CYP1A1, CYP1B1, GSTM1 and *GSTT1* genetic variants and breast cancer risk in Mexican women

Angélica García-Martínez, DSc,[1] Brenda Gamboa-Loira, MSc,[1] M Elizabeth Tejero, PhD,[2] Adolfo Sierra-Santoyo, DSc,[3] Mariano E Cebrián, PhD,[3] Lizbeth López-Carrillo, DPH.[1]

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Abstract

Objective. To evaluate if variants in the genes *CYP1A1* (T3801C and A4889G), *CYP1B1* (G119T), *GSTM1* (indel) and *GSTT1* (indel) are associated with breast cancer (BC) among Mexican women. **Materials and methods.** 952 incident cases with histologically confirmed BC were matched by age (± 5 years) and zone of residence with 998 healthy population controls. Genetic variants in genes *CYP1A1*, *CYP1B1, GSTM1* and *GSTT1*were genotyped by allelic discrimination and multiplex PCR. In a subsample of women, 105 markers for ancestry were determined. **Results.** An increased BC risk, independent of other BC risk factors, was observed among carriers of *CYP1B1* G119T genotype (T/T *vs*. G/G: OR=1.9; 95%CI 1.4-2.5). **Conclusion.** Our results support the existence of genetic susceptibility for BC conferred by *CYP1B1* G119T variant among Mexican women.

Keywords: breast neoplasms; case-control studies; genetic susceptibility; Mexico

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Resumen

Objetivo. Evaluar si las variantes en los genes *CYP1A1* (T3801C y A4889G), *CYP1B1* (G119T), *GSTM1* (indel) y*GSTT1* (indel), se asocian con el cáncer de mama (CM) en mujeres mexicanas. **Material y métodos.** Se parearon por edad (± 5 años) y zona de residencia 952 casos incidentes de CM histológicamente confirmado con 998 controles sanos poblacionales. Se genotipificaron variantes en los genes *CYP1A1*, *CYP1B1, GSTM1* y *GSTT1* por discriminación alélica y PCR multiplex. En una submuestra de mujeres, se determinaron 105 marcadores de ancestría. **Resultados.** Se observó un aumento del riesgo de CM, independiente de otros factores de riesgo, entre las portadoras del genotipo *CYP1B1* G119T (T/T *vs*. G/G: RM=1.9; 95%CI 1.4-2.5). **Conclusiones.** Nuestros resultados soportan la existencia de susceptibilidad genética para CM conferida por la variante *CYP1B1* G119T en mujeres mexicanas.

Palabras clave: neoplasias mamarias; estudios de casos y controles; susceptibilidad genética; México

(1) Instituto Nacional de Salud Pública. México.
(2) Instituto Nacional de Medicina Genómica. México.
(3) Departamento de Toxicología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional. México.

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Corresponding author: Lizbeth López-Carrillo. Instituto Nacional de Salud Pública.
Av. Universidad 655, Col. Santa María Ahuacatitlán. 62100 Cuernavaca, Morelos, México.
E-mail: lizbeth@insp.mx

Globally, breast cancer (BC) is a major growing health problem with an important worldwide variation. In Mexico it is the leading cause of female cancer with around 20 000 new cases per year.[1] Age at BC diagnosis differs significantly between less developed countries, where 47.37% of new BC cases occur before 50 years of age, and developed countries, where only 18.5% of new cases occur before such age.[2] The lower BC incidence and younger age at onset in developing countries may be partially explained by the scarcity of BC screening programs and cancer registries in them and by the fact that these countries have a much younger population than developed ones. However, these differences across countries may also be the result of differences in exposure to environmental, reproductive and genetic BC risk factors.

Variants in cytochrome P450 *1A1* (*CYP1A1*) and *1B1* (*CYP1B1*) as well as the glutathione S-transferase *mu1* (*GSTM1*), *theta1* (*GSTT1*) and *pi1* (*GSTP1*), all of which codify enzymes that are involved in detoxification pathways via C-or N-hydroxylation as well as in estrogen metabolism, may be related to BC susceptibility, yet scarce information is available.[3]

The aim of this study was to evaluate if variants in the *CYP1A1* (T3801C and A4889G), *CYP1B1* (G119T), *GSTM1* (indel) and *GSTT1* (indel) genes, are associated with BC among Mexican women.

Materials and methods

This is a secondary report from a case–control study, conducted between 2007 and 2011 in five Northern States of Mexico (Sonora, Chihuahua, Coahuila, Nuevo León and Durango) to identify the environmental and genetic risk factors for BC in that area. Detailed information about the study design and recruitment methods is available elsewhere.[4]

Study population

Eligible cases were women of at least 18 years of age with no prior diagnosis of cancer, who were residents of the study areas for at least one year prior to the interview. Patients were identified in 17 public tertiary care hospitals. Population controls were randomly selected from women living in the same residence zones of cases for at least one year prior to the study, with no previous medical history of cancer, and were matched to the cases by age (±5 years).

After signing the informed consent, cases were interviewed at the hospital before receiving any specific treatment (hormonal therapy, chemotherapy and/or radiotherapy), while controls were interviewed at their homes. Information on medical and reproductive history, sociodemographic characteristics and tobacco and alcohol consumption was obtained through face-to-face interviews. Anthropometric measurements (height and weight), as well as a blood sample (10 ml), were obtained from each woman. Incentives were given in the form of grocery vouchers, to increase the response rate. The response rate among cases was 96.4% (n=1045/1084) and 99.9% (n=1030/1031) among controls. The main reason for not participating in the study was lack of interest. This study was approved by the Ethics Committee of Mexico's National Institute of Public Health.

DNA extraction

Buffy coat was obtained from blood samples from which DNA was extracted with the Quick-gDNAMidiPrep kit (Zymo Research). Spectrophotometry was used to quantify and determine DNA purity at 260/280 nm and 260/230 nm wavelengths. DNA samples with a ratio of 1.7 to 1.9 and 2.0 to 2.2, respectively, were considered as acceptable.[5] DNA integrity was visually assessed (2% agarose gels stained with ethidium bromide) in a 10% randomly chosen sample. One hundred twenty-five (31 controls and 94 cases) of the 2 075 available DNA samples were not considered acceptable, yielding 952 cases and 998 controls for further analysis.

Genotyping

SNP variants in *CYP1A1* and *CYP1B1*

SNP variants of *CYP1A1*: rs1048943 (A4889G), rs4646903 (T3801C) and *CYP1B1:* rs1056827 (G119T), were genotyped by allelic discrimination, using TaqMan assays (ABI 7900 Sequence Detection System, Applied Biosystems, Inc.), under the following conditions: denaturalization at 95°C for 10 minutes, 40 cycles of alignment to 92°C for 15 seconds and amplification at 60°C for 1 minute. Sequences from T3801C and G119T, which were not available in the Applied Catalog, were obtained from the National Center of Biotechnology Information. Conditional upon DNA availability, samples were analyzed in duplicate. Negative controls were included on each plate. Amplification failures were as follows: T>C3801 (29 cases and 20 controls), A4889G (25 cases and 11 controls) and G119T (146 cases and 131 controls), which rendered final sample sizes for subsequent analysis of: 923 cases and 978 controls for T>C3801, 927 cases and 987 controls for A4889G, and 806 cases and 867 controls for G119T.

Indel variants in *GSTM1* and *GSTT1*

Indel variants in *GSTM1* and *GSTT1* were identified by Multiplex PCR with the following conditions: enzyme activation at 95°C for 15 minutes, amplification for 40 cycles at 95°C for 30 seconds, alignment at 59°C for 35 seconds and 72°C for 60 seconds, followed by an extension of 10 minutes at 72°C. Two sets of primers were used to amplify segments of 215 pb in *GSTM1* and 480 pb in *GSTT1*.[6] The reaction mixture was prepared in a final volume of 25 µl (1x) including: 20 ng/µl genomic DNA, 0.13 µl HotStarTaq polymerase (QIAGEN, INC.), 0.2 µl *GSTM1* primer, 0.1 µl *GSTT1* primer, 0.6 µl dNTPs and 0.2 µl *DHFR* (dihydrofolate reductase) as positive control. In addition, a mixture without DNA was assessed as negative control. A molecular weight marker from 100 to 3000 pb was used (DNA Ladder, Qiagen). Genotyping was carried out by visual inspection in 10µl of amplified product by electrophoresis in agarose gels (2%). Twenty-five samples from cases and 43 samples from controls did not amplify; therefore, the final sample size for further analysis was: 927 cases and 955 controls.

Ancestry

A panel of 105 ancestry markers previously developed and validated by the Latin American Cancer Epidemiology (LACE) Consortium was used to obtain the percentage of ancestry (Native-American, European and African) on a sub-sample of 1 267 women by employing the ADMIXTURE software.[7,8]

Statistical analysis

Genotype distributions of interest were assessed among controls through the Hardy-Weinberg Equilibrium Test. Linkage disequilibrium was also evaluated for *CYP1A1* variants, with the SNPstats software.[9] Odds ratios (OR), for each reproductive, sociodemographic and lifestyle risk factor for BC considered, were obtained through unconditional logistic regression models, adjusted for age (20-24, 25-29, …. years) and years of schooling; the latter variable was used as a proxy for socioeconomic level.[10] Tests for trend were performed for the corresponding variables in continuous scale.

Association between BC and each genetic variant of interest was evaluated using an unconditional logistic regression model with adjustment for age (20-24, 25-29, …. years), years of schooling, first degree relative with BC (yes, no), age at first full term pregnancy (<21, 21-24, ≥25 years, nulliparous), breastfeeding at first birth (no/nulliparous, 1-6, 7-12, >12 months), consumption of alcohol (yes, no) and tobacco (yes, no). *CYP*s genotypes were evaluated according to the dominant, recessive and co-dominant models. However, only those from the co-dominant model are shown in detail, since results for the other two models were similar. On a subsample of 656 cases and 611 controls, a sensitivity analysis to assess ancestry as a potential confounder was performed. Statistical analyses were conducted with Stata software, version 13 (Stata Corp., College Station, TX, USA).

Results

Due to the study design, there were no significant differences between cases and controls regarding age (approximately 54 years) and place of residence. Compared to controls, BC cases had a significantly higher educational level (8.2 *vs*. 5.9 years of schooling, respectively, p=<0.01) (data not included in table I). BC risk was significantly increased by nulliparity, older age at first full pregnancy, first-degree family BC history, and alcohol and tobacco consumption. In contrast, breastfeeding of first child and body mass index among pre-menopausal women were inversely associated with BC (table I).

Regarding the association between BC and the genetic variants of interest, we only found a statistically significant association of BC with *CYP1B1 (G119T)* polymorphism (table II). After adjustment for other risk factors, the odds of developing BC were 1.9 (95% CI: 1.4 - 2.5) times higher in carriers of the T/T genotype in *CYP1B1* than in carriers of the G/G genotype (co-dominant model) (p<0.05). The corresponding adjusted OR under the dominant (T/T + G/T *vs*. G/G) and recessive models (T/T *vs*. G/G + G/T) were 1.4 (95% CI: 1.1 – 1.8) and 1.7 (95% CI: 1.3 – 2.2), respectively (p<0.05) (data not included in table II). A marginally positive association occurred between *GSTM1* deletion and BC (OR=1.1; 95% CI 0.9-1.4). A borderline significant inverse association was found between BC and GSTT1 deletion (OR= 0.77; 95% CI: 0.62 - 0.97). All genotype distributions were in Hardy-Weinberg Equilibrium. Linkage disequilibrium was observed in *CYP1A1* variants.

The ancestry profile was (mean ± *SD)*: 49.8 ± 15.9% Native-American, 43.3 ± 16.9% European and 6.9 ± 5.4% African among the controls, and 46.9 ± 16.8% Native-American, 45.8 ± 17.5% European and 7.3 ± 6.2% African among the cases (data not included in tables).

Discussion

We found that carriers of the T/T *CYP1B1* G119T genotype were at increased BC risk in the Northern Mexican states. To our knowledge, this is the first report from Latin America showing an increased BC risk due to the variant *CYP1B1* G119T.

Table I

ASSOCIATION BETWEEN BREAST CANCER AND REPRODUCTIVE AND LIFESTYLE RISK FACTORS IN THE STUDY POPULATION. NORTHERN MEXICO, 2007-2011

Characteristics	*Cases (n=952)**	*Controls (n=998)**	*OR (95%CI)‡*
Age at menarche (years)			
>12	558	622	1
≤12	394	376	1.08 (0.89-1.30)
Number of live births			
≥4	463	638	1
1 to 3	414	333	1.42 (1.15-1.76)
Nulliparous	74	27	2.94 (1.83-4.74)
p for trend			0.000
Age at first full-term pregnancy (years)			
<21	380	610	1
21 to 24	228	226	1.31 (1.04-1.66)
≥25	255	132	2.22 (1.71-2.88)
p for trend			0.000
Breastfeeding of first child (months)			
No/Nulliparous	336	161	1
1 to 6	300	275	0.52 (0.40-0.67)
7 to 12	179	349	0.28 (0.21-0.37)
>12	130	210	0.35 (0.26-0.47)
p for trend			0.000
Menopause§			
No	357	337	1
Yes	595	661	0.84 (0.63-1.12)
First degree relative with breast cancer#			
No	831	989	1
Yes	121	9	13.50 (6.77-26.92)
Body Mass Index (kg/m^2)			
Premenopause			
<25	96	67	1
25 to 29.9	133	101	0.90 (0.59-1.39)
30 to 34.9	85	91	0.67 (0.42-1.06)
≥35	36	78	0.36 (0.21-0.61)
p for trend			0.000
Postmenopause			
<25	98	106	1
25 to 29.9	204	224	1.08 (0.76-1.53)
30 to 34.9	172	197	1.06 (0.74-1.51)
≥35	116	133	1.10 (0.75-1.63)
p for trend			0.699
Alcohol consumption&			
No	725	884	1
Yes	225	114	2.07 (1.60-2.68)
Tobacco smoke			
No	341	524	1
Yes	611	474	1.91 (1.58-2.30)

* Differences in total sample size across risk factors in cases or controls are due to missing values
‡ Separate unconditional logistic regression models were fitted for each risk factor. All ORs are adjusted for age (in five-year periods) and years of schooling
§ Menopause ≥365 days without menstrual bleeding
\# Mother, sister or daughter
& Mean (SD), min-max in grams of ethanol per day, among consumers = 1.39 (4.26), 0.05 - 63.23

Table II
Association between breast cancer and the genetic variants of interest. Northern Mexico, 2007-2011

Genetic variant	*Cases/Controls*	*Adjusted OR* (95% CI)*
CYP1A1 (T3801C)‡		
T/T	288/307	1
T/C	450/484	0.98 (0.78-1.24)
C/C	185/187	1.12 (0.84-1.50)
Hardy-Weinberg chi-square test *p*-value		0.88
CYP1A1 (A4889G)‡		
A/A	368/338	1
A/G	409/488	0.77 (0.62-0.96)
G/G	150/161	0.87 (0.65-1.17)
Hardy-Weinberg chi-square test *p*-value		0.50
CYP1B1 (G119T)		
G/G	189/264	1
G/T	342/404	1.16 (0.90-1.51)
T/T	275/199	1.88 (1.41-2.51)
Hardy-Weinberg chi-square test *p*-value		0.06
GSTM1		
Wild-type	472/533	1
Deletion	455/422	1.17 (0.96-1.43)
GSTT1		
Wild-type	682/662	1
Deletion	245/293	0.77 (0.62-0.97)

* Separate unconditional logistic regression models were fitted for each genetic variant. All ORs are adjusted for age (in five-year periods), years of schooling, first degree relative with breast cancer (no, yes), age at first full-term pregnancy (<21, 21-24, ≥25, nulliparous), breastfeeding at first birth (no/nulliparous, 1-6, 7-12, >12 months), consumption of alcohol (no, yes) and tobacco (no, yes)
‡ Linkage equilibrium (T3801C vs A4889G, D'= 0.46, $p \leq 0.001$)

Our results are similar to those observed among the Asian women but not among the African-American or Caucasian women that were included in a recent meta-analysis (9 453 BC cases and 10 607 controls). Among the Asian women, the OR for *CYP1B1* G119T variant was 2.3 (95%CI 1.2–4.5), with the co-dominant model (T/T *vs.* G/G); 2.0 (95%CI 1.3–3.1) with the dominant model, and 1.8 (95% CI 1.1-3.0) with the recessive model. The prevalence of the T/T genotype in our controls was 22.8% compared to 1.1% to 11.6% among populations included in the meta-analysis and 31.0% in Brazilian males of European descent.[11] *CYP1B1* G119T polymorphism results in a substitution of alanine by serine, which enhances the catalytic enzymatic activity in T/T genotype carriers compared to wild-type carriers; its overexpression increases the formation of quinones capable to form DNA adducts.[12]

We found that *GSTM1* deletion seemed to marginally increase BC risk. This result is very close to that found in a meta-analysis of 15 studies that also included Asian women (OR=1.2; 95%CI 1.1–1.3), and in another pooled analysis of 61studies (OR=1.1; 95%CI 1.1-1.2).[13,14] However, a recent, smaller study among Mexican women found a stronger association between *GSTM1* deletion and BC risk (OR=2.1; 95%CI 1.5-3.2).[15] Null genotype carriers might be at higher risk of BC because of a complete absence of GSTM1 enzyme activity in the detoxification of toxic compounds and endogenous hormones.[13,16]

Despite the biological evidence suggesting that the variants *CYP1A1* T3801C and A4889G are related to the formation of carcinogenic metabolites[17], and that *GSTT1* deletion is associated with a reduced detoxification capacity, our results showed that neither of them is

significantly associated to BC risk, a fact that supports the findings of several previous studies. At least four meta-analyses have shown a lack of association between T3801C variant and BC risk,[18-22] as well as between A4889G variant and BC.[18] Moreover, a non-significant association between A4889G carriers and BC has been reported among Mexican women.[23] Likewise, another pooled analysis[24] and two Mexican studies[15,23] have found no association between *GSTT1* deletion and BC risk. These findings are in contrast to the increased BC risk that has been observed in non-native American populations.[14,25-27]

Some methodological considerations should be taken into account to interpret our results. The genotype distributions of interest did not deviate from the expected values; which implies that our study population was not genetically atypical. It has been suggested that, within the Hispanic population, BC risk may differ depending on the amount of the European *vs.* American Indian genetic heritage. Therefore, a panel of 105 ancestry markers was determined in a subsample of 1 267 women. The analysis of this subsample showed that ancestry did not confound the results for most of the variants of interest; however, it did not help us to determine this situation, for *CYP1B1* G119T variant that was not in Hardy-Weinberg equilibrium (table III). All laboratory personnel were blinded to case-control status, to reduce the likelihood of differential error;

Table III
Breast cancer risk according to the genetic variants in a subsample of 1267 women: ancestry sensitivity analysis. Northern Mexico, 2007-2011

Genetic variant	*Cases/Controls*	*Model*	
		1 OR* (95% CI)	*2* OR‡ (95% CI)
CYP1A1 (T3801C)			
T/T	198/194	1	1
T/C	306/298	1.05 (0.79-1.39)	1.04 (0.78-1.38)
C/C	134/105	1.33 (0.93-1.91)	1.32 (0.92-1.88)
Hardy-Weinberg chi-square test *p*-value		0.61	
CYP1A1 (A4889G)			
A/A	235/198	1	1
A/G	288/295	0.75 (0.57-0.99)	0.75 (0.57-0.99)
G/G	113/108	0.86 (0.60-1.22)	0.85 (0.60-1.22)
Hardy-Weinberg chi-square test *p*-value		0.92	
CYP1B1 (G119T)			
G/G	150/147	1	1
G/T	226/233	1.00 (0.73-1.37)	1.00 (0.73-1.37)
T/T	160/133	1.21 (0.85-1.72)	1.21 (0.85-1.72)
Hardy-Weinberg chi-square test *p*-value		0.04	
GSTM1			
Wild-type	327/331	1	1
Deletion	304/237	1.31 (1.02-1.69)	1.32 (1.02-1.69)
GSTT1			
Wild-type	454/394	1	1
Deletion	177/174	0.80 (0.61-1.06)	0.80 (0.61-1.06)

* Model 1: A Separate unconditional logistic regression models were fitted for each genetic variant. All ORs are adjusted for age (in five-year periods), years of schooling, first degree relative with breast cancer (no, yes), age at first full-term pregnancy (<21, 21-24, ≥25, nulliparous), breastfeeding at first birth (no/nulliparous, 1-6, 7-12, >12 months), consumption of alcohol (no, yes) and tobacco (no, yes)
‡ Model 2: ORs adjusted for the same covariates in Model 1 plus percentage of ancestry (Native-American, European and African)

however, we cannot rule out that our estimates may be underestimated, due to non-differential errors resulting from the less than total sensitivity and specificity of the laboratory techniques.

In conclusion, our results support the existence of genetic susceptibility for BC conferred by the variant *CYP1B1* G119T among Mexican women. The potential interaction between the exposure to carcinogenic compounds and genetic susceptibility warrants further attention.

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