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ORIGINAL PAPER

Pathological characteristics, survival, and risk of breast cancer associated with estrogen and xenobiotic metabolism polymorphisms in Mexican women with breast cancer

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Abstract

Prolonged exposure to estrogens is the main factor associated with the risk and prognosis of breast cancer (BC). The genes involved in the biotransformation of estrogens and xenobiotics have allelic variants with modified enzymatic activities. We investigated the association of nine polymorphisms of some genes from the classical estrogen pathway with the risk of breast cancer and their role in the clinicopathological characteristics of poor clinical prognosis in a sample of Mexican women with BC. Methods: We included 150 controls and 150 cases matched by age. To analyze the selected polymorphisms, TaqMan assays and high-resolution melting (HRM) analysis were used. Results: The polymorphisms of the genes *ERα*, *CYP1A1*, *CYP1B1*, *COMT*, *MGMT*, and *XRCC1* were positively associated with the BC risk. We found negative associations between *CYP1B1*$^{G/G}$ genotype and tumor size, and status of lymph node, estrogen receptor, triple negative, and survival. Conclusions: The polymorphisms included in this study are associated not only with the risk of BC, but also with some clinicopathological characteristics for poor prognosis of patients with breast cancer, highlighting the important role of *CYP1B1* Leu432Val polymorphism.

Keywords Breast cancer · Genetic polymorphism · Mexican women · Prognosis · Breast cancer

Introduction

Breast cancer (BC) is the most common cancer among women worldwide. Many factors such as age, sex, genetic background, lifestyle, and ethnicity are associated with the risk of developing breast cancer. However, prolonged exposure to estrogens is considered to be the main factor associated with both risk and prognosis of disease development [1].

Classical estrogen pathways include ligand binding to the estrogen receptor (ERα) in the cytoplasm, after which the receptor dimerizes, translocates to the nucleus, and binds to estrogen response elements (EREs) located near the promoters of genes of phase I metabolism [2]. On the other hand, polycyclic aromatic hydrocarbons (PAHs) are widespread environmental contaminants that interact in a complex manner with both the aryl hydrocarbons receptor (AhR) and estrogen receptors (ERs). Their potential endocrine-disrupting activities may depend on both inhibitory AhR–ER crosstalk and AhR-dependent metabolic production of estrogenic PAH metabolites. After binding its ligand, AhR translocates into the nucleus and dimerizes with an AhR nuclear translocator (ARNT) [3]

Activation of ERs and AhRs includes relevant proposed mechanisms of crosstalk between their signaling pathways from the step of heterodimerization (for AhR with ARNT) or homodimerization (for ERs). AhR has been reported to

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inhibit ER activity through a combination of different mechanisms: direct inhibition by the activated AhR/ARNT heterodimer through binding to inhibitory xenoestrogen receptor (iXRE) present in ER target genes and squelching of shared coactivators, including ARNT.

Inside the cell, estrogens and xenobiotics, after binding to their specific receptors, are transformed by enzymes of phase I metabolism (CYP1A1 and CYP1B1) and phase II metabolism [glutathione S-transferases (GSTs) and catechol *O*-methyl transferase (COMT)], generating products that could interact with DNA to form adducts. These adducts can induce mutations that may initiate cancer processes. However, there are enzymes capable of reverting the damage caused to the DNA, which are known as repair enzymes, such as methylguanine-DNA methyltransferase (MGMT) [4] and X-ray repair cross-complementing (XRCC1) [5].

The genes involved in the biotransformation of estrogens and xenobiotics and the metabolism of agents used in the treatment of breast cancer have allelic variants with modified enzymatic activities (Table 1). These alleles have been widely studied in different populations, including the Mexican population. In 2013, our work group determined the associations of the polymorphisms *CYP1A1* rs1048943, *CYP1B1* rs1056836, *COMT* rs4680, *GSTT1* null, and *GSTM1* null, finding a significant association (OR = 1.95, CI 1.13–3.36) between *CYP1A1* rs1048943 polymorphism and risk of breast cancer. The results showed that breast cancer risk significantly increases in women with three to six risk polymorphisms [6]. Due to this important association between breast cancer risk and the studied genes, we decided to include the *AhR* rs2066853, *ER*α rs2234693 *MGMT* rs12917, and *XRCC1* rs25487 polymorphisms to provide further information about the importance of genes of the catechol pathway and determine whether these nine polymorphisms are associated with breast cancer risk, clinicopathological characteristics, and survival in our sample of Mexican women.

Materials and methods

Subjects

We included 150 Mexican Mestizo women who attended the Instituto Nacional de Cancerología (Mexico City) from 2006 to 2007. These patients were diagnosed with in situ (38 cases) or invasive (112 cases) breast carcinoma. All patients were over 30 years old and had no history of hereditary BC syndrome, according to the specifications of the US National Cancer Institute and the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. The clinicopathological and survival data were taken from the clinical records of the Instituto Nacional de Cancerología.

We included 150 controls. Healthy Mexican Mestizo women were selected from blood donors who attended the Hospital "20 de Noviembre" in Mexico City from October 2001 to November 2004. Women filled out a questionnaire, which included data about age, birthplace, parents' and grandparents' birthplace, and lifestyle. Controls were healthy age-paired women without diagnosis of BC.

Informed consent was obtained from all participants, who also answered a questionnaire about risk factors for BC; all participants and their parents and grandparents were born in Mexico.

The research protocol was approved by the Bioethics Committees of the Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México and the Instituto Nacional de Cancerología (Mexico City). The Hospital "20 de Noviembre" gave permission to use the buffy coat of blood bank samples.

Table 1 Genetic polymorphisms involved in estrogen and xenobiotic metabolism

Gene	Role in biotransformation of estrogens and xenobiotics	Genotype	Functional effect	References
AhR (rs2066853)	Ligand-activated transcription factor	G → A	Increased activity	[7]
ERα (rs2234693)		C → T	*Affects the binding of the transcription factor*	[8]
CYP1A1 (rs1048943)	Activation by hydroxylation	A → G	Increased activity	[9]
CYP1B1 (rs1056836)		C → G	Increased activity	[10]
COMT (rs4680)	Detoxification by methylation	G → A	Four times reduced methylation activity	[11]
GSTT1 (deletion)	Detoxification by glutathionylation	Null	Lack of enzyme	[12]
GSTM1 (deletion)		Null	Lack of enzyme	
MGMT (rs12917)	Repair O^6-alkylguanine adducts	C → T	Lack of enzyme	[4]
XRCC1 (rs25487)	Base excision repair pathway	A → G	Lack of enzyme	[13]

DNA samples

DNA samples used for genotyping analyses were extracted from blood samples collected and stored at −20°C until use. Mononuclear white cells and genomic DNA were isolated as described by Lahiri and Cols [7].

Genotyping

The *CYP1A1* rs1048943, *CYP1B1* rs1056836, *COMT* rs4680, and *XRCC1* rs25487, GSTT1 and GSTM1 polymorphisms were determined as mentioned before [5, 6]. TaqMan assays were used for genotyping of *AhR* rs2066853 and *ERα* rs2234693 according to manufacturer specifications. The polymorphism *MGMT* rs12917 was determined by high-resolution melting (HRM) analysis. The sequences of primers were as follows: 5-CTGCTAATGCCTATTTCC-3 (forward primer) and 5-AACACCGCAGATGGCTTAGT-3 (reverse primer). PCR consisted of initial denaturing at 94 °C for 5 min, followed by 35 cycles of denaturing at 94 °C for 20 s, annealing at 62 °C for 20 s, and extension at 72 °C for 20 s, with final extension at 72 °C for 10 min. HRM analysis was performed using temperatures in the range from 80–90 °C in 0.1 °C increments. PCR amplifications using EvaGreen were carried out in 10 µL volumes containing 2× HRM master mix (contains HotStar Taq Plus DNA Polymerase, EvaGreen dye, 10 µM each primer, and 10 ng template DNA). PCR and subsequent melt curve analysis was carried out in a Rotor-Gene 6000 (Corbett Research). The increase and decrease in fluorescence of EvaGreen during PCR and the melt phase was acquired on the HRM of the Rotor-Gene.

Statistical Analyses

Hardy–Weinberg equilibrium (HWE) was tested separately in cases and controls for each polymorphism, when applicable, using statistical package GenePop version 4.0.10 (http://genepop.curtin.edu.au).

Epidemiological risk factors, risk of developing BC, and the associations between polymorphisms and the clinicopathological characteristics of patients were examined using the chi-square test with Yates correction for data $n \leq 5$ to calculate the crude odds ratio (OR) with 95% confidence interval (CI). The former two tests were carried out using GraphPad Prism 5 software. Assuming a biological activity gradient (codominant model), the heterozygous and homozygous variant genotypes of these genes were compared with the homozygous wild-type genotype. Groups having the lowest risk were used as reference.

Survival distributions were estimated by the Kaplan–Meyer method and compared by log-rank test.

Statistical differences were considered significant for $p \leq 0.05$. All p-values reported are two tailed.

Results

The genotypes tested were under HWE. Table 2 presents the allelic and genotypic frequencies of the nine polymorphisms studied.

A statistically significant negative association with BC risk was found for *AhR* A (OR = 0.55; $p = 0.01$) and $AhR^{A/G}$ (OR = 0.50; $p = 0.03$). On the other hand, a positive association with BC risk was observed for the polymorphisms *ER* alpha C (OR = 1.98; $p = < 0.0001$), $ER\alpha^{C/C}$ (OR = 3.2; $p = 0.0006$), $CYP1A1^{G/G}$ (OR = 1.95; $p = 0.01$), *CYP1B1* G (OR = 1.48; $p = 0.02$),*COMT* A (OR = 1.42; $p = 0.04$), *MGMT* T (OR = 1.42; $p = 0.04$), $MGMT^{T/T}$ (OR = 3.77; $p = < 0.0001$), *XRCC1* G (OR = 1.92; $p = 0.0004$), and $XRCC1^{G/G}$ (OR = 3.85; $p = 0.0006$). It is important to clarify that Table 2 shows data previously published by our group, which are highlighted in bold.

The clinicopathological characteristics of breast cancer patients are presented in Table 3. Most breast cancer patients included were over 35 years old. With respect to tumor stage, 37.3% were classified as IIIA and 30.6% as IIIB, 74.6% showed invasive carcinomas, 26% showed lobular histopathological type, and 39.3% were triple negative.

To determine whether the polymorphisms have an effect on the different clinical features of breast cancer patients, we analyzed associations between the nine polymorphisms and different clinical parameters (age at diagnosis, tumor stage, malignant lesions, tumor size, lymph node status, distant metastasis, histological type of cancer, estrogen receptor status, progesterone receptor status, HER-2/neu status, and triple-negative status); we mention only the associations that were statistically significant.

We found a negative association between $CYP1B1^{G/G}$ polymorphism and tumor size > T2 (OR = 0.40; $p = 0.05$) and lymph node status N2 + N3 (OR = 0.34; $p = 0.04$) an,d between $AhR^{G/A}$ polymorphism and lymph node status N2 + N3 (OR = 0.28; $p = 0.02$) (Table 4).

When we examined the association between polymorphisms and negative status of estrogen receptor, we only found a negative association for the *CYP1B1* rs1056836 polymorphism ($CYP1B1^{C/G}$ OR = 0.39; $CYP1B1^{G/G}$ OR = 0.29) (Table 5).

The associations between polymorphisms and triple-negative status showed statistical significance for $CYP1B1^{G/G}$ (OR = 3.9; $p = 0.01$) (Table 6).

Interestingly, we found that $CYP1B1^{G/G}$ was associated negatively with survival ≤ 5 years (OR = 0.07; $p = 0.01$) (Table 7).

In addition, we plotted Kaplan–Meier curves for survival versus time (months) for all polymorphisms included in this study, finding a significant relationship for the $CYP1B1^{C/C}$ genotype (Fig. 1).

Table 2 Allele/genotype frequency of polymorphisms from breast cancer patients and control women, and the association with risk of breast cancer

Gene rs	Allele/ genotype	Cases $n=150$	Controls $n=150$	OR (95% CI)	p-Value
AhR	G	**n (%)**	**n (%)**	1[a]	0.01*
rs2066853	A	266 (88.6)	244 (81.3)	0.55 (0.35–0.88)	
		34 (11.3)	56 (18.6)		
	G/G	123 (82)	105 (70)	1[a]	0.03*
	G/A	20 (13.3)	34 (22.6)	0.50 (0.27–0.92)	0.23
	A/A	7 (4.6)	11 (7.3)	0.54 (0.20–1.45)	
ERα	T	90 (30)	138 (46)	1[a]	< 0.0001*
rs2234693	C	210 (70)	162 (54)	1.98 (1.42–2.78)	
	T/T	18 (12)	36 (24)	1[a]	0.18
	T/C	54 (36)	66 (44)	1.63 (0.83–3.20)	0.0006*
	C/C	78 (52)	48 (32)	3.2 (1.66–6.35)	
CYP1A1	A	115 (38.3)	157 (52.3)	1[a]	0.0008
Rs1799814	G	185 (61.6)	143 (47.6)	1.76 (1.27–2.44)	
	A/A	**39 (27.3)**	**57 (37.3)**	**1 [a]**	**0.65**
	A/G	**37 (26.0)**	**43 (30.0)**	**1.18 (0.65–2.1)**	**0.01***
	G/G	**74 (46.6)**	**50 (32.6)**	**1.95 (1.13–3.36)**	
CYP1B1	C	100 (33.3)	128 (42.6)	1[a]	0.02*
rs1056836	G	200 (66.6)	172 (57.3)	1.48 (1.06–2.07)	
	C/C	**27 (18)**	**33 (20.6)**	**1 [a]**	**0.62**
	C/G	**46 (30.6)**	**62 (42)**	**0.83 (0.44–1.59)**	**0.15**
	G/G	**77 (51.3)**	**55 (37.3)**	**1.57 (0.84–2.93)**	
GSTT1	**Wild type**	**103 (68.6)**	**108 (72)**	**1 [a]**	**0.61**
	Null	**47 (31.3)**	**42 (28)**	**1.17 (0.71–1.92)**	
GSTM1	**Wild type**	**85 (56.6)**	**89 (58.6)**	**1 [a]**	**0.81**
	Null	**65 (43.3)**	**61 (41.3)**	**1.08 (0.68–1.71)**	
COMT	G	170 (56.6)	195 (65)	1[a]	0.04*
rs4680	A	130 (43.3)	105 (35)	1.42 (1.02–1.97)	
	G/G	**52 (34.6)**	**68 (44.6)**	**1 [a]**	**0.15**
	G/A	**66 (44.0)**	**59 (38.6)**	**1.46 (0.88–2.43)**	**0.14**
	A/A	**32 (21.3)**	**23 (16.6)**	**1.64 (0.87–3.1)**	
MGMT	C	151 (50.3)	204 (68)	1[a]	0.04*
rs12917	T	149 (49.6)	96 (32)	1.42 (1.02–1.97)	
	C/C	53 (35.3)	73 (48.3)	1[a]	0.89
	C/T	45 (30)	58 (38.6)	1.06 (0.63–1.80)	< 0.0001*
	T/T	52 (34.6)	19 (12.6)	3.77 (2.00–7.10)	
XRCC	A	188 (62.6)	229 (76.3)	1[a]	0.0004*
rs25487	G	112 (37.3)	71 (23.6)	1.92 (1.34–2.73)	
	A/A	67 (44.6)	89 (59.3)	1[a]	0.20
	A/G	54 (36)	51 (34)	1.40 (0.85–2.31)	0.0006*
	G/G	29 (19.3)	10 (6.6)	3.85 (1.75–8.45)	

*Significant values

[a]Reference value; *OR* odds ratio; *CI* confidence interval. Letters in bold are previously published data [6]

Table 3 Clinicopathological features of breast cancer patients

Variable	$n = 150$ (%)
Age at diagnosis (years)	
≤ 35	16 (10.6)
> 35	134 (89.3)
Tumor stage	
IIA	1 (0.66)
IIIA	56 (37.3)
IIB	37 (24.6)
IIIB	46 (30.6)
IIIC	7 (4.6)
IV	3 (2.0)
Malignant lesions	
In situ	38 (25.3)
Invasive carcinomas	112 (74.6)
Tumor size	55 (36.6)
≤ T2	95 (63.3)
> T2	
Lymph node status	83 (55.3)
NO + N1	67 (44.6)
N2 + N3	
Distant metastasis	144 (96)
M0	6 (4)
M1	
Histological type of cancer	
Ductal	111 (74)
Lobular	39 (26)
Estrogen receptor status	
ER negative (−)	75 (50)
ER positive (+)	75 (50)
Progesterone receptor status	
PR negative (−)	101 (67.3)
PR positive (+)	49 (32.6)
HER-2/neu status	
Negative (−)	125 (83.3)
Positive (+)	25 (16.6)
Triple-negative status	
Negative (−)	91 (60.6)
Positive (+)	59 (39.3)

Discussion

The allelic and genotypic frequencies determined in our study for *AhR* rs2066853 are similar to those reported for a population of Mexican women by Sierra-Martinez in 2016 [8]. However, they did not find any association with breast cancer risk, while in our study we found significant negative associations, both with the heterozygous variant and the homozygous mutant. These differences may be due to the smaller size used: They had 96 cases and 111 controls [8], while we used 150 cases and 150 controls. On the other hand, Sierra-Martinez does not report an association between *ERα* rs2234693 polymorphism and the risk of breast cancer in postmenopausal women [8], while we found a risk association with the T allele (OR = 1.98), and the C/C genotype (OR = 3.2).

When we compared the alleles of *CYP1B1* we found a positive association between breast cancer risk and the Val allele, which may be because the C4326G transition (*CYP1B1*3* C/G) leading to the corresponding amino acid transition is associated with increased catalytic activity. A possible cause of this increase in catalytic activity might be changes in the tertiary (or quaternary) structure of the CYP1B1 protein, as the *CYP1B1*3* polymorphism is located near a catalytically important heme-binding domain in *CYP1B1* [9]. Furthermore, the *CYP1B1*3* transition is also responsible for significant increases in AhR-mediated *CYP1B1* gene expression during AhR-mediated signaling event.

We found that homozygous mutants *MGMT* $^{T/T}$ are associated with risk of BC, and this could be related to the Leu84Phe polymorphism in the *MGMT* gene, since it has been reported in other populations that such polymorphism affects DNA repair capability and enzymatic activity, thereby leading to the risk of breast cancer [14].

The relationship between breast cancer risk and *XRCC1* polymorphism rs25487 could be because the *XRCC1* gene is necessary for maintenance of genetic stability, and its DNA repair capacity can be reduced due to the change of Arg for Gln, which could lead to accumulated DNA damage, mutations, and subsequently development of diseases such as cancer. On the other hand, it has been indicated that

Table 4 Associations between polymorphisms and tumor size and lymph node status

Gene rs	Genotype	Patients, *n* (%)		OR (95% CI)	*p*-Value	Patients, *n* (%)		OR (95% CI)	*p*-Value
		Tumor size				Lymph node status			
		> T2 *n* = 95	≤ T2 *n* = 55			N2 + N3 *n* = 67	N0 + N1 *n* = 83		
AhR	G/G	81 (85.2)	42 (76.3)	1[a]	0.21	57 (85.0)	66 (79.5)	1[a]	0.02*
rs2066853	G/A	10 (10.5)	10 (18.1)	0.51 (0.20–1.34)	0.94[1]	4 (5.97)	16 (19.2)	0.28 (0.09–0.91)	0.10[1]
	A/A	4 (4.2)	3 (5.4)	0.69 (0.17–2.85)		6 (8.95)	1 (1.20)	6.94 (1.06–80.81)	
ERα	T/T	13 (13.6)	5 (9.0)	1[a]	0.40[1]	9 (13.4)	9 (10.8)	1[a]	0.79
rs2234693	T/C	31 (32.6)	23 (41.8)	0.51 (0.18–1.57)	0.78[1]	25 (37.3)	29 (34.9)	0.86 (0.29–2.50)	0.60
	C/C	51 (53.6)	27 (49.0)	0.72 (0.26–2.07)		33 (49.2)	45 (54.2)	0.73 (0.26–2.04)	
CYP1A1	A/A	36 (37.8)	22 (40)	1[a]	1.0	24 (35.8)	34 (40.9)	1[a]	0.68
Rs1799814	A/G	30 (31.5)	17 (30.9)	1.07 (0.48–2.39)	0.83	17 (25.3)	30 (36.1)	0.80 (0.36–1.77)	0.11
	G/G	29 (30.5)	16 (29.0)	1.10 (0.49–2.48)		26 (38.8)	19 (22.8)	1.93 (0.88–4.26)	
CYP1B1	C/C	53 (55.7)	20 (36.3)	1[a]	0.48	40 (59.7)	33 (39.7)	1[a]	0.09
rs1056836	C/G	28 (29.4)	22 (40)	0.48 (0.22–1.02)	0.05*	19 (28.3)	31 (37.3)	0.50 (0.24–1.05)	0.04*
	G/G	14 (14.7)	13 (23.6)	0.40 (0.16–1.03)		8 (11.9)	19 (22.8)	0.34 (0.13.0.89)	
GSTT1	Wild type	71 (74.7)	34 (61.8)	1[a]	0.10	46 (68.6)	59 (71.0)	1[a]	0.85
	Null	24 (25.2)	21 (38.1)	0.54 (0.26–1.11)		21 (31.3)	24 (28.9)	1.12 (0.55–2.26)	
GSTM1	Wild type	55 (57.8)	27 (49.0)	1[a]	0.31	33 (49.2)	49 (59.0)	1[a]	0.25
	Null	40 (42.1)	28 (50.9)	0.70 (0.35–1.36)		34 (50.7)	34 (40.9)	1.48 (0.77–2.84)	
COMT	G/G	33 (34.7)	20 (36.3)	1[a]	1.0	27 (40.2)	26 (31.3)	1[a]	0.45
rs4680	G/A	37 (38.9)	24 (43.6)	0.93 (0.43–1.99)	0.5	26 (38.8)	35 (42.1)	0.71 (0.34–1.50)	0.28
	A/A	25 (26.3)	11 (20)	1.37 (0.55–3.39)		14 (20.8)	22 (26.5)	0.61 (0.25–1.44)	
MGMT	C/C	31 (32.6)	23 (41.8)	1[a]	1.0	18 (26.8)	36 (43.3)	1[a]	0.21
rs12917	C/T	26 (27.3)	19 (34.5)	1.01(0.45–2.26)	0.09	21 (31.3)	24 (28.9)	1.75 (0.77–3.95)	0.03*
	T/T	38 (40)	13 (23.6)	2.16 (0.94–4.97)		28 (41.7)	23 (27.7)	2.43 (1.10–5.36)	
XRCC	A/A	81 (85.2)	42 (76.3)	1[a]	0.21	31 (46.2)	35 (42.1)	1[a]	1.0
rs25487	A/G	10 (10.5)	10 (18.1)	0.51 (0.20–1.34)	0.94[1]	26 (38.8)	29 (34.9)	1.01 (0.49–2.07)	0.36
	G/G	4 (4.21)	3 (5.45)	0.69 (0.17–2.85)		10 (14.9)	19 (22.8)	0.59 (0.24–1.47)	

*Significant values; [1] *p*-Value with Yates correction

[a]Reference value; *OR* odds ratio; *CI* confidence interval

polymorphisms in *XRCC1* play a contributing role in the formation of DNA adducts and an increased risk of developing cancer [12].

We found a negative association between *CYP1B1* G/G polymorphism and tumor size, lymph node status, and estrogen receptor status. These associations may be due to increased activity of *CYP1B1* because of polymorphism rs1056836, and increased catabolism of estradiol reflected by the decrease in estradiol levels and induction of ERα, favoring reduction of tumor size and lymph node status. This theory can be supported by reports describing a close relationship between this polymorphism and clinicopathological characteristics leading to poor prognosis [9, 13].

The negative relationship between *CYP1B1*3* polymorphism and clinicopathological characteristics of poor prognosis may be congruent with the positive association between this polymorphism and the increase in survival of patients with the G/G genotype.

Table 5 Associations between polymorphisms and estrogen receptor status

Gene rs	Genotype	Patients, *n* (%)			
		Estrogen receptor status			
		ER negative (−) *n* = 75	ER positive (+) *n* = 75	OR (95% CI)	*p*-Value
AhR	G/G	62 (82.6)	61 (81.3)	1[a]	0.81
rs2066853	G/A	11 (14.6)	9 (12.0)	1.20 (0.46–3.10)	0.46[1]
	A/A	2 (2.6)	5 (6.6)	0.39 (0.07–1.96)	
ER	T/T	7 (9.3)	11 (14.6)	1[a]	0.28
rs2234693	T/C	30 (40)	24 (32.0)	1.96 (0.66–5.83)	0.60
	C/C	38 (50.6)	40 (53.3)	1.49 (0.52–4.25)	
CYP1A1	A/A	29 (38.6)	29 (38.6)	1[a]	0.43
Rs1799814	A/G	19 (25.3)	28 (37.3)	0.67 (0.31–1.47)	0.32
	G/G	27 (36)	18 (24.0)	1.5 (0.68–3.29)	
CYP1B1	C/C	46 (61.3)	27 (36.0)	1[a]	0.01*
rs1056836	C/G	20 (26.6)	30 (40.0)	0.39 (0.18–0.81)	0.01*
	G/G	9 (12)	18 (24.0)	0.29 (0.11–0.74)	
GSTT1	Wild type	52 (69.3)	53 (70.6)	1[a]	1.00
	Null	23 (30.6)	22 (29.3)	1.06 (0.52–2.14)	
GSTM1	Wild type	41 (54.6)	41 (54.6)	1[a]	1.00
	Null	34 (45.3)	34 (45.3)	1.0 (0.52–1.90)	
COMT	G/G	26 (34.6)	27 (36.0)	1[a]	0.57
rs4680	G/A	26 (34.6)	35 (46.6)	0.77 (0.36–1.61)	0.19
	A/A	23 (30.6)	13 (17.3)	1.83 (0.77–4.37)	
MGMT	C/C	22 (29.3)	32 (42.6)	1[a]	0.31
rs12917	C/T	23 (30.6)	22 (29.3)	1.52 (0.68–3.37)	0.07
	T/T	30 (40)	21 (28.0)	2.07 (0.95–4.52)	
XRCC	A/A	35 (46.6)	31 (41.3)	1[a]	0.46
rs25487	A/G	25 (33.3)	30 (40.0)	0.73 (0.36–1.51)	1.00
	G/G	15 (20.0)	14 (18.6)	0.94 (0.39–2.27)	

*Significant values; [1] *p*-Value with Yates correction [a] Reference value; *OR* odds ratio; *CI* confidence interval

Another possible explanation for the association between the genotype and an increase in breast cancer patients' survival may be that CYP1B1 is involved in the metabolism of some clinically relevant anticancer agents used in the treatment of cancers [9].

Although the sample included in this study is adequate, when dividing it by clinicopathological characteristics, it may be insufficient, but the data obtained show statistically significant associations between the polymorphisms included and the prognosis and survival of Mexican women with breast cancer.

Conclusions

We demonstrate, for the first time, that genes involved in phase I and II metabolism of xenobiotics and estrogens are associated not only with the risk of breast cancer but also with the clinicopathological characteristics of poor prognosis of patients with breast cancer, highlighting the important role of $CYP1B1^{G/G}$, as it has also been shown to be associated with longer survival in Mexican Mestizo women with breast cancer.

Table 6 Associations between polymorphisms and triple-negative status

Gen rs	Genotype	Patients, *n* (%)		OR (95% CI)	*p*-Value
		Triple negative *n* = 25	Not triple negative *n* = 125		
AhR	G/G	24 (96)	99 (79.2)	1[a]	0.20[1]
rs2066853	G/A	1 (4)	19 (15.2)	0.21 (0.02–1.41)	–
	A/A	0	7 (5.6)	–	
ER	T/T	1 (4)	17 (13.6)	1[a]	0.21[1]
rs2234693	T/C	12 (48)	42 (33.6)	4.8 (0.71–54.8)	0.47[1]
	C/C	12 (48)	66 (52.8)	3.09 (0.46–34.9)	
CYP1A1	A/A	8 (32)	50 (40)	1[a]	0.45
rs1799814	A/G	9 (36)	38 (30.4)	1.48 (0.52–4.19)	0.57
	G/G	8 (32)	37 (29.6)	1.35 (0.46–3.93)	
CYP1B1	C/C	7 (28)	66 (52.8)	1[a]	0.10
rs1056836	C/G	10 (40)	40 (32)	2.35 (0.83–6.68)	0.01*
	G/G	8 (32)	19 (15.2)	3.9 (1.27–12.36)	
GSTT1	Wild type	13 (52)	92 (73.6)	1[a]	0.03
	Null	12 (48)	33 (26.4)	2.57 (1.06–6.20)	
GSTM1	Wild type	13 (52)	69 (55.2)	1[a]	0.76
	Null	12 (48)	56 (44.8)	1.13 (0.48–2.68)	
COMT	G/G	9 (36)	44 (35.2)	1[a]	0.88
rs4680	G/A	11 (44)	50 (40)	1.07 (0.40–2.83)	0.92[1]
	A/A	5 (20)	31 (24.8)	0.78 (0.27–2.67)	
MGMT	C/C	8 (32)	46 (36.8)	1[a]	0.22
rs12917	C/T	11 (44)	34 (27.2)	1.86 (0.67–5.12)	0.64
	T/T	6 (24)	45 (36)	0.76 (0.24–2.38)	
XRCC	A/A	14 (56)	52 (41.6)	1[a]	0.34
rs25487	A/G	8 (32)	47 (37.6)	0.63 (0.24–1.64)	0.32[1]
	G/G	3 (12)	26 (20.8)	0.42 (0.66–8.12)	

*Significant values; [1] *p*-Value with Yates correction

[a]Reference value; *OR* odds ratio; *CI* confidence interval

Table 7 Associations between studied polymorphisms and survival

Gene rs	Genotype	Patients, *n* (%)		OR (95% CI)	*p*-Value
		Survival			
		≤5 years *n* = 36	>5 years *n* = 114		
AhR	G/G	32 (88.8)	91 (79.8)	1[a]	0.43[1]
rs2066853	G/A	3 (8.33)	17 (14.9)	0.50 (0.14–1.80)	0.80[1]
	A/A	1 (2.77)	6 (5.26)	0.47 (0.40–3.13)	
ER	T/T	4 (11.1)	14 (12.2)	1 a	1.0
rs2234693	T/C	11 (30.5)	43 (37.7)	0.89 (0.24–3.26)	0.77
	C/C	21 (58.3)	57 (50.0)	1.28 (0.38–4.36)	
CYP1A1	A/A	14 (38.8)	44 (38.5)	1[a]	0.63
Rs1799814	A/G	9 (25)	38 (33.3)	0.74 (0.28–1.91)	0.65
	G/G	13 (36.1)	32 (28.0)	1.27 (0.52–3.08)	
CYP1B1	C/C	25 (69.4)	48 (42.1)	1[a]	0.10
rs1056836	C/G	10 (27.7)	40 (35.0)	0.48 (0.20–1.11)	0.004*[1]
	G/G	1 (2.7)	26 (22.8)	0.07 (0.00–0.47)	
GSTT1	Wild type	26 (72.2)	79 (69.2)	1[a]	0.83
	Null	10 (27.7)	35 (30.7)	0.86 (0.37–1.99)	
GSTM1	Wild type	17 (47.2)	65 (57.0)	1[a]	0.34
	Null	19 (52.7)	49 (42.9)	1.48 (0.69–3.14)	
COMT	G/G	15 (41.6)	38 (33.3)	1[a]	0.17
rs4680	G/A	10 (27.7)	51 (44.7)	0.49 (0.20–1.22)	0.81
	A/A	11 (30.5)	25 (21.9)	1.11 (0.44–2.81)	
MGMT	C/C	14 (38.8)	40 (35.0)	1[a]	0.46
rs12917	C/T	8 (22.2)	37 (32.4)	0.61 (0.23–1.64)	1.0
	T/T	14 (38.8)	37 (32.4)	1.08 (0.452.56)	
XRCC	A/A	15 (41.6)	51 (44.7)	1[a]	0.67
rs25487	A/G	15 (41.6)	40 (35.0)	1.27 (0.55–2.91)	1.0
	G/G	6 (16.6)	23 (20.1)	0.88 (0.30–2.57)	

*Significant values; [1] *p* value with Yates correction

[a]Reference value; *OR* odds ratio; *CI* confidence interval

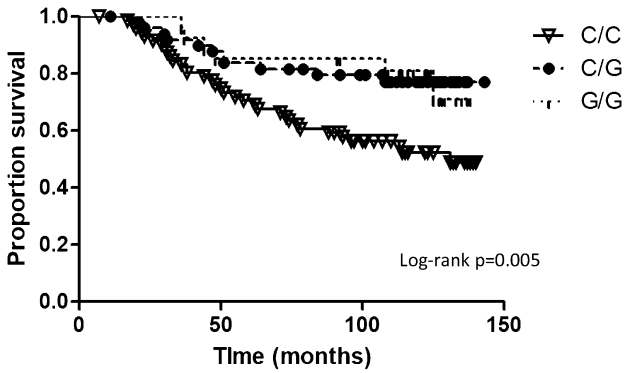

Fig. 1 Effect of *CYP1B1* rs1056836 on survival proportion

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Data availability Data available.

Code availability Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare that they do not have any conflicts of interest.

Ethical approval The research protocol was approved by the Bioethics Committees of the Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México and the Instituto Nacional de Cancerología (Mexico City).

Consent to participate Informed consent was obtained from all participants.

References

1. Hussain T, Alrokayan S, Upasna U et al (2018) Meta-analysis of genetic polymorphisms in xenobiotic metabolizing enzymes and their association with breast cancer risk. J Genet 97:523–537. https://doi.org/10.1007/s12041-018-0946-4

2. Klinge CM (2001) Estrogen receptor interaction with estrogen response elements. Nucleic Acids Res 29:2905–2919. https://doi.org/10.1093/nar/29.14.2905
3. Hirabayashi Y, Inoue T (2009) Aryl hydrocarbon receptor biology and xenobiotic responses in hematopoietic progenitor cells. Biochem Pharmacol 77:521–535. https://doi.org/10.1016/j.bcp.2008.09.030
4. Molina E, Pérez-Morales R, Rubio J et al (2013) The GSTM-1null (deletion) and MGMT84 rs12917 (Phe/Phe) haplotype are associated with bulky DNA adduct levels in human leukocytes. Mutat Res - Genet Toxicol Environ Mutagen 758:62–68. https://doi.org/10.1016/j.mrgentox.2013.09.007
5. Pérez-Morales R, Méndez-Ramírez I, Castro-Hernández C et al (2011) Polymorphisms associated with the risk of lung cancer in a healthy Mexican Mestizo population: Application of the additive model for cancer. Genet Mol Biol 34:546–552. https://doi.org/10.1590/S1415-47572011005000053
6. Martínez-Ramírez OC, Pérez-Morales R, Castro C et al (2013) Polymorphisms of catechol estrogens metabolism pathway genes and breast cancer risk in Mexican women. Breast 22:335–343. https://doi.org/10.1016/j.breast.2012.08.004
7. Lahiri DK, Numberger JI (1991) A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. Nucleic Acids Res 19:5444. https://doi.org/10.1093/nar/19.19.5444
8. Sierra.Martinez M, Hernández-Cadena L, García-Sánchez J, et al (2018) Predictive polymorphisms for breast cancer in postmenopausal Mexican women. J Cancer Res Ther 14:640. https://doi.org/10.4103/0973-1482.179109
9. Sissung TM (2006) Pharmacogenetics and regulation of human cytochrome P450 1B1: Implications in hormone-mediated tumor metabolism and a novel target for therapeutic intervention. Mol Cancer Res 4:135–150. https://doi.org/10.1158/1541-7786.mcr-05-0101
10. Howell WM, Turner SJ, Collins A et al (2002) Influence of TNF?? and LT?? single nucleotide polymorphisms on susceptibility to and prognosis in cutaneous malignant melanoma in the British population. Eur J Immunogenet 29:17–23. https://doi.org/10.1046/j.1365-2370.2002.00269.x
11. Lu Y, Cao M, Gao K et al (2015) The role of O 6 -methylguanine-DNA methyltransferase polymorphisms in colorectal cancer susceptibility: a meta analysis. Curr Genomics 8:791–799
12. Bidel Z, Nazarzadeh M, Moghaddam HS et al (2017) XRCC1 gene polymorphisms and breast cancer risk: a systematic review and meta-analysis study. Asian Pacific J Cancer Prev 17:323–335. https://doi.org/10.7314/apjcp.2016.17.s3.323
13. Pesch B, Pierl CB, Dippon J et al (2007) The CYP1B1_1358_GG genotype is associated with estrogen receptor-negative breast cancer. Breast Cancer Res Treat 111:171–177. https://doi.org/10.1007/s10549-007-9762-x
14. Qiu J, Du Z, Liu J, Zhou Y, Liang F, Lü Q (2018) Association between polymorphisms in estrogen metabolism genes and breast cancer development in Chinese women: a prospective case-control study. Medicine 97(47):e13337. https://doi.org/10.1097/MD.0000000000013337