RESEARCH ARTICLE

Human Papillomavirus Genotypes among Females in Mexico: a Study from the Mexican Institute for Social Security

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Abstract

Background: The aetiological relationship between human papillomavirus (HPV) infection and cervical cancer (CC) is widely accepted. Our goal was to determine the prevalence of HPV types in Mexican women attending at the Mexican Institute for Social Security from different areas of Mexico. Materials and Methods: DNAs from 2,956 cervical samples were subjected to HPV genotyping: 1,020 samples with normal cytology, 931 with low-grade squamous intraepithelial lesions (LGSIL), 481 with high grade HGSIL and 524 CC. Results: Overall HPV prevalence was 67.1%. A total of 40 HPV types were found; HPV16 was detected in 39.4% of the HPV-positive samples followed by HPV18 at 7.5%, HPV31 at 7.1%, HPV59 at 4.9%, and HPV58 at 3.2%. HPV16 presented the highest prevalence both in women with altered or normal cytology and HPV 18 presented a minor prevalence as reported worldwide. The prevalence ratio (PR) was calculated for the HPV types. The analysis of PR showed that HPV16 presents the highest association with CC, HPV 31, -33, -45, -52 and -58 also demonstrating a high association. Conclusions: The most prevalent HPV types in cervical cancer samples were -16, -18, -31, but it is important to note that we obtained a minor prevalence of HPV18 as reported worldwide, and that HPV58 and -52 also were genotypes with an important prevalence in CC samples. Determination of HPV genotypes is very important in order to evaluate the impact of vaccine introduction and future cervical cancer prevention strategies.

Keywords: Human papillomavirus - genotypes - cervical cancer - Mexico

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Introduction

Human papillomavirus (HPV) infection is currently accepted as the main risk factor for Cervical Cancer (CC) development. Among all identified HPV types, high-risk HPV16 and -18 are the most frequent viral types, encompassing approximately 60% of the CC cases worldwide. Several reports have been published with respect to HPV frequencies in cervical lesions (Munoz et al., 2003; Bruni et al., 2010; Ciapponi et al., 2011; Li et al., 2011; Chinchai et al., 2012; Guan et al., 2012; Natphopsuk et al., 2013; Panigoro et al., 2013; Sui et al., 2013; Othman et al., 2014).

CC is one of the most disturbing public health problems in Mexican women, representing the second most common female neoplasm, with 15.5% incidence and 12.8% mortality (Jemal et al., 2011). Some studies concerning HPV in Mexico have shown some differences in the prevalence reported. Such differences range from 4.8% to 40.9% and suggest a variability of HPV frequencies regarding geographical zone (Torroella-Kouri et al., 1998; Gonzalez-Losa et al., 2004; Pina-Sanchez et al., 2006; Sanchez-Anguiano et al., 2006; Lopez-Revilla et al., 2008; Velazquez-Marquez et al., 2009; Canul-Canche et al., 2010; Illades-Aguilar et al., 2010; Orozco-Colin et al., 2010; Velazquez-Marquez et al., 2010).

The present work represents a large collaborative effort to have a more precise knowledge about HPV presence in females cared for at the Mexican Institute for Social Security, which covers health services for around half of the Mexican population.

Materials and Methods

Data and biological samples were collected from women who assisted to Cancer Prevention Clinics, at the Dysplasia Clinics and Oncology Hospitals at IMSS located in the following cities and geographical areas according to the National Institute of Statistics and Geography [http://www.inegi.org.mx/]: Metropolitan Area (Mexico City and Cuernavaca, Morelos State); Eastern Area (Atlixco, Izucar and Puebla Cities at Puebla State; Tlaxcala City at Tlaxcala State, and Las Choapas at Veracruz State); Western Area (Guadalajara, Jalisco State); Northeastern area (Monterrey, Nuevo Leon State) and Center Area (Leon, Guanajuato State) during 2006-2012 period.

The protocols were approved either by the Local Research Committee or the National Ethical and Research Committees, and written informed consent was obtained from the participants. The present work was considered as a cross-sectional study.

Selection criteria

The study included any women attending the Cancer Prevention Clinics, Dysplasia Clinics, or Oncology Hospital, independently of age, economic and education levels, number of pregnancies and sexual partners, age of sexual activity onset, drug and alcohol consumption, hormone intake, or infection with other pathogens with known diagnosis.

Cervical samples were grouped on the basis of their cytological diagnosis in: normal cervix (without cytological alterations), low-grade squamous intraepithelial lesion (LGSIL), high-grade squamous intraepithelial lesion (HGSIL) and cervical cancer (classification according to the World Health Organization, WHO criteria).

DNA isolation and purification

Cervical scrapes were obtained with cytobrush from women with normal cervix or SILs tissues.

For CC lesions, a biopsy was obtained which was divided in two sections. One section was used for genomic DNA extraction and the remaining tissue was fixed with 70% ethanol overnight and paraffin-embedded. Hematoxylin and eosin stained sections were analyzed to confirm the presence of at least 80% of tumor cells in each sample. The CC samples were classified as squamous cervical carcinoma.

For DNA extraction the Wizard Genomic kit (Promega, Madison,WI, USA) was used according to the manufacturer's instructions. DNA was purified, then quantified in a NanoDrop Spectrophotometer ND-1000, and resolved in 1% ethidium bromide stained agarose gel.

HPV detection and genotyping were performed by polymerase chain reaction (PCR) using consensus primers GP5+/GP6+ for a 150 bp fragment region of the L1 gene, or type specific probes for HPV16/18 and/or reverse hybridization. For internal control in PCR assays, the samples were primarily subjected to glyceraldehyde 3-phosphate dehydrogenase (GAPDH), tubulin or cyclophiline genes amplification (amplicon <200 bp). After 5 min of denaturation at 94°C, 100 ng of DNA were subjected to 35 amplification cycles with the following parameters: 94°C for 1 min., 44°C for 1 min and 72°C for 1 min., with a final extension step of 72°C for 10 min. The amplified products were purified employing the Wizard SV gel and PCR-clean-up System kit (Promega, Madison,Wi, USA) and labeled using the Big Dye sequencing kit (Applied Biosystems, Foster City, CA, USA). The labeled products were then sequenced on an Applied Biosystems 373 automated DNA sequencer (Applied Biosystems), and the sequences obtained were aligned and compared with the existing databases utilizing the Blast local alignment search tool (BLAST) program [http://www.ncbi.nlm.nih.gov/BLAST/]. Nearly one third of the samples were genotyped by reverse hybridization according to manufacturer's protocol (Linear Array Roche Diagnostics, CA, USA and InnoLipa, Innogenetics, Gent-Belgium).

Statistical analysis

Percentages, frequencies, and prevalence ratio (ratio of the percentages of CC divided to the normal patient percentage for each HPV genotype) were calculated. χ^2 test or Fisher exact test were used to estimate the association between HPV genotypes with cervical cancer or cervical-normal samples. Statistical analysis was performed using SPSS v19 for Windows XP (SPSS UK, Ltd, Woking, UK). Odds ratio (OR) was calculated with CI 95%. $p<0.05$ was regarded as significant.

Results

More than 3,000 women were initially involved in the present study; their cervical samples were obtained and analyzed for HPV detection. However, <10% of the samples were excluded because of insufficient DNA or PCR non-amplification of the internal controls. Therefore, our study population consisted of 2,956 women aged 18 to 70 years (mean age 43.7 ± 6.8 years). Partial data included in the present study has already been published (Pina-Sanchez et al., 2006; Velazquez-Marquez et al., 2009; Velazquez-Marquez et al., 2010; Pina-Sanchez et al., 2011).

Overall HPV prevalence was estimated by dividing the total number of subjects by the number of HPV-positive cases, thus HPV was identified in 1,986 from 2,956 samples representing 67.1%. Since patients were classified according to cervical cytology the HPV prevalence for each group was estimated as follow: in 344/1020 samples with normal cytology (33.8%); in 720/931 samples with LGSIL (77.3%); in 445/481 samples with HGSIL (92.4%); and 477/524 samples with CC (91.2%).

In total 40 HPV types were detected, the most prevalent oncogenic HPV types in samples with normal cytology were HPV16 (6.2%), HPV59 (5.4%), HPV18 (2.6%), and HPV31 (1.8%); for LGSIL were HPV16 (22.1%), HPV18

Table 1. Frequencies and Prevalence ratio (PR) of High and Low Risk HPV Detected in Mexican Woman

Genotype	Normal	LGSIL		HGSIL		CC		Total
	Frequency	Frequency	PR	Frequency	PR	Frequency	PR	
High Risk HPV genotype								
Negative	66.6% (676)	23.7% (211)		7.5% (36)		9.0% (47)		970
16	6.2% (63)	22.1% (206)	3.56	44.3 (213)	7.15	57.0% (301)	9.19	783
18	2.6% (27)	6.9% (64)	2.65	4.6% (22)	1.77	6.9% (36)	2.65	149
31	1.8% (18)	6.7% (62)	3.72	7.7% (37)	4.28	4.6% (24)	2.56	141
33	0.9% (9)	2.7% (25)	3	3.5% (17)	3.89	1.5% (8)	1.67	59
34	0.1% (1)	0.2% (2)	2	0	0	0.4% (2)	4	5
35	0.7% (7)	2.3% (21)	3.29	1.7% (8)	2.43	0.4% (2)	0.57	38
39	0.4% (4)	1.4% (13)	3.5	1.7% (8)	4.25	1.1% (6)	2.75	31
45	1.0% (10)	1.0% (9)	1	1.0% (5)	1	3.8% (20)	3.8	44
51	0.7% (7)	2.5% (23)	3.57	4.2% (20)	6	0.4% (2)	0.57	52
52	0.7% (7)	3.8% (35)	5.43	4.8% (23)	6.86	2.3% (12)	3.29	77
53	0.8% (8)	1.0% (9)	1.25	0.2% (1)	0.25	0.6% (3)	0.75	21
56	0.5% (5)	1.4% (13)	2.8	1.5% (7)	3	0.6% (3)	1.2	28
58	1.0% (10)	2.4% (22)	2.4	4.0% (19)	4	2.7% (14)	2.7	65
59	5.4% (55)	3.4% (32)	0.63	1.5% (7)	0.28	1.0% (5)	0.19	99
68	0.4% (4)	0.5% (5)	1.25	0.2% (1)	0.5	1.1% (6)	2.75	16
69	0	1.2% (11)		1.0% (5)		0.2% (1)		17
Low Risk HPV genotype								
Negative	66.6% (676)	23.7% (211)		7.5% (36)		9.0% (47)		970
6	1.3% (13)	3.3% (31)	2.54	1.7% (8)	1.31	0.6% (3)	0.46	55
11	1.3% (13)	1.2% (11)	0.92	0.6% (3)	0.46	0.8% (4)	0.62	31
26	0.1% (1)	0	0	0	0	0.2% (1)	2	2
30	0.1% (1)	0	0	0	0	0	0	1
42	0.5% (5)	0.6% (6)	1.2	0.2% (1)	0.4	0.2% (1)	0.4	13
43	0.1% (1)	0	0	0.2% (1)	2	0	1	2
54	0.2% (2)	3.0% (28)	15	2.7% (13)	13.5	0.2% (1)	0	44
55	0.3% (3)	0.3% (3)	1	0	0	0	0.33	6
61	0.6% (6)	0.5% (5)	0.83	0	0	0.2% (1)	0.44	12
62	0.9% (9)	0.5% (5)	0.56	0	0	0.4% (2)	0.22	16
66	0.9% (9)	0.8% (8)	1	0.4% (2)	0.44	0.2% (1)	0	20
67	0.2% (2)	0.1% (1)	0.5	0.4% (2)	2	0	0.5	5
70	0.4% (4)	0.4% (4)	1	1.0% (5)	2.5	0.2% (1)	0	14
71	0.2% (2)	0.2% (2)	1	0	0	0	0	4
72	0.1% (1)	0.1% (1)	1	0.4% (2)	4	0	0	4
73	0.2% (2)	0.3% (3)	1.5	0.2% (1)	1	0	0	6
81	0.4% (4)	0.5% (5)	1.25	0	0	0	0	9
82	0.2% (2)	0.1% (1)	0.5	0	0	0	0	3
83	0.2% (2)	1.2% (11)	6	1.7% (8)	8.5	0	0	21
84	0.9% (9)	0.2% (2)	0.22	0	0	0	0	11
87	0.1% (1)	0	0	0.2% (1)	2	0	0	2
89	0.1% (1)	0	0	0	0	0.2% (1)	0.02	2
91	0.1% (1)	0.1% (1)	1	0	0	0	0	2
97	0.1% (1)	0	0	0	0	0	0	1
ND*	1.4% (14)	4.3% (40)		1% (5)		3.1% (16)		75
HPV+	344	720		445		477		2956
Total	1020	931		481		524		

*ND: HPV not determined

Table 2. Cervical Cancer and Cervical Normal Samples Asociation with Different HPV Genotypes

Genotype	CC	Normal	Total	OR	95% IC	p value
6	3	13	16	3.31	0.913-12.06	0.05
11	4	13	17	4.42	1.38-14.11	0.006
16	301	63	364	68.72	45.99-102.7	0.0001
18	36	27	63	19.18	10.74-34.26	0.0001
31	24	18	42	19.18	9.72-37.82	0.0001
33	8	9	17	12.78	4.71-34.66	0.0001
45	20	10	30	28.77	12.73-64.98	0.0001
52	12	7	19	24.66	9.27-65.58	0.0001
58	14	10	24	20.14	8.48-47.77	0.0001
59	5	55	60	1.3	0.49-3.42	0.3
Negative	47	676				

*All data were performed with a contingency table related every genotype with negative frequencies

(6.9%), HPV31 (6.7%), HPV52 (3.8%), for HGSIL were HPV16 (44.3 %), HPV31 (7.7%), HPV52 (4.8%), HPV18 (4.6%), and in CC were HPV16 (57%), HPV18 (6.9%), HPV31 (4.6%), HPV45 (3.8%), (Table 1).

Respect to low-risk HPV types, the most frequently found in HGSIL were HPV54, -6, -83, -69, and -70, which ranged from 2.7-1.0%; while in CC samples the most frequent were HPV11 and -6 with 0.8 and 0.6%, respectively (Table 1).

The probability that CC patients were exposed with the most frequently found HPV types were calculated. Interestingly, HPV6 and -11 types have some probability to have some relationship to CC (Table 2). As expected, HPV16 showed the highest OR value (68.72; 45.99-102.7) followed by HPV45, -52, -58 for HPV18 and HPV31 showed similar values (Table 2). These results could suggest a strong association between HPV16, -18, -31, -33, -52 and -45 and CC development.

Discussion

Cervical cancer is one of the most important health problems in Mexican women. Huge efforts derived from studies in 22 countries have revealed HPV DNA in nearly all CC cases (99.7%) (Clifford et al., 2003). Epidemiological studies have shown that approximately 40 distinct HPV types infect the female genital tract, but at least 14 of these are significantly associated with progression to CC. Among these, HPV16 (≈50%) and HPV18 (≈15%) are the most frequently found in CC (Clifford et al., 2003). Our present data is showing that HPV16 prevalence (57%) is slightly higher than worldwide data and is supported by previous reports showing that HPV16 is the most prevalent papillomavirus in malignant and normal cervical tissues. Indeed, we found that HPV16 could be present in almost 2 of 3 CC patients (57%). For instance, it has been reported that the high prevalence of HPV16 is associated with its high capacity for replication efficiency, thus avoiding cell death (Bernard et al., 2006). On the other hand, this high replication rate could act as a dominant factor generating a genomic stability (chronic event) evading the cell defense mechanism, which confers high biological advantages (Bernard et al., 2006; Lizano et al., 2009).

We detected a prevalence of 5.4% for HPV59 in normal tissue and 1% in CC samples. We suggest this prevalence to be taken as an example of an oncogenic virus with scarce adaptive fitness in which the neoplastic cells could be targeted by the immune system.

Interestingly, HPV18 was present in <8% of cases of CC, comprising nearly one half of the worldwide report (Clifford et al., 2003). As we noted, HPV18 showed a consistent distribution through the spectra of cervical lesions. A supposed aggressive role of HPV18 has been reported; thus, strong damage originated by HPV18 could cause cell death and the cleaning of virus infection concomitantly (Bernard et al., 2006). It is also likely that transformed cells could not support genomic instability generated by HPV18 genome expression. In this case, a low replication rate and the extreme cellular damage induced by HPV18 would result in poor presence of this virus type in our population (Bernard et al., 2006). We did not discard the presence of poor oncogenic HPV18 variants competing with aggressive HPV18 variants. Previous reports on "benevolent" HPV18 variants could also support our present data (Lizano et al., 2009).

Other HPV types were also detected in CC, of which HPV31, -33, -45, and -58 collectively accounted for a prevalence >13%. Altogether HPV16, -18, and these comprise >90% of CC cases in our studied population. Similar findings have been previously reported (Clifford et al., 2003), but certain members of the A9 HPV group (HPV16, -31, -35, and -58), and A7 group as HPV18 and -45, practically comprise the total cases of CC. It is noteworthy that in Asia a larger proportion of CC is associated with HPV52, -59, and -58 (Wu et al., 2008; Wang et al., 2012). Similar findings on HPV distribution in some other countries of the American Continent have been already reported (Berumen et al., 2001; de Sanjose et al., 2010). In this context, our present results could show a mix of those same HPV prevalences.

Today, we stand in the post-vaccination era against HPV infection; considering the highest frequencies of HPV16 and -18 (Tota et al., 2011), either of the two vaccines that are currently in use would induce >70% protection in the vaccinated population. However, we must consider in the prevention strategies other HPV types, such as HPV58, which represents an extremely important factor in our population (Lizano et al., 2006). A new HPV vaccine has been reported that covers the most frequent HPV types (Shi et al., 2001). Nonetheless, the use of any HPV vaccines should be based on local epidemiological data to avoid loss of efficiency due to variations in HPV distribution. To this respect, a recent meta-analysis of HPV prevalence that included >8,000 subjects throughout Mexico reported some variations in the HPV prevalence (Peralta-Rodriguez et al., 2012). This data, combined with the one resulting from different research, might have important implications in the design of new HPV screening systems and the development of new HPV vaccines. This supports the recently published about the potential impact of a nine-valent vaccine against HPV (Serrano et al., 2012).

In conclusion, the behavior of HPV16 and HVP18 in Mexico, while similar to worldwide data, differs in terms of prevalence percentages. The role of HPV31, -33, -45,

-52 and -58 are also representing an important factor within our population. Current epidemiological data on HPV genotypes is relevant in order to evaluate the impact of vaccine introduction and future cancer prevention strategies. Therefore, a customized HPV vaccine could be required for the prevention and treatment of cervical lesions in Mexican females..

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