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ORIGINAL ARTICLE

# Association of rs2234693 and rs9340799 polymorphisms of *ESR1* gene in breast cancer of Mexican population

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## *Summary*

***Purpose:*** *The rs2234693 and rs9340799 ESR1 polymorphisms have shown contradictory results in studies of breast cancer (BC). The purpose of this study was to determine the frequency and association of ESR1 polymorphisms (rs2234693 and rs9340799) in BC patients of Mexican population.*

***Methods:*** *PCR was used to genotype rs2234693 and rs9340799 polymorphisms in the ESR1 gene in Mexican healthy subjects and breast cancer (BC) patients.*

***Results:*** *The frequency of cases and control groups of rs2234693 and rs9340799 polymorphisms in the ESR1 was similar, and none has shown any association with increased BC risk (p>0.05), although the association between the haplogenotypes (rs2234693 and rs9340799 polymorphisms) and BC patients with miscarriages [CTAG variant, adjusted odds ratio (OR) 1.83 (95%CI 1.17-2.86);p=0.011] and tobacco consumption [CCGG variant, adjusted OR 1.88 (95%CI 1.11-3.19);p=0.018] was evident. Also, the homozygous genotype TT [rs2234693, OR 1.49 (95%CI 1.02-2.19);p=0.042] and GG [rs9340799, OR 2.85 (95%CI 1.144-7.10);p=0.024] showed marginal association with BC, indicating that these factors may contribute significantly to the susceptibility of risk to BC. The TA haplotype was more common in controls than in CG. BC patients with a frequency around 0.71 among study groups, but without significant difference (p>0.05).*

***Conclusion:*** *rs2234693 and rs9340799 polymorphisms in the ESR1 gene were not associated with susceptibility for BC. However, the haplogenotypes CTAG and CCGG of rs2234693 and rs9340799 polymorphisms could contribute significantly to the susceptibility of risk in BC positive at miscarriage and tobacco consumption in this sample population.*

***Key words:*** *rs2234693, rs9340799, ESR1, breast cancer, polymorphism, Mexican population*

## Introduction

Breast cancer (BC) contributes to highest healthcare costs and is been considered a public health problem in females around the world [1,2]. In Mexico, the incidence rate of BC was 15/100,000 women in 2014, but this incidence varies between different ethnic groups [3,4]. BC is a multifactorial disease caused by transforming normal breast cells to malignant cells by interactions among abnormal genes and environmental factors [4,5]. The nuclear receptors (NR) constitute a family of proteins that function as transcriptional regulators activated by steroid hormones [6] such as estrogen receptor (ER), which participates in the regulation of growth, development of sexual maturation and

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gestation and the physiology of reproduction. The biological functions of estrogens are mediated by the balance between the ERα and ERβ [7,8]. Approximately 75% of primary BCs express ER and more than half of them also express progesterone receptor. In postmenopausal women, exposure to endogenous steroid hormones, particularly estrogens, has been associated with an increased risk of different pathologies including BC [9-14].

Different genes encode ERα and ERβ. The *ESR1* gene (estrogen receptor 1) encodes for the ERα protein expressed in breast and others organs. The chromosomal location of *ESR1* gene is in 6q25.1, which consists of 8 exons. The first intron and the promoter of the gene contain regulatory sequences of other introns. Several single nucleotide polymorphisms (SNPs) and polymorphisms in the number of tandem repeats (VNTR) have been identified in *ESR1*. Two polymorphisms that have been most studied in the *ESR1* gene are the SNPs, rs2234693 (PvuII) and rs9340799 (XbaI), which have a strong linkage disequilibrium with the repetition of VNTR-TA polymorphism in the promoter region, and have been proposed that these SNPs impact the activity of the ER [12].

The intronic variant IVS-410 of the *ESR1* gene (rs2234693) is located in the first intron 397 base pair (bp) upstream of exon 2 in which a cytosine is replaced by thymine and this change is identified by the endonuclease PvuII [9,12]. It has been reported that polymorphisms in intronic regions modify splicing in mRNA transcripts, which leads to significant changes in the function of genes [9]. However, differences in the frequency of these polymorphisms have been described and, depending on the study population, the allele of *T* or *C* has been reported as protective or risk factor with of BC [9-11,13-15]. The *C* allele is considered as the ancestral allele presenting with minor frequency in the general population, however two studies conducted in the Mexican population found a frequency different to that reported worldwide. The first was performed in postmenopausal women (age range 46-80 years) and reported a *C* allele frequency of 30.9% [13], while the second study performed in women younger than 45 years with metabolic syndrome; the *C* allele was present in 25.8% [14].

A meta-analysis reported that premenopausal women carriers of the *T* allele had a slight increase in the risk of developing BC [10]. In Caucasian populations there was a higher risk of *TT* vs *CC* than in Asians [11]. This association has been rarely studied in Mexican population. Thus, the aim of this investigation was to determine the frequency and association of *ESR1* gene polymorphisms (rs2234693 and rs9340799) in healthy controls and in BC patients of Mexican population.

## Methods

DNA was extracted from 417 female healthy blood donor volunteers and 507 patients with clinically and histologically confirmed BC. All patients were residents of the metropolitan area of Guadalajara and all of them signed informed consent. This study was approved by the Hospital's ethics committee (1305, CIBO, IMSS). All the procedures performed in were in accordance with the 1964 Helsinki declaration. Clinical and demographic data were obtained using written questionnaires. The BC patient database and patient DNA samples were also examined for other polymorphisms [4,5].

The amplification of the *ESR1* gene polymorphisms rs2234693 and rs9340799 were performed by PCR using the following primers: 5´ GATATCCAGGGTTATGTGGCA -3´ and 5´- AGGTGTTGCCTATTATATTAACCTTGA -3´, as described previously in 2011 by Lee et al. [16]. The PCR products were digested with PvuII restriction enzyme (New England, Biolabs) to discriminate the genotypes of rs2234693 polymorphism. In the previous

**Table 1.** Demographic data for the breast cancer and control groups

| | *BC patients (n=507)* *n (%)* | *Controls (n=417)* *n (%)* | *OR (IC 95%)** | *p value*** |
|---|---|---|---|---|
| Age (years) | | | | <0.0001 |
| Mean (SD) | 53.54 (11.79) | 44.46 (15.40) | | |
| Tobacco consumption | | | 1.28 (0.95-1.73) | 0.1198 |
| Yes | 138 (27) | 94 (23) | | |
| No | 369 (73) | 323 (77) | | |
| Alcohol consumption | | | 0.75 (0.53-1.07) | 0.1377 |
| Yes | 73 (14) | 76 (18) | | |
| No | 434 (86) | 341 (82) | | |

SD: standard deviation, * OR (odds ratio) from the adjusted regression analysis. ** Student's t-test.

electrophoretic procedure amplified products were separated on 6% polyacrylamide gels (29:1), followed by silver staining [17]. The fragments of 243 bp and 100bp were identified as *TT* genotype, the fragments of 346bp, 234bp and 100bp as *TC* genotype and the fragment of 346pb as *CC* genotype. The rs9340799 polymorphism discrimination performed by XbaI restriction enzyme (New England, Biolabs) identified a band of 198bp and 148bp as genotype *AA*, bands of 346bp, 243bp and 148bp as *AG* genotype and 346bp as *GG* genotype.

*Statistics*

Allele frequencies were obtained by direct counting. The Hardy-Weinberg equilibrium was tested by a goodness-of-fit $x^2$ test to compare the observed genotype frequencies to the expected frequencies among control subjects. Odds ratios (OR) and 95% confidence intervals (CI) were also calculated. A two-tailed $p<0.05$ was considered statistically significant. All statistical analyses were performed using the PASW Statistic Base 18 software, 2009 (Chicago, IL, USA).

Haplotype analysis was performed using the online program http://bioinfo.iconcologia.net/SNPstats.

## Results

Comparative epidemiological data from the BC patients and the control individuals are shown in Table 1. In the BC group, the observed average age was 53.54 years and in the control group 44.46 years. Tobacco and alcohol consumption were not shown to be susceptibility factors to BC ($p>0.05$).

General clinical characteristics of the BC group are presented in Table 2. Most of the BC patients were menopausal (65%), had normal weight (36%), unilateral tumor localization (94%), ductal histological classification (91%), TNM stage III-IV (67%), luminal type A (46%), lymph node positive (72%), and responded to chemotherapy (55%).

Table 3 shows the data of the genotypes and allele frequencies of the *ESR1* (rs2234693 and rs9340799) polymorphisms that were not significantly different in BC patients and controls ($p>0.05$). The genotype distribution of *ESR1* polymorphisms was in Hardy-Weinberg equilibrium in the control group.

The haplotype frequencies were in complete linkage disequilibrium (D'=0.999), although the comparisons among the studied groups were not statistically different (Table 4). In addition, significant differences were found with regards to clinical characteristics of the BC group and genotype, with respect to the heterozygous genotype (*CT*) of rs2234693 polymorphism and miscarriage (adjusted OR 1.83, 95% CI 1.19-2.80, p=0.005), whereas for the homozygotes (CC) with tobacco consumption (adjusted OR 1.81, 95% CI 1.11-3.10, p=0.017) and

**Table 2.** Clinicopathological data of breast cancer patients (n=507)

| | *n* (%) |
|---|---|
| Hormonal status | |
| Menarche, years | |
| 11-13 | 329 (65) |
| 9-10 and 14-18 | 178 (35) |
| Menopausal status | |
| Pre-menopause | 330 (65) |
| Menopause | 177 (35) |
| Body mass index (BMI)** | |
| 18.5-19.9 (underweight) | 115 (23) |
| 20-24.9 (normal weight) | 183 (36) |
| 25-29.9 (overweight) | 135 (27) |
| 30-34.9 (obesity I) | 57 (11) |
| ≥35 (obesity II- III) | 17 (2) |
| Breastfeeding, months | |
| ≤ 6 | 89 (18) |
| > 6 | 302 (60) |
| No | 116 (22) |
| Localization | |
| Unilateral | 478 (94) |
| Bilateral | 29 (6) |
| Histology (adenocarcinoma) | |
| Ductal | 458 (91) |
| Lobular | 42 (8) |
| Mixed | 7 (1) |
| Tumor stage | |
| I-II | 169 (33) |
| III-IV | 338 (67) |
| Histologic type | |
| Luminal A | 233 (46) |
| Luminal B | 99 (20) |
| HER2 | 63 (12) |
| Triple negative | 112 (22) |
| Metastatic node status | |
| Positive | 366 (72) |
| Negative | 141 (28) |
| Metastasis | |
| Yes | 186 (37) |
| No | 321 (63) |
| Chemotherapy | |
| Response | 279 (55) |
| No response | 228 (45) |

** According to OMS classifications (Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Ginebra (Suiza): World Health Organization, 2004)

**Table 3.** Genotype and allelic distribution of rs2234693 and rs9340799 polymorphisms ESR1 gene in breast cancer and control groups

| *Polymorphism* | *BC n (%)* | *Controls*[a] n (%)* | *OR* | *IC(95%)* | *p value* |
|---|---|---|---|---|---|
| rs2234693** | 487 | 401 | | | |
| *TT* | 253 (52) | 199 (50) | 1.09 | 0.84-1.42 | 0.53 |
| *TC* | 196 (40) | 170 (42) | 0.91 | 0.69-1.20 | 0.33 |
| *CC* | 38 (8) | 32 (8) | 0.97 | 0.59-1.60 | 0.97 |
| Alleles [(2n)] | | | | | |
| *T* | 702 (0.72) | 568 (71) | 1.06 | 0.86-1.30 | 0.59 |
| *C* | 272 (0.28) | 234 (29) | 0.94 | 0.76-1.15 | 0.59 |
| rs9340799** | 462 | 334 | | | |
| *AA* | 245 (53) | 158 (47) | 1.25 | 0.94-1.66 | 0.12 |
| *AG* | 175 (38) | 145 (43) | 0.79 | 0.59-1.05 | 0.13 |
| *GG* | 42 (9) | 31 (10) | 0.97 | 0.60-1.59 | 0.97 |
| Alleles [(2n)] | | | | | |
| *A* | 665 (0.72) | 461 (0.69) | 1.15 | 0.92-1.43 | 0.22 |
| *G* | 259 (0.27) | 207 (0.31) | 0.86 | 0.69-1.07 | 0.22 |

* Controls genotype. Hardy-Weinberg equilibrium in controls (chi-square test=0.26674; p=0.6055 for rs2234693 polymorphism and chi-square test=0.0753; p=0.7837 for rs9340799 polymorphism). **The distribution of genotypes was performed only in 487/507 patients and 401/417 controls for the rs2234693 polymorphism. With regard to the rs9340799 polymorphism, it was genotypic only in 462/507 in patients and 334/417 controls

**Table 4.** rs2234693 and rs9340799 haplotype frequencies in the study groups

| *Haplotypes* | | *Frequency* | | | | |
|---|---|---|---|---|---|---|
| *rs2234693* | *rs9340799* | *Total* | *BC* | *Controls* | *OR (95%CI)* | *p value* |
| *T* | *A* | 0.7164 | 0.7279 | 0.7006 | 1 | |
| *C* | *G* | 0.2836 | 0.2721 | 0.2994 | 1.14 (0.91 - 1.43) | 0.25 |

BC=breast cancer, OR=odds ratio, CI=confidence interval. The polymorphisms were found to be in linkage disequilibrium (D'=0.9996 and r´=0.9996)

**Table 5.** Association between the rs2234693 and rs9340799 polymorphisms of ESR1 gene and clinical variables in breast cancer group

| *Genotypes* | | *OR* | *95%CI* | *p value* |
|---|---|---|---|---|
| rs2234693 | | | | |
| *TT* | Advanced stage (III-IV) | 1.49 | 1.02-2.19 | 0.042 |
| *TC* | Miscarriage | 1.83 | 1.19-2.80 | 0.005 |
| *CC* | Tobacco consumption | 1.81 | 1.11-3.10 | 0.017 |
| rs9340799 | | | | |
| *AG* | Miscarriage | 1.68 | 1.09-2.58 | 0.017 |
| *GG* | Tobacco consumption | 1.77 | 1.14-2.74 | 0.011 |
| *GG* | Lymph node metastasis | 2.85 | 1.144-7.10 | 0.024 |
| Haplogenotype | | | | |
| *TCAG* | Miscarriage | 1.83 | 1.17-2.86 | 0.011 |
| *CCGG* | Tobacco consumption | 1.88 | 1.11-3.19 | 0.018 |

OR=odds ratio (adjusted), CI=confidence interval

*TT* with progression of tumor stage III-IV (OR 1.49, 95% CI 1.02-2.19, p=0.042) were a risk factor for BC (Table 5). The rs9340799 polymorphism also showed statistically significant difference in BC patients with *AG* genotype and those with miscarriage (OR 1.68, 95% CI 1.09-2.58, p=0.017), while the *GG* genotype was associated with tobacco consumption (OR 1.77, 95% CI 1.14-2.74, p=0.011), and metastatic lymph nodes (OR 2.85, 95% CI 1.144-7.10, p=0.024) as a risk factor in BC.

The association of haplogenotype rs2234693 and rs9340799 polymorphisms showed the susceptibility to risk in BC patients who had have miscarriages (OR 1.83, 95% CI 1.17-2.86, p=0.011) and tobacco consumption (OR 1.85, 95% CI 1.11-3.19, p=0.018) (Table 5).

## Discussion

BC has complex etiology and its incidence has increased over the last 10 years and is currently one of the leading causes of death of females in Mexico, like in other parts of the world [1,4,5]. This disease occurs at an average age of 50 years [1,4,5] while in our study it was 53.54 ± 11.79 years. Changes in the lifestyle could be one of the causes that contribute to the increased frequency of this disease, reflecting changes of longevity in the Mexican population [4,5].

The development of new diagnostic techniques and changes in health policies have contributed to better understanding of BC, as well as to improving the quality of life of BC patients in our country. However, this has not been enough; we still need to carry out new studies and implement new strategies to detect BC in early stages. In the present study, BC was present in 67% of the patients with TNM III-IV stage, which is consistent with the report of Chavarri et al. in 2012 [1] in a study with BC from Mexican population that clarified the principal factors affecting the early BC detection in Mexico were insufficient mammography coverage, poor quality control, limited access to diagnosis and treatment, and insufficient physical and human resources for clinical care [1].

Many studies on the influence of the mechanisms of estrogens have improved our knowledge of BC. Among these studies are those that have associated polymorphisms in the genes of hormone metabolism, such as *ESR1* [9-15,18,19]. Some authors have demonstrated that the estrogens contribute to stimulation of the mitotic activity in the ductal and lobular BC cells, thus resulting in increased cancer risk [18].

Estrogens can regulate the growing cell by different ways such as: i) the formation of the complex with its receptor (ESRα) and other co-activating proteins; ii) through phosphorylation in specific amino acids of AF-1 domain of ERα; and iii) through proteins involved in angiogenesis and survival. In addition, several reports have been shown ERα as an important prognostic biomarker of BC patients; and essential participation in bone growth and response to hormone therapy [18]. Two of the polymorphisms in *ESR1* gene that have been most studied are rs9340799 and rs2234693, and are in strong linkage disequilibrium with each other. At this moment no biological evidence exists of the functionality of these SNPs, although recent findings support the hypothesis that these polymorphisms impact estrogen activity by influencing the transcription of the *ESR1* gene via altered transcription factor binding. Association studies remained controversial for different reasons: one has been the difficulty to determine the allele associated with the disease and another one is due to the genetic variability that exists in each ethnic population and the variability of each study. There are association studies that have observed increased risk with BC, osteoporosis, as well as a reduced risk of endometriosis. Other studies showed associated risk with the *T* (rs2234693) and *A* (rs9340799) alleles, while others with the alleles *C* (rs2234693) and *G* (rs9340799) [9].

Moreover, little is known regarding the association of rs2234693 and rs9340799 polymorphisms of *ESR1* gene in Mexican BC patients. In our study group, the rs2234693 and rs9340799 polymorphisms of *CC* genotype was 8%, similar in controls and in BC patients, suggesting that they were not susceptibility-risk factors for BC (p>0.05), either by allele, genetic model and as haplotypes. This data is consistent with a recent meta-analysis in BC [20]. The association of *TT* genotype rs2234693 has shown higher risk for BC in Caucasian populations compared with Asian populations with *CC* genotype [10].

Notably, two previous studies performed in Mexican population showed a frequency of *C* allele (rs2234693) of 30.9% in postmenopausal women, [13], and 25.8% in women younger than 45 years with metabolic syndrome [14]. Similar data were corroborated in the present study, when observing a frequency of *C* allele of 29% and *G* allele (rs9340799) of 31%.

Also, there was strong corroborating linkage disequilibrium of rs2234693 and rs9340799 analyzed in the present study; these showed a D´ of 0.9996, which means that there was only enough to analyze one of the two polymorphisms for association studies of disease susceptibility in a Mexican population.

The association of the *CC* (rs2234693), *GG* (rs9340799) genotypes and *CCGG* haplogenotype as risk factors in BC stratified by tobacco consumption was also demonstrated. It is known that smoking tobacco contains many toxic substances that can damage DNA by formation of adducts, and in individuals with the homozygous genotypes (*CCGG*) these adducts could modify the recognition sequences in the *ESR1* gene while the estrogens affect the transcription of the gene by recognition of transcription factors that alter the function of this gene [21]. In 2013, Tang et al. [22] demonstrated that the association of the *TC/CC* genotype of *ESR1* rs2234693 in premenopausal women under passive smoking environment significantly increased the risk of BC.

Nevertheless, *TC, AG* genotypes and *TCAG* haplogenotype were proven as risk factors for miscarriage in BC patients. In 2014, Pan et al. [23] observed the association of *CG* haplotype with increased risk in unexplained recurrent spontaneous abortions in women of China Han population. A plausible explanation of the findings observed in the present study would be that the *C* or *G* alleles are probably consequences of estrogen recognition that regulate the transcription of *ESR1* gene, and this has an impact in the deregulation of estrogens with implications in the gestational process and is associated with miscarriage in BC.

Additionally, we also observed that this polymorphism had marginal association of *TT* allele (rs2234693) with TNM III-IV stage and *GG* allele (rs9340799) with presence of metastatic lymph nodes in BC. With respect to progression of advanced-stage tumors, several hypotheses have been proposed to explain this association, which influences the growth of tumor cells and BC prognosis. It was proposed that the *T* allele (rs2234693) polymorphisms in *ESR1* might be able to modify ERα activity as a result of recognitions of sites of genes and proteins that may modify the expression of ERα, and thus promote tumor progression in BC reflecting tumor aggressiveness [24]. In 2010, Ding et al. observed that different polymorphisms in the intron 1 of *ESR1* gene showed an association with worse clinical phenotypes, including late stage disease [18].

In fact, controversial results have been shown in some studies with respect to rs2234693 and rs9340799 *ESR1* polymorphisms; some of the studies have observed an association with *T* allele of PvuII, conferring a higher susceptibility risk of BC [25,26], while others did not show such an association [15]. Therefore, it is important to mention that there are different factors that can influence the variability of association studies, especially with polymorphisms of the *ESR1* gene, such as the characteristics of the population studied in terms of age, gender, diet, ethnicity, organ function, tumor biology and genetic factors [10,15].

In conclusion, our results do not support an association of the *ESR1* polymorphism between BC patients and controls. The rs2234693 and rs9340799 *ESR1* polymorphisms in BC patients were associated with: a) *TT* genotypes and progressive tumor (stage III-IV); b) heterozygous genotypes (*TC,AG*) and miscarriage; and c) homozygous genotypes (*CC,GG*) with tobacco consumption and *GG* with metastatic lymph nodes. These findings confirmed that the above-mentioned factors might contribute significantly to BC susceptibility, depending on the clinical outcomes in this population. Further studies are required to confirm or reject these observations.

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## Conflict of interests

The authors declare no conflict of interests.

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