

Original Article



AURKA Gene Variants rs1047972, and rs8173 Are Associated With Breast Cancer

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ABSTRACT



Purpose: Association between variants rs1047972 and rs8173 of the *AURKA* gene in healthy women and breast cancer (BC) in a Mexican population.

Methods: Genomic DNA samples from 409 healthy women and 572 patients with BC were analyzed for variants rs1047972 and rs8173 of the *AURKA* gene by polymerase chain reaction-restriction fragment length polymorphism.

Results: TT genotype (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.22–5.11; $p = 0.0015$) and the T allele (OR, 1.16; 95% CI, 1.23–2.12; $p = 0.0007$) of the rs1047972 variant were associated as risk susceptibility for BC relative to the control group. Contrarily, the GG genotype (OR, 0.64; 95% CI, 0.43–0.94; $p = 0.029$) was associated as a protective factor of susceptibility of BC of the variant rs8173 of the *AURKA* gene. Differences were observed in the patients with BC who were carriers of the CT genotype of the rs1047972 variant with overweight, obesity, estrogen receptor-positive plus obesity, Ki-67 ($\geq 20\%$) plus history familial positive of cancer; and for variant rs8173 the BC patients who were CG carriers and presented chemotherapy gastric toxicity, hormonal receptor positive plus chemotherapy gastric toxicity, and menopause status plus chemotherapy gastric toxicity ($p < 0.05$). Two common haplotypes were identified in the study groups: CG and TC genotypes, were associated as a protective and risk factor, respectively ($p < 0.05$).

Conclusion: Variants rs1047972 and rs8173 of the *AURKA* gene and the TC haplotype were associated as risk susceptibility factors for BC in this population.

Keywords: Aurora Kinase A; Breast Neoplasms; DNA Restriction Enzymes; Genotype; Risk Factors

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Conflict of Interest

The authors declare that they have no competing interests.

Authors Contributions

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INTRODUCTION

Breast cancer (BC) is the most frequently diagnosed malignancy and the primary cause of death among women in Mexico and the world [1,2]. According to data provided by the Global Cancer Observatory (GLOBOCAN), it is estimated that up to eight million cases were diagnosed and nearly two million new cases were reported in 2020, along with 684,996 deaths, representing the type of cancer with the highest prevalence, incidence, and mortality among women worldwide [1,2].

In Mexico, this disease is reported as the neoplasia with the highest prevalence, incidence, and mortality, with just under thirty thousand new cases diagnosed in 2020 and nearly eight thousand deaths reported during that year (GLOBOCAN) [1]. Previous studies have shown that BC represents a public health problem, which some developed countries have managed to face and drastically reduce mortality rates by implementing new advances in the diagnosis and treatment of this disease; however, this is not the case in underdeveloped countries, where an increase in mortality rates has been observed [3,4].

Although BC is a multifactorial disease, the genetic component plays an important role in the appearance and behavior of this pathology; therefore, the study of variants and especially single nucleotide variants (SNV) in genes involved in the carcinogenesis process is of particular interest. Studying SNVs makes it possible to understand the genomic changes that may increase the susceptibility to developing this pathology, or influence the therapeutic response, and contribute to the clinicopathological characteristics making this type of cancer a very heterogeneous disease [5-7].

One of the genes of interest is the Aurora kinase (AURK) A (*AURKA*) gene located in 20q13.2, which is part of the AURK family, whose members, the *AURKA*, AURK B (*AURKB*), and AURK C (*AURKC*) genes, play an important role in the formation of the mitotic spindle, and consequently, an important role in cell division by guaranteeing correct chromosome segregation, therefore, defects in any of the genes of this family can promote genetic instability and polyploidies, characteristics already described in numerous neoplasms [8,9].

The *AURKA* gene plays an important role in numerous mitotic activities, such as centrosome maturation, progression to mitosis, and mitotic spindle assembly, through coupling with other proteins, thus ensuring the phosphorylation of key proteins in the regulation of the cell cycle, including P53 and breast cancer gene (BRCA) 1 [10,11]. Thus, the deregulation of this gene being directly related to carcinogenic processes is unsurprising. Furthermore, *AURKA* is overexpressed in numerous tumor tissues and the overexpression of this gene in breast cancer is related to aggressive highly proliferative tumors, with basal phenotypes and Ki-67 positivity [8]. Similarly, the overexpression of this gene plays an important role as a prognostic marker in adrenocortical carcinoma, clear and papillary renal cell carcinoma, hepatocellular carcinoma, lung adenocarcinoma, mesothelioma, and uveal melanoma. Thus, the *AURKA* gene is considered a therapeutic target of great importance in precision medicine for identifying variants that may influence the development, prognosis, therapeutic response, and progression of the disease [12-16].

Variants of this gene have been associated with the appearance, development, and poor prognosis of different types of cancer. For example, the rs2273535 variant is associated with the appearance of multiple types of cancer, especially BC. Additionally, the

variants rs2064863 and rs6024836 have been reported to be associated with different clinicopathological characteristics in patients with urothelial cell carcinoma. The rs1047972 variant has also been correlated with high rates of hepatocellular carcinoma [17-19].

The rs1047972 variant is a non-synonymous SNV that mediates the substitution of a valine residue for an isoleucine residue at position 57 (V57I) [20] and has been extensively studied. However, there have been contradictory results in some studies showing protective factors, especially in BC [21,22], others as risk factors [23-25], and others have not been shown to be associated [26]. However, the three prime untranslated region (3'UTR) region of the *AURKA* gene plays an important role in the miRNA expression in the tumor microenvironment [27]. Additionally, miR-124 acts as a tumor suppressor by significantly decreasing the expression of *AURKA* in a glioma cell line [28]. Thus, the presence of SNVs in the 3'UTR region of numerous genes modify the binding sites to regulatory miRNAs, which is associated with different human pathologies and the therapeutic response of some of them, including cancer [12].

Although SNVs rs1047972 and rs8173 have been extensively studied in different populations, no association studies have been reported for BC or any other type of cancer in the Mexican population. Therefore, in this study, we analyzed the association of the variants rs1047972 (T>C) and rs8173 (G>C), located in exon 3 and the 3'UTR region of the *AURKA* gene, respectively.

METHODS

The present study was approved by the local ethics committee (1305) of the “Centro de Investigación Biomédica de Occidente, Instituto Mexicano del Seguro Social”. DNA samples from 572 women with clinically and histologically confirmed BC, and 409 healthy women were used in this study. Sample collection was performed after written informed consent was provided by each subject in addition to obtaining clinical data. All the study procedures were performed in accordance with the Declaration of Helsinki.

The rs1047972 variant was tested in 304 patients with BC and 272 controls. The polymerase chain reaction (PCR) amplification was carried out using the forward 5'-CTCTCCATTCTAGGCTAC-3' and reverse 5'-CAGTGGCCTGGAGACAG-3' primers designed according to the gene sequence (<http://www.ncbi.nlm.nih.gov/SNP/>). A fragment of 247 bp was amplified with the following program: 95°C for 5 minutes; 35 cycles of 95°C for 30 seconds, 62°C for 45 seconds, and 72°C for 30 seconds. The genotype identification was performed by restriction fragment length polymorphism (RFLP) method, using the restriction enzyme BstUI (New England Biolabs, Ipswich, USA) that recognizes the G allele. In a polyacrylamide gel 8% (19:1), the fragment was separated by electrophoresis after staining with silver nitrate. The CC genotype was identified by a band of 247 bp, the GT by bands of 247, 139, and 108 bp, and the GG genotype by bands of 139 and 108 bp.

The rs8173 variant was analyzed in 572 patients with BC and 409 controls. A fragment of 184 bp was amplified by PCR with the forward 5'-GTGCCGGACAGACACACAG-3' and reverse 5'-GGAGCTGTGCAATAACC-3' primers designed according to the sequence of the gene (<http://www.ncbi.nlm.nih.gov/SNP/>). Using the 35 cycles of alignment temperature at 59°C for 5 seconds, 57°C for 5 seconds, 55°C for 20 seconds, and 72°C for 30 seconds. Genotypes were identified prior to digestion with the restriction enzyme HaeIII (New England Biolabs, Ipswich, USA) and the fragments were separated on 8% polyacrylamide gels (19:1) after

staining with silver nitrate. The following fragments were used to identify the genotypes: CC, 184 bp; CG, 184, 136, and 48 bp; and GG 136 and 48 bp.

Statistical analysis

The percentage of genotypes was analyzed by direct count, and Hardy-Weinberg equilibrium (HWE) was used for the control group using the χ^2 goodness-of-fit test to compare the observed genotype frequencies with the expected frequencies. For genotype association analysis, odds ratios were calculated, and binary logistic regression was performed using SPSS Statistics Base 24 software (IBM, Chicago, USA). The SHEsis Online Version program was used to analyze pairwise linkage disequilibrium (D') and haplotype frequency [29]. The allelic frequencies from other populations were taken from the Ensembl database using the reference genome "CRCh38.p13."

RESULTS

The average age observed in the study groups was 52.02 ± 11.72 and 51.78 ± 11.65 years for the BC and control groups, respectively, which did not show statistically significant differences when compared to each other ($p > 0.05$). Moreover, the comparative analysis of tobacco and alcohol consumption showed no significant differences between the study groups ($p > 0.05$).

The frequencies of clinical variables in the BC group are shown in **Table 1**. Among the most frequent variables were, the presence of menarche between 11 and 13 years old (69%), menopause (62%), family history of cancer (44%), obesity (47%), less than five gestations (68%), breastfeeding more than 6 months (50%), location of cancer in the unilateral breast (96%), ductal type (92%); stage II (32%), and III (30%), positive metastatic nodes (72%); luminal A 39%, and luminal B (25%), no responders (60%), and gastric toxicity (62%) to chemotherapy.

In the rs1047972 variant the TT genotype frequency, (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.22–5.11; $p = 0.015$), T allele (OR, 1.6; 95% CI, 1.23–2.12; $p = 0.0007$), dominant model (OR, 1.6; 95% CI, 1.18–2.29; $p = 0.003$), and recessive model (OR, 2.5; 95% CI, 1.22–5.11; $p = 0.015$) were observed as risk factors for BC. However, in the rs8173 variant, the GG genotype frequency, and recessive model, (OR, 0.64; 95% CI, 0.43–0.94; $p = 0.029$), were observed as a protective factor for BC (**Table 2**).

Comparative analysis of rs1047972 and rs8173 variants of the *AURKA* gene in the control group of Mexican women in this study with a control group of other populations showed statistically significant differences in allelic distribution (**Table 3, Figure 1**).

No statistically significant differences were observed for either rs1047972 or rs8173 variants regarding the variables age (stratified in ≥ 50 years and ≤ 49 years), and tobacco and alcohol consumption between the BC and control groups.

In the BC group, the CT genotype (OR, 2.6; 95% CI, 1.26–5.67; $p = 0.010$) and the dominant model (OR, 2.3; 95% CI, 1.17–4.46; $p = 0.016$) of the rs1047972 variant were associated with overweight and obesity (CT genotype: OR, 3.2; 95% CI, 1.60–6.66; $p = 0.001$ and dominant model: OR, 2.5; 95% CI, 1.32–4.87; $p = 0.005$) as risk factors for BC susceptibility. Likewise, the dominant model (OR, 1.9; 95% CI, 1.03–3.68; $p = 0.038$) showed an association of susceptibility to BC risk with those patients who had a family history of cancer (**Table 4**).

Table 1. Clinical data for the breast cancer group

Variables	BC patients (n = 572)
Menarche status	
7 at 10 years old	52 (9.1)
11 at 13 years old	396 (69.2)
14 at 18 years old	124 (21.7)
Menopause status	
Premenopausal	216 (37.8)
Postmenopausal	356 (62.2)
Family history of cancer	
Breast*	130 (22.7)
Other type*	118 (20.6)
Body mass index (kg/m²)	
18–24.9 (normal weight)	154 (26.9)
25–29.9 (overweight)	149 (26.0)
≥ 30 (obesity)	269 (47.0)
Hormonal consumption*	218 (38.1)
Pregnancies status	
≤ 4	390 (68.2)
≥ 5	121 (21.2)
nulliparity	61 (10.7)
Miscarriage*	133 (23.3)
Breastfeeding (months)	
≤ 6	213 (37.2)
> 6	288 (50.3)
No	71 (12.4)
Localization (breast left or right)	
Unilaterality	547 (95.6)
Bilateral	25 (4.4)
Histology (adenocarcinoma)	
Ductal	526 (92.0)
Lobular	35 (6.1)
Mixed	11 (1.9)
Tumor stage	
I	63 (11.0)
II	183 (32.0)
III	172 (30.1)
IV	154 (26.9)
Lymph node status	
Positive*	413 (72.2)
Molecular type	
Luminal A	224 (39.2)
Luminal B	145 (25.3)
Her-2	93 (16.3)
Triple negative	110 (19.2)
Ki-67 (≥ 20%)	284 (49.7)
Ki-67 (< 20%)	288 (50.3)
Chemotherapy status	
Response	230 (40.2)
No response	342 (59.8)
Personal medical history	
Benign breast disease- uterine fibroids*	178 (31.1)
DM2-hypertension*	132 (23.1)
Chemotherapy toxicity	
Gastric	355 (62.1)
Hematologic	217 (37.9)

Values are presented as number of patients (%).
 BC = breast cancer; DM2 = type 2 diabetes mellitus.
 *On base 572.

Table 2. Genotype and allelic distribution of the rs1047972, and rs8173 variants of AURKA gene in the studied groups

Variants	BC	Controls*	OR (95% CI)	p-value
rs1047972				
Genotypes	n = 304	n = 272		
CC	159 (52.3)	175 (64.3)	1.0	
CT	116 (38.2)	86 (31.6)	1.3 (0.94–1.88)	0.1
TT	29 (9.5)	11 (4.0)	2.5 (1.22–5.11)	0.015
Dominant				
CC	159 (52.3)	175 (64.3)		
CT+TT	145 (47.7)	97 (35.7)	1.6 (1.18–2.29)	0.003
Recessive				
TT	29 (9.5)	11 (4.0)	2.5 (1.22–5.11)	0.015
CC+CT	275 (90.5)	261 (96.0)		
Alleles	2n = 608	2n = 544		
C	434 (71.4)	436 (80.1)	0.61 (0.46–0.81)	0.0007
T	174 (28.6)	108 (19.9)	1.6 (1.23–2.12)	0.0007
rs8173				
Genotypes	n = 572	n = 409		
CC	202 (35.3)	145 (35.5)	1.0	
CG	311 (54.4)	202 (49.4)	1.22 (0.94–1.57)	0.140
GG	59 (10.3)	62 (15.2)	0.64 (0.43–0.94)	0.029
Dominant				
CC	202 (35.3)	145 (35.5)		
CG+GG	370 (64.7)	264 (64.5)	1.0 (0.77–1.31)	0.964
Recessive				
GG	59 (10.3)	62 (15.2)	0.64 (0.43–0.94)	0.029
CC+CG	513 (89.7)	347 (84.8)		
Alleles	2n = 1,144	2n = 818		
C	715 (62.5)	492 (60.1)	1.10 (0.91–1.32)	0.312
G	429 (37.5)	326 (39.9)	0.90 (0.75–1.08)	0.312

p-value less than 0.05 considered statistically significant.

BC = breast cancer; OR = odds ratio; CI = confidence interval.

*Hardy-Weinberg equilibrium for the control group: variants rs1047972 (χ^2 test = 0.0113, $p = 0.915$), and rs8173 (χ^2 test = 0.373; $p = 0.541$).

Regarding the rs8173 variant, the CG genotype (OR, 1.6; 95% CI, 1.05–2.46; $p = 0.029$), and dominant model (OR, 1.7; 95% CI, 1.11–2.72; $p = 0.015$) were associated with chemotherapy gastric toxicity as BC susceptibility risk factors (Table 4).

Patients with BC who were carriers of the CTTT genotype of the rs1047972 variant with elevated Ki-67 and who have a familial antecedent with cancer (OR, 2.66; 95% CI, 1.14–6.2; $p = 0.023$), showed risk factor of the susceptibility of BC (Table 4).

The haplotype and frequency comparisons among the studied group were significantly different in CG (OR, 0.7; 95% CI, 0.53–0.93; $p = 0.014$), and TC (OR, 1.6; 95% CI, 1.11–2.32; $p = 0.010$) (Table 5). The linkage disequilibrium of the rs1047972 and rs8173 variants was $D' = 0.072$ and $r' = 0.003$, in the control group.

DISCUSSION

BC is a major health concern worldwide. In Mexico, it is the main cause of death in women, and its incidence has been increasing in the last 10 years, with the highest frequency observed in women aged approximately 50 years. This finding is consistent with the average age data observed in the present study. However, in developed and developing countries such as Mexico, the presence of reproductive and hormonal risk factors and those related to lifestyle

Table 3. Allelic distribution of the rs1047972, and rs8173 variants of *AURKA* in controls from different populations

Population	rs1047972					rs8173				
	Allele C	No.	Allele T	No.	p-value	Allele C	No.	Allele G	No.	p-value
ACB	0.818	157	0.182	35	0.70	0.380	73	0.620	119	0.0001 [†]
ASW	0.746	91	0.254	31	0.21	0.320	39	0.680	83	0.0001 [†]
ESN	0.823	186	0.177	35	0.23	0.202	40	0.798	158	0.0001 [†]
GWD	0.823	186	0.177	40	0.55	0.314	71	0.686	155	0.0001 [†]
LWK	0.864	171	0.136	27	0.06	0.258	51	0.742	147	0.0003 [†]
MSL	0.876	149	0.124	21	0.035 [†]	0.218	37	0.782	133	0.0001 [†]
YRL	0.833	180	0.167	36	0.36	0.250	54	0.750	162	0.0001 [†]
CLM	0.840	158	0.160	30	0.28	0.601	113	0.399	75	0.0001 [†]
MXL	0.898	115	0.102	13	0.01 [†]	0.500	64	0.500	64	0.038 [†]
PEL	0.965	164	0.035	6	0.0001 [†]	0.353	60	0.647	110	0.0001 [†]
PUR	0.885	184	0.115	24	0.01 [†]	0.692	144	0.308	64	0.01 [†]
CDX	0.871	162	0.129	24	0.04 [†]	0.339	63	0.661	123	0.0001 [†]
CHB	0.845	174	0.155	32	0.21	0.417	86	0.583	120	0.0001 [†]
CHS	0.886	186	0.114	24	0.008 [†]	0.400	84	0.600	126	0.0001 [†]
JPT	0.870	181	0.130	27	0.03 [†]	0.370	77	0.630	131	0.0001 [†]
KHV	0.914	181	0.086	17	0.0004 [†]	0.354	70	0.646	129	0.0001 [†]
CEU	0.843	167	0.157	31	0.23	0.768	152	0.232	46	0.0001 [†]
FIN	0.808	160	0.192	38	0.92	0.717	142	0.283	56	0.003 [†]
GBR	0.819	149	0.181	33	0.68	0.725	132	0.275	50	0.002 [†]
IBS	0.855	183	0.145	31	0.10	0.668	143	0.332	71	0.06
TSI	0.766	164	0.234	50	0.33	0.715	153	0.285	61	0.002 [†]
BEB	0.826	142	0.174	30	0.55	0.570	98	0.430	74	0.49
GIH	0.883	182	0.117	24	0.01 [†]	0.670	138	0.330	68	0.08
ITU	0.794	162	0.206	42	0.90	0.608	124	0.392	80	0.93
PJL	0.870	167	0.130	25	0.044 [†]	0.625	120	0.375	72	0.60
STU	0.873	178	0.127	26	0.03 [†]	0.515	105	0.485	99	0.03 [†]
MX*	0.801	436	0.199	108		0.601	492	0.399	346	

ACB = African Caribbean in Barbados, by its acronym in Spanish; ASW = African Caribbean in Barbados; ESN = Esan in Nigeria; GWD = Gambian in Western Division; LWK = Luhya in Webuye, Kenya; MSL = Mende in Sierra Leone; YRI = Yoruba in Ibadan, Nigeria; CLM = Colombian in Medellin; MXL = Mexican Ancestry in Los Angeles, California; PEL = Peruvian in Lima; PUR = Puerto Rican in Puerto Rico; CDX = Chinese Dai in Xishuangbanna; CHB = Han Chinese in Beijing; CHS = Southern Han Chinese; JPT = Japanese in Tokyo; KHV = Kinh in Ho Chi Minh City, Vietnam; CEU = Utah residents with Northern and Western European ancestry; FIN = Finnish in Finland; GBR = British in England and Scotland; IBS = Iberian Populations in Spain; TSI = Tuscan in Italy; BEB = Bengali in Bangladesh; GIH = Gujarati Indian in Houston; ITU = Indian Telugu in the UK; PJL = Punjabi in Lahore, Pakistan; STU = Sri Lankan Tamil in the UK; MX = Mexican population.

*MX studied the T and G alleles of rs1047972, and rs8173 variants of *AURKA* respectively, were too compared with other population.

[†]p < 0.05. The frequencies were taken from Ensembl CRCh38.p13.

reflects the increase in the incidence of BC [1,2,30]. Among the clinical features observed as a prevalent pattern in the samples analyzed in this study were menopause, obesity, less than five pregnancies, location of unilateral cancer, ductal type, advanced stages II and III, positive lymphoma nodules, and luminal A/B type of cancer. A characteristic fact It should be highlighted that most patients are in the advanced stages of the disease.

AURKA is a protein that participates in the formation of microtubules and stabilization of chromosomes during the cell cycle; its expression levels are high in the lung, breast, and testis, which makes it an important molecule in the microenvironment and proliferation of this type of tumor. Different studies in the literature have described contradictory results, some have described the association of the rs1047972 (Aurora-A V57I) variant with reduced risk of developing cancer, others with susceptibility to the risk of developing cancer, and others have not described an association [12,18,21-28].

In the present study, the TT and CTTT (dominant model) genotypes and the T allele of variant rs1047972 were associated with the risk of developing BC (p < 0.05). This is the first study carried out in a Mexican population where this association of susceptibility to the risk of developing BC is evidenced. Previous studies carried out on BC in other populations have

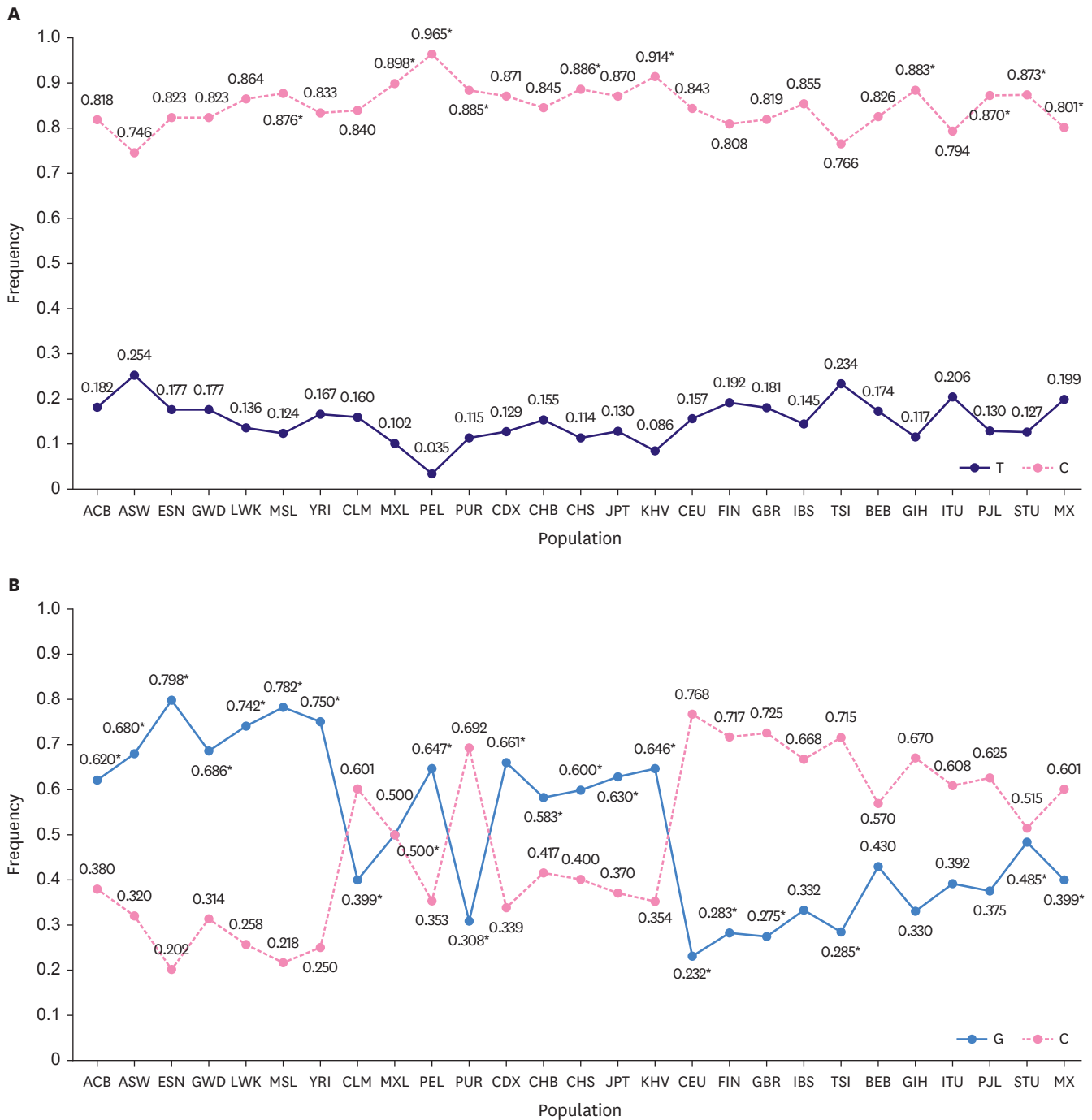


Figure 1. Allelic frequency comparison of the rs1047972 (A) and rs8173 (B) variants of the *AURKA* gene in the Mexican women control group with controls from other populations.

When comparing the frequency of the T and C alleles of the rs1047972 and C and G alleles of the rs8173 variant in the Mexican population with those of other populations, significant differences were observed ($p < 0.05$).

ACB = African Caribbean in Barbados; ASW = African Ancestry in Southwest US; ESN = Esan in Nigeria; GWD = Gambian in Western Division, The Gambia; MSL = Mende in Sierra Leone; YRI = Yoruba in Ibadan, Nigeria; CLM = Colombian in Medellin, Colombia; MXL = Mexican Ancestry in Los Angeles, California; PEL = Peruvian in Lima, Peru; PUR = Puerto Rican in Puerto Rico; CDX = Chinese Dai in Xishuangbanna, China; CHB = Han Chinese in Beijing, China; CHS = Southern Han Chinese, China; JPT = Japanese in Tokyo, Japan; KHV = Kinh in Ho Chi Minh City, Vietnam; CEU = Utah resident with Northern and Western European ancestry; GBR = British in England and Scotland; BEB = Bengali in Bangladesh; ITU = Indian Telugu in the UK; STU = Sri Lankan Tamil in the UK; MX = Mexican population from our study.

*Data were presented in **Table 3** and in the text and the frequencies were taken from Ensembl database using the reference genome “CRCh38.p13.”

Table 4. rs1047972 and rs8173 variants of the *AURKA* gene and their association with the breast cancer group

Variant	Genotype	Variable	OR (95% CI)	p-value
rs1047972	CT	Overweight	2.6 (1.26–5.67)	0.010
	CTTT		2.3 (1.17–4.46)	0.016
	CT	Obesity	3.2 (1.60–6.66)	0.001
	CTTT		2.5 (1.32–4.87)	0.005
	CTTT	Family history of cancer	1.9 (1.03–3.68)	0.038
	CTTT	Estrogen receptor plus obesity	2.5 (1.11–5.79)	0.027
	CTTT	Ki-67 (≥ 20%) plus family history of cancer	2.66 (1.14–6.2)	0.023
rs8173	CG	Chemotherapy gastric toxicity	1.6 (1.05–2.46)	0.029
	CGGG		1.7 (1.11–2.72)	0.015
	CGGG	Estrogen receptor plus chemotherapy gastric toxicity	2.0 (1.15–3.48)	0.013
	CGGG	Progesterone receptor plus chemotherapy gastric toxicity	2.6 (1.42–4.9)	0.002
	CGGG	Menopause plus chemotherapy gastric toxicity	2.0 (1.15–3.7)	0.014

p-value less than 0.05 considered statistically significant.
OR = odds ratio; CI = confidence intervals.

Table 5. Haplotype frequency of the rs1047972 and rs8173 variants of the *AURKA* gene in studied groups

rs1047972	rs8173	BC (2n = 548)	Controls (2n = 446)	OR (95% CI)	p-value
C	C	259 (47.3)	218 (48.9)	0.9 (0.73–1.20)	0.629
C	G	130 (23.7)	138 (30.9)	0.7 (0.53–0.93)	0.014
T	C	93 (17.0)	51 (11.4)	1.6 (1.11–2.32)	0.010
T	G	66 (12.0)	41 (9.2)	1.3 (0.88–2.02)	0.162

All those frequencies < 0.03 were not taken into account for the analysis. Values are presented as number (%) not otherwise specified.

BC = breast cancer; OR = odds ratio; CI = confidence interval.

found a protective association, when it comes to case-control studies [19,21,22]. However, a study conducted on patients with BC and mutations in the *BRCA1* gene in a Chinese population observed an association between cancer risk and variants of the *AURKA* gene [31].

In the rs8173 variant, we observed that the GG genotype and the recessive model were associated with protective factors against the development of BC ($p < 0.05$). There are no association studies with BC and a control group; however, our data are consistent with a study conducted on children with Wilms tumors in a Chinese population [32].

When comparing the T and G alleles of rs1047972 and rs8173, respectively, of our Mexican women control group with the control groups of other populations, similarities and differences were observed in Asian, African, Latin, and Caucasian populations. These results show the genetic heterogeneity of these variants in other populations, and it is important to highlight the importance of the sample size used in different population analyses [30,33].

We observed that the CT and CTTT carriers of the rs1047972 variant and CG and CGGG carriers of the rs8173 variant were risk factors for the development of BC, as stratified by different clinicopathological parameters, such as overweight, obesity, family history of cancer, chemotherapy gastric toxicity, estrogen receptor-positive plus obesity, Ki-67 > 20% plus family history of cancer, and estrogen receptor-positive plus chemotherapy gastric toxicity. Although no existing studies support these findings, these confounding factors show that stratification is important in contributing to the differences in rs1047972 and rs8173 variants and their associations with BC risk. However, an association study with variants of the *AURKA* gene and clinical pathological characteristics of BC in patients from Swedish and Polish families showed that the G allele of the rs8173 variant of the *AURKA* gene was associated with steroid hormone receptor status; moreover, they suggested that this same allele may be associated with worse survival in patients with BC in hormone-dependent tumors [34].

AURKA overexpression has been shown to be essential for tumor survival, and its activity is modulated by various recognition sites that bind *AURKA* to regulate its expression such as epidermal growth factor receptor, signal transducer and activator of transcription 5, Ajuba, forkhead box M1, targeting protein for Xklp2, and pumilio RNA-binding family member 2 [12]. Furthermore, *AURKA* protein participates in the modulation of various cell regulation pathways, such as kinase cascades, growth factors, Kirsten rat sarcoma viral oncogene homolog, regulation of centromeres, cell cycle, binding of estrogen receptor α to DNA, and promotion of cell proliferation in cancer and chemoresistance. Probably, the variant alleles of rs1047972 (T) and rs8173 (G) of *AURKA* are located at the target sites of cell recognition and modulation, and as a consequence, may influence the imbalance of *AURKA* and the survival of cancer cells [12].

Our study investigated the rs8173 (C>G) variant and found that the GG genotype was a protective factor, consistent with previous findings. Specifically, normal tissues have shown that the CC genotype has a statistically significant difference in median expression compared to the GG genotype in cultured fibroblasts [32]. In addition, another study reported that the rs2273535 variant, which has an effect similar to that of rs1047972, is associated with poor prognosis in gastric cancer in the Chinese population. According to their bioinformatics analysis, the variant genotype could lead to higher expression of the *AURKA* gene, which is also associated with poor prognosis of the disease [35].

Regarding the study limitations and concerning the sample size, a larger population sample might aid in adjusting our statistical findings. Additionally, no molecular screening for cancer-related pathogenic variants (such as *BRCA1/2*) was carried out in our study groups. Thus, excluding these subjects would generate a better fit for our statistical analyses.

The *AURKA* variants analyzed in this study were not in linkage disequilibrium. Two frequent haplotypes rs1047972 and rs8173 were observed in the study groups analyzed. The CG haplotype, present in 31% of controls and 24% of patients with BC, is a protective factor for the development of BC. Haplotype TC, present in 11% of the control group and 17% of the patient group, was associated with susceptibility to BC. Unfortunately, no studies on BC have analyzed this association. Thus, the combination of the two variants of *AURKA* analyzed in this study may confer a significant association with risk predisposition for BC, especially with the rs1047972 and rs8173 variants.

Our results showed characteristic phenotypes in patients with BC: histological ductal type, luminal types A/B, lymph node metastasis, and advanced stages III–IV. The rs1047972 variant was found to be an associated risk factor for BC when controls and patients with BC with the genotype TT, allele T, and the dominant model (CTTT genotype) were compared. The rs8173 variant was found to be a protective factor against BC when the groups with the GG genotype were compared.

In addition, we observed statistically significant differences in the rs1047972 variant showing a risk association when the group of patients with BC was stratified by the CT genotype and the dominant model (CTTT), with overweight and obesity, and the presence of a history of familial antecedents of cancer, estrogen receptor marker positivity plus obesity, and marker Ki-67 > 20% plus a family history of cancer.

The rs8173 variant was also identified as a risk factor when the BC patient group carrier of the CT genotype was stratified by chemotherapy gastric toxicity, model-dominant CTTT with hormonal receptor plus chemotherapy gastric toxicity, and chemotherapy gastric toxicity plus menopausal status. The presence of the TC haplotype is a risk factor for BC. However, further studies are needed to confirm these findings.

As a future perspective, the inclusion of more variants related to the *AURKA* gene, quantification of the expression levels, and their correlation with other related genes might be helpful in further association studies in our population.

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