ADIPOQ single nucleotide polymorphisms and breast cancer in northeastern Mexican women

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Abstract

Background: Adiponectin gene (ADIPOQ) polymorphisms have been shown to affect adiponectin serum concentration and some have been associated with breast cancer (BC) risk. The aims of this study were to describe the frequency of single nucleotide polymorphisms (SNPs) of ADIPOQ in Mexican women with BC and to determine if they show an association with it.

Methods: DNA samples from 397 patients and 355 controls were tested for the ADIPOQ gene SNPs: rs2241766 (GT) and rs1501299 (GT) by TaqMan allelic discrimination assay. Hardy–Weinberg equilibrium (HWE) was tested. Multiple SNP inheritance models adjusted by age and body mass index (BMI) were examined for the SNP rs1501299.

Results: We found that in the frequency analysis of rs1501299 without adjusting the BMI and age, the genotype distribution had a statistically significant difference (P = 0.003). The T allele was associated with a BC risk (OR, 1.99; 95% CI 1.13–3.51, TT vs. GG; OR, 1.53; 95% CI 1.12–2.09, GT vs. GG). The SNP rs2241766 was in HW disequilibrium in controls. In conclusion, the rs1501299 polymorphism is associated with a BC risk.

Conclusions: Identification of the genotype of these polymorphisms in patients with BC can contribute to integrate the risk profile in both patients and their relatives as part of a comprehensive approach and increasingly more personalized medicine.

Keywords: Breast cancer, Single nucleotide polymorphisms, Adiponectin, ADIPOQ, Mexican women

Background

Breast cancer (BC) is the most common cancer in adult women in the world [1]. Different risk factors have been implicated in BC initiation and progression such as overweight (OW) and obesity (OB) [2]. OB is increasingly recognized as an oncogenic factor and is associated with many metabolic disorders, such as type 2 diabetes mellitus, coronary heart disease, and hypertension, and with cancer in different tissues, such as colon, prostate, and breast [3–5]. Moreover, it has been shown that excess adipose tissue promotes metastasis and recurrence of BC and is associated with increased mortality.

Adipocytes produce adiponectin and leptin, two highly expressed adipokines that have opposing effects on immune cell function [6]. Adiponectin is secreted

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increased in obese and diabetic subjects [10]. Studies support evidence that decreased adiponectin serum concentration may explain the increased risk of BC in OB2 and that this hormone is a potential diagnostic and prognostic BC biomarker [9].

ADIPOQ polymorphisms have been shown to affect adiponectin serum concentrations, and some have been associated with BC risk [10–12]. Adipokines are associated with several types of obesity-related cancers [13–17]. Previous studies found that homozygous carriers of the T allele of SNP rs1501299 had the highest concentration of adiponectin compared to the GG or TG genotypes [10, 18]. Also, an association of the rs2241766 TG and GG genotypes with increased adiponectin serum concentration and with a decreased risk for breast cancer was reported [10]. SNPs that cause lower adiponectin serum concentrations are associated with increased cancer risk; also, adiponectin levels are inversely correlated with adiposity. Decreased adiponectin serum concentrations may explain the increased risk of breast cancer in obesity [10, 18, 19].

The objectives of this hospital case-control study were: 1. To describe the frequency of two SNPs, rs2241766 (+45T > G) and rs1501299 (+276G > T) of ADIPOQ in a sample of Mexican women from northeastern Mexico with and without BC, and 2. To determine any association between these polymorphisms and BC risk.

Methods
Approval from the scientific and ethics committees
The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Ethics Committee of the University Hospital (registration no. B110–002). All patients were invited to participate in the research project, an interview was performed and once the patients agreed to participate, they signed an informed consent. Afterwards, clinical and epidemiological information was collected, and blood samples were taken.

Study design and population
A hospital case-control study was carried out. Patients were selected among women receiving chemotherapy at two institutions located in Monterrey City, Mexico: the Centro Universitario Contra el Cáncer (Hospital Universitario “Dr. José E. González” (HU), of the Universidad Autónoma de Nuevo León) and the Hospital de Especialidades #25 (Instituto Mexicano del Seguro Social (IMSS)). Both are referral centers for patients affected by this neoplasm who come from five states located in Northeast Mexico (Nuevo León, San Luis Potosí, Zacatecas, Coahuila, and Tamaulipas).

Patient group
All BC patients were older than 18 years, had a confirmatory biopsy, and accepted to participate in the study and signed an informed consent. Because we are studying a low-penetrance gene (ADIPOQ), the study included only patients with sporadic breast cancer, thus, patients with a family history of BC were excluded. Pregnant women were also excluded.

Female BC patients attending the oncology clinics of the two participating hospitals who fulfilled inclusion criteria were invited by the oncologist to participate in the project. An interview was conducted to explain the protocol to the patients and subsequently, women who accepted to participate signed the consent letter. Blood samples were collected in the areas of chemotherapy and consultation. Epidemiological and clinical information was also collected. Only three patients refused to participate in the study. Most of the patients of the case group 288 (72.5%) and all the controls 355 (100%) came from the IMSS, the rest of the cases came from the HU (109/ 27.5%).

Control group
Controls were women older than 18 years of age, without a history of cancer and a BI-RADS 1–2 mammogram who signed an informed consent. Individuals with a family history of BC and pregnant women were excluded.

All control group women were recruited in the radiology areas. They attended a follow-up mammography or were referred for timely detection of cancer by mammography. If the women fulfilled the inclusion criteria, they were invited to participate by interview and after signing the informed consent, a blood sample was taken in the radiology area and epidemiological and clinical information was collected. All 397 patients and 355 controls were Mexican women whose four grandparents were born in Northeast Mexico (Nuevo León, San Luis Potosí, Zacatecas, Coahuila, and Tamaulipas).

DNA preparation
Genomic DNA was extracted from whole peripheral blood either with the QIAamp DNA Blood Kit (Cat No. 51104 Qiagen Inc., CA, USA) according to the manufacturer’s instructions, or using the TSNT method followed by phenol–chloroform extraction and ethanol precipitation [20]. DNA concentrations was measured by NanoDrop 8000 Spectrophotometer (Thermo Scientific, USA). Concentrations was adjusted to 50 ng/μl in purified nuclease-free water.
Analysis of DNA polymorphisms

Samples from patients (n = 397) and controls (n = 355) were tested for the ADIPOQ gene SNPs: rs2241766 (GT) and rs1501299 (GT). All assayed polymorphic sites were genotyped using the TaqMan allelic discrimination assay (Assay ID: C_26426077_10 for rs2241766 and C___7497299_10 for rs1501299, Applied Biosystems, USA). All polymerase chain reactions (PCRs) were done in a volume of 10 μl containing: 5 μl of TaqMan universal PCR Master Mix 2X, 2 μl of DNA (100 ng), 0.2 μl of TaqMan SNP Genotyping Assays 20X, and 2.8 μl of nuclease free water. Thermal cycling conditions were 10 min at 95 °C, and 42 cycles each of 95 °C for 15 s, and 60 °C for 1 min. The Step One Real Time System (Applied Biosystems, USA) was used for genotyping.

Statistical analysis

IBM SPSS version 24.0 was used for descriptive statistical analysis. First, participant characteristics were summarized as arithmetic means with standard deviation (SD) for continuous variables and counts and percentages for categorical variables. Second, the p-values of continuous variables were determined by unpaired t-test, for categorical variables, a chi-square test was used. Third, Hardy–Weinberg equilibrium (HWE) was tested with the public software developed by Tim M Strom and Thomas F. Wienker (http://ihg.gsdf.de/cgi-bin/hw/hwa1.pl) without adjustment by age and BMI. Fourth, Multiple SNP inheritance models (codominant, dominant, recessive, overdominant and Log-additive) adjusted by age and BMI were examined to determine odds ratio (OR) and 95% confidence intervals (CI) (http://bioinfo.iconlogic.net/snpstats/start.htm). Given that this software has a limited sample size to run, a random woman was randomly selected, without adjusted by age and BMI. No significant deviations from HWE were found for the SNP rs1501299. The SNP rs2241766 was in HW disequilibrium in control women (p = 0.005). When we performed the frequency analysis without adjusting the BMI and age, the genotype distribution exhibited a statistically significant difference between cases and controls (P = 0.003 and P = 0.0003 for rs1501299 and rs2241766, respectively) and the T allele of rs1501299 was associated with BC risk (OR 1.99; 95% CI 1.13–3.51, TT vs GG; OR 1.53; 95% CI 1.12–2.09, GT vs GG).

Subsequently, we performed the multiple SNP inheritance models of rs1501299 adjusted by age and BMI. With the codominant model, the genotype distribution exhibited a statistically significant difference between cases and controls (p = 8e-04) and the T allele of rs1501299 was associated with BC protection (OR 0.55; 95% CI 0.34–0.80 GT and OR 0.39; 95% CI 0.20–0.76 TT) (Table 4). The rs2241766 C allele (GT and GG genotypes) was associated with a decreased risk for BC (OR 0.20; 95% CI 0.07–0.51, GG vs TT; add the OR and 95% CI for TG). However, because rs2241766 was out of HWE, these results should be considered with caution. Because this polymorphism is not in HW equilibrium, no multiple SNP inheritance models analysis was made.

We compared our genotypic frequencies with the frequencies reported for a population of 46 Mexican individuals from the National Center for Biotechnology Information (NCBI) web page [21]. The SNP rs2241766 frequencies in the controls (0.22 G allele and 0.78 T allele) were compared with the reported frequencies for the NCBI Hispanic population (0.28 for allele G and 0.71 for allele T). A chi-square test was applied and a significant difference between both populations was found for rs2241766 (X2 = 10.70, p = 0.005 when comparing the cases and X2 = 106.28, p = 1 × 10–7 when comparing the controls). Also, rs1501299 frequencies in the controls (0.76 G allele and 0.24 T allele) were compared with the reported frequencies for the NCBI Hispanic population (0.76 for allele G and 0.24 for allele T). A chi-square test was applied, and we did not find a
significant difference between both populations ($X^2 = 0.006, p = 0.997, X^2 = 3.16, p = 0.206$) respectively.

**Table 1** Comparison of 12 characteristics in case and control groups

| Characteristics                              | (n = 752) | Case (n = 397) | Control (n = 355) | p-value |
|----------------------------------------------|-----------|---------------|-----------------|---------|
| **Demographic factors**                      |           |               |                 |         |
| Age at baseline interview (years)            |           | 52.5 ± 12     | 49.5 ± 10.9     | 0.009*  |
| Height (m)                                   |           | 1.56 ± 0.07   | 1.60 ± 0.07     | 0.871*  |
| BMI > 30 (kg/m²)                             |           |               |                 | 0.001b  |
| Yes                                          |           | 43.1          | 29.9            |         |
| No                                           |           | 50.1          | 68.7            |         |
| n/a                                          |           | 6.8           | 1.4             |         |
| **Reproductive factors**                     |           |               |                 |         |
| Age at menarche (years)                      |           | 12.8 ± 1.6    | 12.7 ± 1.5      | 0.379*  |
| Age at first childbirth (years)              |           | 23.1 ± 5.6    | 23.4 ± 5.3      | 0.598** |
| Number of children born alive               |           | 3.3 ± 2       | 3.2 ± 2.2       | 0.115*  |
| **Children**                                 |           |               |                 |         |
| Yes                                          |           | 85.4          | 88.7            | 0.509 b |
| No                                           |           | 14.6          | 11.3            |         |
| **Breast-feeding**                           |           |               |                 | 0.052b  |
| ≤ 30 years old                               |           | 56.4          | 47.0            |         |
| ≥ 30 years old                               |           | 7.8           | 4.8             |         |
| n/a                                          |           | 35.8          | 48.2            |         |
| **Breast-feeding duration (months)**         |           | 12.2 ± 13.0   | 14.2 ± 22.2     | 0.002*  |
| **Menopausal status**                        |           |               |                 | 0.001b  |
| Yes                                          |           | 63.2          | 44.2            |         |
| No                                           |           | 33.0          | 55.5            |         |
| n/a                                          |           | 3.8           | 0.3             |         |
| **Age at menopause**                         |           | 44.9 ± 5.7    | 45.9 ± 6.3      | 0.797*  |
| **Hormonal factors**                         |           |               |                 |         |
| Use of oral contraceptive                    |           |               |                 | 0.001b  |
| Yes                                          |           | 30.2          | 21.4            |         |
| No                                           |           | 66.0          | 78.6            |         |
| n/a                                          |           | 3.8           | 0.0             |         |

SD standard deviation; BMI Body mass index; n/a not available; t-test*, chi-square test b

**Association of BMI with ADIPOQ genotypes**

We found a statistically significant BMI difference between women with breast cancer and the control group (Table 1). In order to identify if the BMI was associated with the rs1501299 and rs2241766 genotypes, we performed a univariate general linear model. The result between cases and controls was a F vale of 6.29 ($p = 0.012$), for the rs2241766 ($F = 1.473, p = 0.338$) and the s1501299 ($F = 2.417, p = 0.131$). When we realized the interactions between BMI and rs1501299 ($f = 0.30, p = 0.77$) and rs2241766 ($f = 0.18, p = 0.84$), no significance association was found.

**Discussion**

In this study, we found an association between rs1501299 in **ADIPOQ** and BC risk in Mexican women with an OR of 1.53 (95% CI, 1.12–2.09) for the GT.

**Table 2** Breast cancer tumor immunohistochemistry (n = 274)

| Immunohistochemistry | ER status n (%) | PR status n (%) | Her-2 status n (%) | TNBC status n (%) |
|----------------------|-----------------|-----------------|-------------------|-------------------|
| Positive             | 149 (54.4)      | 127 (46.4)      | 114 (41.6)        | 82 (29.9)         |
| Negative             | 125 (45.6)      | 147 (53.6)      | 165 (57.0)        | 192 (70.1)        |

ER Estrogen receptor; PR Progesterone receptor, TNBC Triple Negative Breast Cancer
genotype and 1.99 (95% CI, 1.13–3.51) for TT vs. GG. On the other hand, when information was analyzed adjusted by BMI and age using the five models, all of them showed an OR lower than one, considering a protective association. Besides the codominant model showed the lowest significant p-value (8e-04) and an AIC value of 684.27 with an OR of 0.55 (95% CI 0.34–0.80) for GT genotype, and an OR of 0.39 (95% CI 0.20–0.76) for TT vs GG.

In 2013, Kaklamani et al. found that rs1501299 was associated with BC risk not only in Caucasian population, but also in African American women [11]. Kaklamani associated the genotypes GG and TG with risk of breast cancer and reported that the TT genotype increases circulating adiponectin serum concentrations; this could explain the protective effect of genotype TT observed in our study [11]. Another study reported that variation in the ADIPOQ gene has effects on other types of cancer. They found that the T variation may have a protective effect in the development of endometrial cancer [22]. There is another study with opposite results that report that the GG genotype was associated with a higher adiponectin serum concentration in Kuwait [18]. Gui et al. found no association between genotypes of rs1501299 and adiponectin [23]. Also, there are reports that show an inverse association between adiponectin

Table 3 Frequencies of adiponectin polymorphism in Mexican Women without adjusted by age and BMI

| Polymorphism                | Genotype   | Cases % | Controls % | p-value (cases vs control) | OR    | 95% IC       |
|-----------------------------|------------|---------|------------|----------------------------|-------|--------------|
| rs1501299 (+276 G > T)      | GG³        | 44.4    | 58.3       | 0.003                      | Reference |
|                             | GT         | 45.6    | 35.5       | 1.53                       | 1.12–2.09 |
|                             | TT         | 10.0    | 6.2        | 1.99                       | 1.12–3.51 |
|                             | X²         | 0.434   | 0.231      |                            |        |              |
|                             | p-value HWE| 0.51    | 0.63       |                            |        |              |
| Allele                      | G          | 0.671   | 0.761      |                            |        |              |
|                             | T          | 0.329   | 0.239      |                            |        |              |
| rs2241766 (Gly15Gly, + 45 T > G) | TT³       | 71.0    | 62.8       | 0.0003                     | Reference |
|                             | TG         | 27.2    | 29.6       | 0.81                       | 0.51–1.12 |
|                             | GG         | 1.8     | 7.6        | 0.20                       | 0.07–0.51 |
|                             | X²         | 0.8386  | 7.887      |                            |        |              |
|                             | p-value HWE| 0.360   | 0.005      |                            |        |              |
| Allele                      | T          | 0.847   | 0.776      |                            |        |              |
|                             | G          | 0.153   | 0.224      |                            |        |              |

HWE Hardy-Weinberg Equilibrium

Table 4 ADIPOQ rs1501299 polymorphism using the multiple SNP inheritance models adjusted by age and BMI

| Model          | Genotype | Cases % | Controls % | OR (95% CI) | p-value | AIC  |
|----------------|----------|---------|------------|-------------|---------|------|
| Codominant     | GG       | 41.1    | 58.1       | 1.00        | 8e-04   | 684  |
|                | GT       | 47.3    | 35.7       | 0.55 (0.34–0.80) |         |      |
|                | TT       | 11.6    | 6.2        | 0.39 (0.20–0.76) |         |      |
| Dominant       | GG       | 41.1    | 58.1       | 1.00        | 3e-04   | 683.1|
|                | GT - TT  | 58.9    | 41.9       | 0.52 (0.36–0.74) |         |      |
| Recessive      | GG - GT  | 88.4    | 93.8       | 1.00        | 0.04    | 692.1|
|                | TT       | 11.6    | 6.2        | 0.51 (0.27–0.98) |         |      |
| Overdominant   | GG - TT  | 52.7    | 64.3       | 1.00        | 0.012   | 690  |
|                | GT       | 47.3    | 35.7       | 0.63 (0.44–0.90) |         |      |
| Log-additive   | –        | –       | –          | 0.59 (0.45–0.78) | 2e-04   | 682.5|
concentrations within breast tumors and tumor stage [24]. To date, reports of the association of rs1501299 genotypes with serum adiponectin levels are contradictory. Al Khalidi et al. reported that the T allele and TT genotype of rs1501266 reduce adiponectin levels in serum [18].

Another study reports no association between ADIPOQ SNPs and BC in American white women [25]. Genotypes TG and GG of SNP rs2241766 have also been associated with a decreased risk for BC when compared to the TT genotype, the rs2241766 variation with the G allele and the TG and TG + GG genotypes may have a protective effect in ductal infiltrating breast cancer in Mexican women [26].

In our study, the rs2241766 polymorphism was in HW disequilibrium in controls, so it is not possible to confidently associate it with breast cancer risk. The allelic discrimination plots obtained in the real time PCR were clean and we did not find differences between duplicates.

Some authors have also reported HW disequilibrium in different populations for the rs2241766 polymorphism [24]. The main causes of HW disequilibrium in controls were selection bias or a competing risk of death associated with the mutant gene [25].

We performed a general lineal model to identify if the BMI was associated with the polymorphism. We were able to identify that the polymorphism is associated with breast cancer risk, but not the BMI.

In our study, the controls did not come from the general population but from the radiology area, which may have contributed to selection bias and may partly explain the genotypic imbalance in the case of rs2241766. Another disadvantage of this study is that we were unable to analyze serum ADIPOQ levels due to variability in pre-analytical processes.

Further studies are needed to examine the association of adiponectin serum concentrations with the different gene polymorphisms [10, 19], particularly in Mexican populations.

We estimated associations between SNPs in ADIPOQ and BC risk in a hospital case-control study of Mexican women. To our knowledge, our study is the largest in Mexican population (397 cases and 355 controls) evaluating ADIPOQ SNPs in BC risk.

The Mexican population is Mestizo, and it is important to characterize the distribution of BC risk polymorphisms. Detection of SNP rs1501299 in the Mexican population may play an important role as a BC risk biomarker. Other reports in Mexican women found a positive relation with SNP rs1501299, and the response to chemotherapeutic treatment in patients with BC [19].

Mexico is a developing country where the use of genetic tests is not routine and SNP detection will be useful to support potential benefits of personalized medicine for Mexican population.

Conclusions
In conclusion, we confirmed that rs1501299 polymorphism is associated with BC risk in a large series of Mexican women. The identification of the genotype of these polymorphisms in patients with breast cancer can contribute to integrate the risk profile in both patients and their relatives as part of a comprehensive approach and an increasingly more personalized medicine.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s12881-020-01125-8.

Additional file 1 Table S1. Clinical-pathological characteristics in the case group.

Abbreviations
ADIPOQ: Adiponectin gene; BC: Breast cancer; SNPs: Single nucleotide polymorphisms; HW: Hardy-Weinberg equilibrium; BMI: Body mass index; OW: Overweight; OB: Obesity; TNF: Tumor necrosis factor; IGF: Insulin growth factor; IMSS: Instituto Mexicano del Seguro Social; SDs: Standard deviations; ORs: Odds ratios; CI: Confidence intervals; IDC: Invasive ductal carcinoma; MRA: Modified radical mastectomy; NCBi: National Center of Biotechnology Information

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Authors’ contributions
MLGR, JFGG, and OVG designed the study and obtained funding for this study. GG0, RGG, MAFPC, ALCA, JFGG, OVG, and MLGR recruited patients for the study. KPCC, MPFF, JCAB, RRGG, MAPC, and HFRG carried out the DNA extraction and sample storage in the biobank. HFRG, RMCF, and MLCR designed the sample database, and performed the statistical analysis. KPCC, GG0, IPRS, JCB, and MPVV performed the q-PCR and PCR assays. MLGR, HFRG, OVG, JFGG, HABS, ALCA, and RMCF performed interpretation of data analysis. MLGR, RMCF, HABS, OVG, JFGG, and KPCC drafted the manuscript. All authors substantively read/revised/corrected, and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this manuscript.

The sequences of the SNP were obtained from the NCBI GenBank database (https://www.ncbi.nlm.nih.gov/genbank). The reference genome was GRCm38.p12 and the accession numbers for SNP are: NG_021140.1.g.15430 T > G for rs2241766, and NG_021140.1.g.15661 G > T for rs1501299.
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