.54, 95% CI 1.31-4.91, $p = 0.0073$) and the G allele (OR 1.37, 95% CI 1.09-1.73, $p = 0.007$) of the rs2070424 variant and CC genotype (OR 1.67, 95% CI 1.04-0.2.70, $p = 0.0444$) and allele C (OR 1.58, 95% CI 1.09-2.29, $p = 0.0183$) of the rs1041740 variant of *SOD1* gene were associated as risk factors for BC susceptibility relative to the control group. Study groups comparison of the stratification by menopausal status showed an association of susceptibility to BC risk with carriers of the GG genotype (OR 2.9, 95% CI 1.11-7.81, $p = 0.042$) of the rs2070424 variant and with the premenopausal status of the study group and the TT (OR 2.89, 95% CI 1.73-4.85, $p = 0.001$) genotype of the rs1041740 variant. Furthermore, differences were observed in the patients with BC who were carriers of the CC genotype of the rs4817415 variant with elevated Ki-67 (≥ 20%) and who presented lymph node metastasis and stage III-IV BC ($p<0.05$). Two common haplotypes were identified in the study groups: CAC (protective factor), and CGC (risk factor) ($p<0.05$).

CONCLUSIONS: The rs2070424 and rs1041740 variants of the *SOD1* gene and the CGC haplotype were associated as risk susceptibility factors of BC in this sample analyzed.

Key Words:
Variants, Rs4817415, Rs2070424, Rs1041740, *SOD1*, Breast cancer.

Introduction

Among the neoplastic diseases that affect women, breast cancer (BC) is the most common worldwide[1]. In Mexico, the incidence of BC has been observed[1-3] to increase in young women, and it is one of the major causes of mortality. Epigenetic events are thought[1-5] to influence the transformation of normal cells from breast tissue to a tumor cell. Superoxide dismutases (SODs) are enzymes that participate in the cellular defense of removing agents that generate oxidative stress, generally superoxide-type free radicals or reactive oxygen species (ROS), and their overexpression has often been observed[6] in different diseases, including cancer.

In mammals, three isoforms have been identified: *SOD1*, *SOD2*, and *SOD3*. *SOD1*, which binds to copper and zinc ions, is soluble and localized in the cytosol; its cellular function is to neutralize ROS by regulating redox signals in the plasma

Corresponding Author: Luis E. Figuera, MD; e-mail: luisfiguera@yahoo.com

membrane, cytoplasm, and cell nucleus[4,6]. The *SOD1* gene is located in the long arm of the chromosome (21q22) and has five exons and four introns. Multiple mutations and variants associated with different diseases have been identified[4,6].

One of the variants studied was rs4817415, which is located at position 32,991,661 of the gene. It is characterized by a change of A>C, A>G, or A>T, but the change commonly reported[7] in other populations of the world is A>C, and its function remains unknown. This variant has been studied[8] in multiple amyotrophic lateral sclerosis (ALS). The rs2070424 (A251G, -251A/G) variant is located at position 31,667,007 of the gene and has been reported with a change of A>C, A>G, or A>T; however, the change that has been commonly reported[9] in other populations of the world is A>G. This variant is located in intron 3 of the gene; it participates in the homeostasis of Cu and Zn concentrations and has been shown[10] to increase interleukin-6 concentrations and *SOD1* concentrations in carriers of the GA + GG genotype in an obese population[11].

The rs1041740 intronic variant located at position 31,667,849 of the gene, characterized by a C>T change[12], was found[8,11-15] to be related to an increase in *SOD1* enzyme concentration and has been extensively associated with different types of disease.

Few studies[16] have investigated the association of the variants rs4817415, rs2070424, and rs1041740 of *SOD1* with BC. One study was carried out on 70 patients with BC from a population in Iraq. Another[14] was conducted in 859 BC cases and 1,083 controls from the USA in a study on the US Radiologic Technologists cohort; however, no association between the variant rs2070424 and BC was observed.

In the Mexican population, the association of the *SOD1* variants rs4817415, rs2070424, and rs1041740 in BC remains unknown. Thus, the aim of this investigation was to determine the frequency and association of the *SOD1* variants rs4817415, rs2070424, and rs1041740 in Mexican women with BC.

Patients and Methods

Genomic DNA samples from 146 healthy women and 130 patients clinically and histologically confirmed with BC were included in this study. The study group signed a written informed consent form, and the study was approved by the Ethical Committee (1305) of Centro de Investigación Biomédica de Occidente, Instituto Mexicano del Seguro Social. All procedures performed in the study were in accordance with the Helsinki Declaration. Clinical and demographical data were obtained using written questionnaires.

DNA was extracted *via* the simple salting out method[17]. PCR amplification of the rs4817415, rs2070424, and rs1041740 *SOD1* variants was performed by real-time qPCR with predesigned probes provided by the IDT (2022 Integrated DNA Technologies©, Inc. Coralville, Iowa, USA, available at: www.idtdna.com). The qPCR assay was performed in accordance with the manufacturer's recommendations. Reading was performed using the CFX96 real-time PCR system C1000 touch (Bio-Rad Laboratories©, Inc., Hercules, CA, USA), under the following conditions: 95°C for 10 min; 45 cycles of 95°C for 10 s, 60°C for 45 s, and 68°C for 28 s.

Statistical Analysis

Among the control group, Hardy-Weinberg equilibrium (HWE) was tested using the Chi-square goodness of fit test to compare the observed genotype frequencies with the expected frequencies. The genotype and allele frequencies of each variant were obtained by direct counting. Odds ratios were also calculated, and binary logistic regression was performed using SPSS software version 24 (IBM Corp., Armonk, NY, USA) and statistical significance was $p < 0.05$. The pairwise linkage disequilibrium (D′) and haplotype frequency were analyzed using the SHEsis Online Version program (available at: http://analysis.bio-x.cn)[18].

Results

The epidemiological data from the BC and control groups showed that the mean age of patients with BC was 53.81 ± 12.28 years, which was statistically different from the controls ($p = 0.0001$; Table I).

The frequencies of the characteristic clinical data from the BC group were as follows: a positive familial history for BC in 35%, obesity ≥ 30 in 75%, ductal type in 92%, advanced stage III-IV BC in 57%, presence of lymph nodes in 72%, luminal A and B in 67%, and nonresponders to chemotherapy in 56% (Table II).

The AA genotype frequency in rs4817415 was not significantly different between the BC and

Table I. Demographic data for the study groups.

	BC patients (n=130)		Controls (n=146)		*p*-value
Age at diagnosis (years)					
Mean (SD)	53.81	(12.28)	46.81	(13.46)	0.0001*
≤ 45 years [(n), %]	(37)	28.0	(58)	40.0	0.054
≥ 46 years [(n), %]	(93)	72.0	(88)	60.0	
Hormonal consumption					
Yes [(n), %]	(43)	33.0	(41)	28.0	0.4874
No [(n), %]	(87)	67.0	(105)	72.0	
Tobacco consumption					
Yes [(n), %]	(39)	28.0	(34)	23.0	0.1423
No [(n), %]	(91)	72.0	(112)	77.0	
Alcohol consumption					
Yes [(n), %]	(31)	17.0	(32)	22.0	0.8608
No [(n), %]	(99)	83.0	(114)	78.0	

SD (standard deviation); *Student's *t*-test.

control groups. However, in rs2070424, the GG genotype (OR 2.54, 95% CI 1.31-4.91, $p = 0.0073$), G allele (OR 1.37, 95% CI 1.09-1.73, $p = 0.007$), dominant model (OR 1.69, 95% CI 1.03-2.77, $p = 0.0073$), and recessive model (OR 2.54, 95% CI 1.31-4.91, $p = 0.0073$) were observed as risk factors for BC. Similarly, the rs1041740 variant showed statistically significant differences for the CC genotype (OR 1.67, 95% CI 1.04-0.2.70, $p = 0.0444$), C allele (OR 1.58, 95% CI 1.09-2.29, $p = 0.0183$), and dominant model (OR 1.6, 95% CI 1.03-2.77, $p = 0.048$), suggesting that they are risk factors.

Table II. Clinical data for the BC group.

	(n)	%		(n)	%
Menopause status					
Premenopausal	(41)	32			
Postmenopausal	(89)	68			
Family history of BC			**Tumor stage**		
Yes	(45)	35.0	I	(14)	11.0
No	(85)	75.0	II	(42)	32.0
Body mass index (BMI)			III	(39)	30.0
18-24.9 (normal weight)	(20)	15.0	IV	(35)	27.0
25-29.9 (overweight)	(35)	27.0	**Node status**		
≥30 (obesity)	(75)	58.0	Positive	(94)	72.0
Pregnancies status			Negative	(36)	28.0
≤ 4	(86)	66.0	**Molecular type**		
≥ 5	(44)	34.0	Luminal A	(53)	41.0
Miscarriage			Luminal B	(35)	27.0
Yes	(34)	26	Her-2	(18)	14.0
No	(96)	74	Triple negative	(24)	18.0
Breastfeeding					
≤ 6 months	(28)	22.0	Ki-67	(59)	45.0
> 6 months	(65)	50.0	Ki-67	(71)	55.0
No	(37)	28.0	**Metastatic status**		
Localization			Yes	(95)	73.0
Left	(50)	38.0	No	(35)	27.0
Right	(73)	56.0	**Chemotherapy status**		
Bilateral	(9)	6.0	Response	(57)	44.0
Histology (adenocarcinoma)			No response	(73)	56.0
Ductal	(120)	92.0	**Personal medical history**		
Lobular	(8)	6.0	benign breast disease- uterine fibroids*	(46)	35.0
Mixed	(2)	2.0	DM2-Hypertension*	(37)	28.0

*On base n=130.

Table III. Genotype and allelic distribution of the rs4817415, rs2070424 and rs1041740 variants of *SOD1* in BC patients and controls.

Variant			BC		Controls*		OR	95% (CI)	*p*-value
rs4817415		**Genotype**	(n=130)	%	(n=146)	%			
		AA	(7)	5.5	(6)	4	1.32	(0.43-4.05)	0.8301
		AC	(50)	38.5	(53)	36	1.0	(0.69-1.78)	0.8059
		CC	(73)	56	(87)	60	0.86	(0.53-1.40)	0.6491
	Dominant	AA	(7)	5	(6)	4			
		AC+CC	(123)	95	(140)	96	0.75	(0.24-2.30)	0.8301
	Recessive	CC	(73)	56	(87)	60	0.86	(0.53-1.40)	0.6491
		AA+AC	(57)	44	(59)	40			
		Allele (2n=260)			**(2n=292)**				
		A	(64)	0.246	(65)	0.222	1.14	(0.76-1.69)	0.5810
		C	(196)	0.754	(227)	0.778	0.87	(0.59-1.30)	0.5810
rs2070424									
		AA	(41)	31	(64)	44	0.59	(0.36-0.96)	**0.048**
		AG	(58)	45	(66)	45	0.96	(0.60-1.57)	1.0
		GG	(31)	24	(16)	11	2.54	(1.31-4.91)	**0.0073**
	Dominant	AA	(41)	31	(64)	44			
		AG+GG	(89)	69	(82)	56	1.69	(1.03-2.77)	**0.0481**
	Recessive	GG	(31)	24	(16)	11	2.54	(1.31-4.91)	**0.0073**
		AA+AG	(99)	76	(130)	89			
		Allele (2n=260)			**(2n=292)**				
		A	(140)	0.717	(194)	0.664	0.58	(0.41-0.83)	**0.0033**
		G	(120)	0.283	(98)	0.336	1.69	(1.20-2.39)	**0.0033**
rs1041740									
		CC	(71)	55	(61)	42	1.67	(1.04-2.70)	**0.0444**
		CT	(53)	41	(69)	47	0.76	(0.47-1.23)	0.3358
		TT	(6)	4	(16)	11	0.39	(0.14-1.03)	0.0854
	Dominant	CC	(71)	55	(61)	42			
		CT+TT	(59)	45	(85)	58	1.6	(1.03-2.77)	**0.048**
	Recessive	TT	(6)	4	(16)	11	0.39	(0.14-1.03)	0.0854
		CC+CT	(124)	96	(130)	89			
		Allele (2n=260)			**(2n=292)**				
		C	(195)	0.750	(191)	0.654	1.58	(1.09-2.29)	**0.0183**
		T	(65)	0.250	(101)	0.346	0.63	(0.43-0.91)	**0.0183**

OR (odds ratio), CI (confidence intervals), p-value (significant < 0.05). *Hardy-Weinberg equilibrium in controls for rs4817415 (Chi-square test = 0.3486, $p = 0.5548$), and rs2070424 (Chi-square test = 0.027; $p = 0.8687$) and rs1041740 (Chi-square test = 0.3486, $p = 0.5548$), and rs2070424 (Chi-square test = 0.2881; $p = 0.5914$).

The control group was in HWE for the genotype distribution of the rs4817415, rs2070424, and rs1041740 *SOD1* gene variants (Table III).

The association analysis between the BC and control groups stratified by menopausal status showed statistically significant differences regarding the GG genotype and the dominant model of the rs2070424 variant and with premenopausal status among the study groups and the TT genotype of the rs1041740 variant. By contrast, the rs4817415 variant was not statistically significant (Table IV).

Patients with BC who were carriers of the CC genotype of the rs4817415 variant with elevated Ki-67 and who presented with lymph node metastasis (OR 3.2, 95% CI 1.33-7.7, $p = 0.014$) and stage III-IV (OR 3.6, 95% CI 1.2-10.3, $p = 0.026$) showed risk susceptibility (Table V).

The linkage disequilibrium of rs4817417 and rs2070424 variants showed a D′0.356 and r′ = 0.035, the rs2070424 with rs1041740 variants had a D′ = 0.467 and r′ = 0.058; and the rs4817417 and rs1041740 variants had a D′0.271 and r′ = 0.008) in the control group. The haplotype and frequency comparisons among the BC and control groups were statistically significantly different in CAC (OR 0.779, 95% CI 0.58-1.04, $p = 0.004$), and CGC (OR 2.1, 95% CI 1.44-3.08, $p = 0.001$; Table VI).

Table IV. Association of the rs2070424 and rs1041740 variants of *SOD1* gene with menopause status in the BC patients and controls.

Variant	Genotype	Variable	OR	95% (CI)	*p*-value
rs2070424	GG	Menopause	2.9	(1.11-7.81)	0.042
	AGGG		2.8	(1.43-5.44)	0.003
rs1041740	TT	Pre-menopause	2.89	(1.73-4.85)	0.001

OR (odds ratio), CI (confidence intervals), *p*-value (significant < 0.05).

Table V. Association of the rs4817415 variant of *SOD1* gene with clinical variables of BC patients.

Variant	Genotype	Clinical variable		OR	95% (CI)	*p*-value
rs4817415	**CC**	Ki-67 (≥20%)	Lymph nodes	3.2	(1.33-7.7)	0.014
			III-IV tumor stage	3.6	(1.2-10.3)	0.026

OR (odds ratio), CI (confidence intervals), *p*-value (significant < 0.05).

Discussion

BC is a global health problem[1,2]. In Mexico, the incidence and mortality of BC have increased considerably in the last 10 years[4,5,19]. It has been observed[4,5] in women around 50 years old, which is consistent with the average age observed in the present study.

SOD1 is the main line of cellular defense. It participates in the elimination of ROS and is actively present in the nuclear membrane, nucleus, and cell cytoplasm[6]. It is highly expressed in the nuclei of BC tumor cells[20]; hence, it has an important role in the microenvironment and tumor proliferation[6,20].

Evidence showing an association between the rs4817415 variant, and BC is lacking. This study is the first to analyze this. However, the distribution of genotypes did not show a risk association with BC. This variant has also been studied[8] in patients with ALS, demonstrating no association.

In contrast, the rs2070424 variant has been associated[10,11,21] with various diseases, including BC. However, its risk association has not been demonstrated[14,16] in BC.

In the present study, the GG, AG/GG (dominant model) genotypes, and the G allele were associated with a risk of developing BC ($p < 0.05$). In a study conducted on gastric cancer and the rs2070424 variant, the GG genotype showed a low risk of developing gastric cancer[22].

Another study[11] conducted in a Mexican population observed a risk association in AG/GG carriers with obesity. However, in the present study, this association was not evident in the group of patients with BC.

The rs1041740 variant has been associated with various diseases, such as ALS[8], renal damage[13], and cardiovascular diseases[23]. In BC, it has been associated[14] with psychomotor speed. This variant, among 64 variants most analyzed in head and neck cancer, also showed a lack of association[24].

Table VI. Haplotype frequency of the distribution of the rs4817415, rs2070424 and rs1041740 variants of *SOD1* in BC patients and controls.

SOD1 gene			Patients (2n=260)		Controls (2n=292)			
rs4817415	rs2070424	rs1041740	n	%	n	%	OR 95% (CI)	*p*-value
A	A	C	(40)	15	(30)	10	0.779 (0.58-1.04)	0.067
A	A	T	(7)	3	(13)	4	0.693 (0.46-1.03)	0.288
A	G	C	(12)	5	(7)	3	1.250 (0.85-1.82)	0.192
A	G	T	(6)	2	(15)	5	1.986 (1.20-3.26)	0.067
C	**A**	**C**	(49)	19	(93)	32	0.779 (0.58-1.04)	**0.004**
C	A	T	(44)	17	(58)	20	0.693 (0.46-1.03)	0.380
C	**G**	**C**	(93)	36	(61)	21	2.108 (1.44-3.08)	**0.001**
C	G	T	(9)	3	(15)	5	1.986 (1.20-3.26)	0.296

In the current study, we observed that the CC, CT/TT, and allele C genotypes were statistically significant and were associated with risk susceptibility in BC. This is the first study conducted on BC in the Mexican population in which this association was analyzed.

We observed that the carrier heterozygous rs2070424 and rs1041740 (AC) variants were risk factors for susceptibility to the development of BC when the BC and control groups were stratified by menopausal status. Menopause is a state in which a decrease in estrogen produces an increase in ROS levels, especially in the presence of catechol[25]. In this sense, the presence of cytokines and pro-oxidants has been proposed[25] as a potential generator of ROS in postmenopausal status.

Moreover, we observed that the CC carrier of the rs4817415 variant was a risk factor for susceptibility to the development of BC, as stratified by the different clinicopathological parameters, namely, the presence of ki-67 > 20% more lymph nodes and advanced stage BC (III-IV). Although no existing studies support these findings, these confounding factors show that this stratification is important for contributing to differences in the rs4817415 variant and their associations with BC risk[26].

In BC cell lines, *SOD1* overexpression has been shown[20] to be essential for tumor survival, and its activity is modulated by various recognition sites that bind *SOD1* to regulate its expression as sirtuin 3 (SIRT3) and ER Alpha. Furthermore, *SOD1* participates in the modulation of various cell regulation pathways, such as kinase cascades, Kirsten rat sarcoma viral oncogene homolog (KRAS), growth factors, and fibroblast growth factor receptors (FGFR)[6,20,27]. Probably, the polymorphic alleles of rs2070424 (G) and rs1041740 (C) *SOD1* gene are located in target sites of cell recognition and modulation and, as a consequence, may influence the imbalance of ROS elimination and influence the survival of cancer cells.

The *SOD1* variants analyzed in this study were not shown to be in linkage disequilibrium. Two frequent haplotypes in rs4817415, rs2070424, and rs1041740 were observed in the study groups analyzed. The CAC haplotype, present in 32% of the controls and 19% of the patients with BC, was associated with a protective susceptibility factor for the development of BC. The haplotype CGC, present in 21% of the control group and in 32% of the patient group, was associated as a factor of susceptibility to the risk of BC. Unfortunately, no study on BC has analyzed this association. Thus, the combination of the three variants of *SOD1* analyzed in this study may confer a significant association of risk predisposition in BC, especially with the rs2070424 and rs1041740 variants.

Conclusions

Our results showed characteristic phenotypes in the group of patients with BC: the presence of obesity, histological ductal type, luminal types A and B, lymph nodes metastasis and advanced stage III-IV BC. The rs2070424 variant was an associated risk factor for BC when the controls and the patients with BC with the genotype GG, allele G, and dominant model (CGGG genotype) were compared. Furthermore, differences were observed when the group of patients and controls classified by hormonal status carriers of the GG and CGGG genotypes (dominant model) were compared. The rs1041740 variant also showed an association of susceptibility to the risk of BC in carriers of the CC genotype, allele C, and CTCC (dominant model) and with the premenopausal state in carriers of the TT genotype when comparing the two groups.

The rs4817415 variant did not show statistically significant differences when comparing the study groups. However, the patients with BC stratified by CC genotype carriage and the presence of tumor marker Ki-67 > 20% showed an association of susceptibility to risk with the lymph nodes metastasis and advanced stage III-IV BC. The presence of the CGC haplotype was an associated risk susceptibility factor in BC. More studies are needed to confirm the observed findings. The number of variants analyzed was limited, and more studies that include other *SOD1* gene variants should be conducted in women with BC in the Mexican population.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Approval

This study was approved by Local Ethics and Research Committees (1305, CIBO, IMSS). The integrity of the patients was respected in accordance with good ethical practices and the Declaration of Helsinki and their modifications.

Informed Consent

A written informed consent was obtained from control and patients.

Availability of Data and Materials

Data and materials are available in the article.

Funding

This research was financially supported by the Proyecto 320484, Ciencia Básica y/o Frontera, Modalidad: Paradigmas y Controversias de la Ciencia 2022, CONACYT, Fundación IMSS and CIBO, IMSS grants.

Authors' Contributions

MPGA, LEF, GMZG: analysis, experimentation and data collection; MGMR, BCGM, AMPP, ALZP, JIDS: experimentation and analysis; and MPGA, LEF, GMZG, BCGM: financing support.

ORCID ID

Gallegos-Arreola Martha Patricia: 0000-0003-4539-1693.
Márquez-Rosales María Guadalupe: 0000-0002-1261-008X.
Gómez-Meda Belinda Claudia: 0000-0003-2774-6390.
Zúñiga-González Guillermo: 0000-0003-1257-4637.
Puebla-Pérez Ana María: 0000-0002-7625-7385.
Zamora-Pérez Ana Lourdes: 0000-0002-2756-4792.
Delgado-Saucedo Jorge Iván: 0000-0001-7961-0108.
Figuera Luis: 0000-0002-6096-4579.

References

1) Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca Cancer J Clin 2021; 71: 209-249.
2) Shoemaker ML, White MC, Wu M, Weir HK, Romieu I. Differences in breast cancer incidence among young women aged 20-49 years by stage and tumor characteristics, age, race, and ethnicity, 2004-2013. Breast Cancer Res Treat 2018; 169: 595-606.
3) Villarreal-Garza C, Lopez-Martinez EA, Muñoz-Lozano JF, Unger-Saldaña K. Locally advanced breast cancer in young women in Latin America. Ecancermedicalscience 2019; 13: 894.
4) Gallegos-Arreola MP, García Verdín PM, Magaña-Torres MT, Figuera L E, Zúñiga-González GM, Rosales-Reynoso MA, Gómez-Meda BC, Puebla-Pérez A M. Association between rs61764370, rs9266, and rs140080026 polymorphisms of the KRAS gene and breast cancer risk in a Mexican population. Eur Rev Med Pharmacol Sci 2021; 25: 6454-6464.
5) Gallegos-Arreola MP, Zúñiga-González GM, Figuera LE, Puebla-Pérez AM, Márquez-Rosales MG, Gómez-Meda BC, Rosales-Reynoso MA. ESR2 gene variants (rs1256049, rs4986938, and rs1256030) and their association with breast cancer risk. PeerJ 2022; 10: e13379.
6) Xu J, Su X, Burley S K, Zheng X. Nuclear SOD1 in growth control, oxidative stress response, amyotrophic lateral sclerosis, and cancer. Antioxidants (Basel) 2022; 11: 427.
7) Reference SNP (rs) Report. rs4817415. Available at: https://www.ncbi.nlm.nih.gov/snp/rs4817415. Accessed on October 2022.
8) Garcia C, Vidal-Taboada JM, Syriani E, Salvado M, Morales M and Gamez J. Haplotype analysis of the first A4V-SOD1 spanish family: two separate founders or a single common founder? Front Genet 2019; 10: 1109.
9) Reference SNP (rs) Report. rs2070424. Available at: https://www.ncbi.nlm.nih.gov/snp/ rs2070424. Accessed on October 2022.
10) Ściskalska M, Ołdakowska M, Marek G, Milnerowicz H. Changes in the activity and concentration of superoxide dismutase isoenzymes (Cu/Zn SOD, MnSOD) in the blood of healthy subjects and patients with acute pancreatitis. Antioxidants (Basel) 2020; 9: 948.
11) Hernández-Guerrero C, Hernández-Chávez P, Romo-Palafox I, Blanco-Melo G, Parra-Carriedo A, Pérez-Lizaur A. Genetic Polymorphisms in SOD (rs2070424, rs7880) and CAT (rs7943316, rs1001179) enzymes are associated with increased body fat percentage and visceral fat in an obese population from central Mexico. Arch Med Res 2016; 47: 331-339.
12) Reference SNP (rs) Report. rs1041740. Available at: https://www.ncbi.nlm.nih.gov/snp/rs1041740. Accessed on October 2022.
13) Corredor Z, da Silva Filho MI, Rodríguez-Ribera L, Catalano C, Hemminki K, Coll E, Silva I, Diaz JM, Ballarin JA, Henández A, Försti A, Marcos R, Pastor S. Loci associated with genomic damage levels in chronic kidney disease patients and controls. Mutat Res Genet Toxicol Environ Mutagen 2020; 852: 503167.
14) Koleck TA, Bender CM, Sereika SM, Brufsky AM, Lembersky BC, McAuliffe PF, Puhalla SL, Rastogi P, Conley YP. Polymorphisms in DNA repair and oxidative stress genes associated with pre-treatment cognitive function in breast cancer survivors: an exploratory study. Springerplus 2016; 5: 422.
15) Xu P, Zhu Y, Liang X, Gong C, Xu Y, Huang C, Liu XL, Zhou JC. Genetic polymorphisms of superoxide dismutase 1 are associated with the serum lipid profiles of Han Chinese adults in a sexually dimorphic manner. PLoS One 2020; 15: e0234716.
16) Abd-al-abbas H, Abdullah Jebor M. Lack of Association between genetic polymorphisms of cu/znsod (rs2070424) and the risk of breast cancer. Annals of RSCB 2021; 25: 13827-13832.

17) Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 1988; 16: 1215.

18) Shi YY, He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell Res 2005; 15: 97-98.

19) Chávarri-Guerra Y, Marcum CA, Hendricks CB, Wilbur D, Cescon T, Hake C, Abugattas J, Rodriguez Y, Villarreal-Garza C, Yang K, Cervantes A, Sand S, Castillo D, Herzog J, Mokhnatkin J, Sedrak MS, Soto-Perez-de-Celis E, Weitzel J N. Breast cancer associated pathogenic variants among women 61 years and older with triple negative breast cancer. J Geriatr Oncol 2021; 12: 749-751.

20) Papa L, Manfredi G, Germain D. SOD1, an unexpected novel target for cancer therapy. Genes Cancer 2014; 5: 15-21.

21) Bizoń A, Tchórz A, Madej P, Leśniewski M, Wójtowicz M, Piwowar A, Franik G. The Activity of superoxide dismutase, its relationship with the concentration of zinc and copper and the prevalence of rs2070424 superoxide dismutase gene in women with polycystic ovary syndrome-preliminary Study. J Clin Med 2022; 11: 2548.

22) Ebrahimpour S, Saadat I. Association of CAT C-262T and SOD1 A251G single nucleotide polymorphisms susceptible to gastric cancer. Mol Biol Res Commun 2014; 3: 223-229.

23) Otaki Y, Watanabe T, Nishiyama S, Takahashi H, Arimoto T, Shishido T, Miyamoto T, Konta T, Shibata Y, Sato H, Kawasaki R, Daimon M, Ueno Y, Kato T, Kayama T, Kubota I. The impact of superoxide dismutase-1genetic variation on cardiovascular and all-cause mortality in a prospective cohort study: the Yamagata (Takahata) study. PLoS One 2016; 11: e0164732.

24) Hakenewerth AM, Millikan RC, Rusyn I, Herring AH, North KE, Barnholtz-Sloan, JS, Funkhouser WF, Weissler MC, Olshan AF. Joint effects of alcohol consumption and polymorphisms in alcohol and oxidative stress metabolism genes on risk of head and neck cancer. Cancer Epidemiol Biomarkers Prev 2011; 20: 2438-2449.

25) Doshi SB and Agarwal A. The role of oxidative stress in menopause. J Midlife Health 2013; 4: 140-146.

26) Dimitrov G, Atanasova M, Popova Y, Opova K, Vasileva Y, Milusheva Y, Troianova P. Molecular and genetic subtyping of breast cancer: the era of precision oncology. WCRJ 2022; 9: e2367.

27) Caputo R, Cianniello D, Giordano A, Piezzo M, Riemma M, Trovò M, Berretta M, De Laurentiis M. Gene Expression Assay in the Management of Early Breast Cancer. Curr Med Chem 2020; 27: 2826-2839.