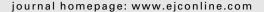


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The risk of developing cervical cancer in Mexican women is associated to CYP1A1 MspI polymorphism

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ABSTRACT

The aim of the study was to evaluate the association of two CYP1A1 polymorphisms (Msp1 and exon 7) with cervical cancer in Mexican women considering their smoking habit. The polymorphisms were determined in 310 individuals (155 with cervical cancer and 155 healthy controls). Women with MspI T/C or C/C showed increased risk of developing cervical cancer (3.7- and 8.3-fold increase, respectively) compared to women with T/T genotype. When smoking habit was considered, the risk for non-smokers with T/C and C/C genotypes was similar (5.2 and 4.1, respectively), whereas smoking women with C/C genotype showed a 19.4-fold increase of cervical cancer. Number of child births, number of sexual partners and marital status were strong risk factors for developing cervical cancer in women with T/T genotype; however, in women with T/C genotype, only the number of child births and sexual partners had a significant influence. These results suggest an important role of the CYP1A1 MspI polymorphism in the risk of developing cervical cancer.

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1. Introduction

Cervical cancer is the result of a process that starts with a human papilloma virus (HPV) infection. This virus has more than 100 types, but types 16, 18, 33 and 45 have been identified as the cause of 80% of the cases of cervical cancer diagnosed throughout the world. This disease is more common in Latin American women than in Jewish or European women, and its prevalence is greatest amongst women in the lowest socio-economic level. The major risk factors associated are multiple sexual partners, beginning sexual relations at a young age, cervical inflammatory processes and smoking. Many of these factors are surrogate markers of HPV infection. Smoking has been studied importantly in association with the disease for the toxic, mutagenic and carcinogenic compounds found in smoke. Signature is a process of the start of the start

The P450 cytochrome system (CYPs) is a group of enzymes that have an important role in activating or detoxifying carcinogenic elements found in tobacco and other compounds. 10,11 CYP1A1 is the main metabolising enzyme of the aromatic polycyclic hydrocarbons (PAHs), which include benzo(a)pyrene and dimethylbenzoanthracene. These compounds are carcinogenic and are found in tobacco smoke. 12 This enzyme is located in several tissues such as lungs, mammary glands and placenta, and several studies demonstrate its relationship with cancers. 12-14 It is encoded by a polymorphic gene located in chromosome 15. Two polymorphic sites located on the CYP1A1 gene (Msp1 and exon 7) have been associated with a genetic susceptibility to several types of cancer. The first position is located in the 3'- flanking region of the gene (T6235C position). The presence of C at this position (*m2 allele) has been associated with genetic susceptibility to lung cancer and it has also been reported that individuals with this susceptible genotype are at high risk of developing squamous cell carcinoma. 15 A previous study pointed out that the homozygous variant (*m2) of CYP1A1-Msp1 is associated with 3.4-fold increased risk of developing cervical intraepithelial lesions. 16 The second polymorphism, A4889G, located in the heme-binding region of exon 7 at codon 462, alters the protein structure by replacing an isoleucine for a valine (*Val allele)17 and may render the carriers more susceptible to lung cancer, cigarette-induced severe coronary atherosclerosis and diabetes. 18,19 The aim of the present study was to evaluate the association of the CYP1A1 polymorphisms with the risk of developing cervical cancer in Mexican women. We also evaluated the potential effect of the smoking habit on this association.

2. Materials and methods

2.1. Studied population

Between January 2002 and January 2003, patients with the diagnosis of cervical cancer who attended the Oncology Hospital of the Instituto Mexicano del Seguro Social (IMSS), the Instituto Nacional de Cancerología and the Hospital General de México were included in the study. Only Mexico City residents were selected. All cases presented invasive cancer and positive HPV-16 infection. The cases were evaluated by two pathologists and only the confirmed ones were included. Wo-

men without intraepithelial cervical dysplasia or cancer were selected as controls from first stage medical units. They had class I or II Papanicolau study negative to high-risk HPV infection and had a normal colposcopy.

The whole population was Mexican Mestizo with a history of three previous generations being born in Mexico.

The present study was approved by the Bioethics and Research Committee and all study subjects signed an informed consent letter.

2.2. HPV sampling procedure

A sample was taken from endocervix using a cytobrush (Digene Cervical SamplerTM, Digene Corporation, Gaithersburg MD, USA). Specimens for HPV DNA testing were stored at -4 °C and were sent to the Molecular Biology Laboratory for masked high-risk HPV test using Hybrid capture II method with specific primers for HPV16 at the L1 region (nt 6028–6179).

Specimens were denatured, and liberated single-stranded DNA was hybridised in a solution with a bionucleic acid (RNA) probe mix consisting of HPV type 16. Each mixture reaction containing any RNA/DNA hybrid forms was transferred to a capture tube coated with antibodies against RNA/ DNA hybrids. Unreacted material was removed by washing and a dioxetane-based chemiluminescent substrate, which binds to alkaline phosphatase, was added. Light produced by the ensuing reaction was measured by a luminometer (DML 2000™, Digene Corp.). Light measurements were expressed as relative lights units (RLU). Solutions of HPV16 at 10 pg/ml served as positive controls. All RLU measurements of specimens were divided by the RLU of appropriate positive controls to a yield ratio. A specimen ratio of ≥1.0 was regarded as positive for HPV DNA, while a ratio <1.0 was regarded as negative. Because the amount of light produced by the HC capture assay is proportional to the amount of target DNA in each specimen, results are quantitative: the higher the ratio, the greater the amount of target HPV DNA in the specimen.

2.3. CYP1A1 polymorphism detection

Genomic DNA from whole blood containing EDTA was extracted by standard techniques (Kit Genomic DNA Isolation BD tactTM).

2.3.1. Exon 7 polymorphism detection

Exon 7 genotype was determined by allele-specific polymerase-chain-reaction (PCR) as described by Hayasi et al. ¹⁹ Each DNA sample was amplified in two separate reactions using one of the 5' primers: even 5'-GAAGTGTATCGGTGAGACCA-3' or 5'-GAAGTGTATCGGTGAGACCG-3'. All reactions included the 3' primer 5'-GTAGACAGAGTCTAGGCCTCA-3'. The samples were amplified in a Perkin–Elmer thermocycler model 9700 (Foster City, CA, USA) with an initial denaturalisation temperature of 95 °C followed by 30 cycles of 95 °C for 1 min, 65 °C for 1 min and 72 °C for 1 min, with a final extension temperature of 72 °C for 5 min. Products were analysed by electrophoresis of a 1.5% agarose gel and visualised by ethidium bromide stain on a UV transilluminator.

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