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Human Papillomavirus Infections in Mexican Women With Normal Cytology, Precancerous Lesions, and Cervical Cancer: Type-Specific Prevalence and HPV Coinfections

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The prevalence and genotype distribution of human papillomavirus (HPV) provides the basis for designing HPV prevention programs. The prevalence rates of type-specific HPV and coinfections in samples of Mexican women were investigated in 822 women aged 18–87 years. HPV detection was performed using a Linear Array™ genotyping test. HPV infection was found in 12.4% of controls, 46.3% of those with cervical intraepithelial neoplasia 1, and 100% of those with cervical intraepithelial neoplasia 3 or cervical cancer. HPV 16 was the most prevalent type in all diagnosis groups. The HPV types most frequently found in cervical cancers were 16, 18, 45, 52, 58, and 39; HPV types 16, 62, 51, 84, 18, 53, and CP6108 were the most prevalent in control women. Considering HPV-positive samples only, coinfections occurred most often in controls (63%) and were less frequent in those with cervical cancer (26%). The most frequent viral types in coinfections with HPV 16 in control women were HPV 62, 51, and 84; in women with cervical cancers, HPV 18, 39, and 70 were most common. In conclusion, in addition to HPV types 16 and 18, types 45, 39, 58, 52, and 71 were found in cervical cancers in Mexican women (78%); among them, only 65% were attributable to HPV types 16 and 18. Therefore, it is necessary to consider these viral types in the design of new vaccines, and to determine whether certain HPV types coinfecting with HPV 16 in precursor lesions determine tumor progression or regression. ***J. Med. Virol. 87:871–884, 2015.*** © 2015 Wiley Periodicals, Inc.

KEY WORDS: human papillomavirus; cervical cancer; Linear Array® HPV genotyping test; coinfections; Mexico

INTRODUCTION

Human papillomavirus (HPV) infection is the main factor associated with cervical cancer [Zur Hausen, 2009a,b]. At present, >170 HPV types have been

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registered [Bernard et al., 2010; Van Doorslaer et al., 2013]. However, there are approximately 40 types that infect the genitourinary tract and—based on the relationship between prevalence and the specific viral types found in women with normal cytology and in those with cervical cancers—only the following 12 have been classified as being type 1 carcinogenic: types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 [Bouvard et al., 2009; IARC_Working_Group, 2012]. HPV 68, on the other hand, has been classified as "probably carcinogenic to humans" (class 2A), whereas types 26, 53, 66, 67, 70, 73, 82, 30, 34, 69, 85, and 97 have been classified as "possibly carcinogenic" (class 2B) [Bouvard et al., 2009]. The main HPV types associated with cervical cancers worldwide are 16, 18, and 45 [Bouvard et al., 2009; IARC_Working_Group, 2012]. In addition, depending on the geographical region, some viral types are more frequently found than others. For example, HPV types 33 and 31 are more prevalent in Europe and the USA, types 35 and 45 are found more frequently in Africa, and types 52 and 58 are more frequently observed in Asia [de Sanjose et al., 2010; Guan et al., 2012; Tjalma et al., 2013].

In Mexico, cervical cancer is the second most frequent neoplasia and the second most frequent cause of death by cancer in women [Jemal et al., 2011]. It has been reported that HPV types 16, 18, 58, 31, and 45 are the most prevalent in cervical samples from Mexican patients [Giuliano et al., 2001; Montoya-Fuentes et al., 2001; Rodriguez-Reyes et al., 2003; Pina-Sanchez et al., 2006; Sanchez-Anguiano et al., 2006; Velazquez-Marquez et al., 2009; Illades-Aguiar et al., 2010; Lopez Rivera et al., 2012]. However, the majority of such studies have been limited because of the restricted screening and genotyping methodologies utilized (identification of only certain specific HPV types) or because the methods employed did not permit the identification of coinfections in the same sample. A few years ago, a more sensitive and more specific method based on polymerase chain reaction (PCR) amplification and reverse line blot hybridization enabled the detection of 37 HPV types and coinfections in the same sample [Coutlee et al., 2006; Giuliani et al., 2006; Stevens et al., 2006; Castle et al., 2008; Wentzensen et al., 2012; Koshiol et al., 2013]. To increase knowledge of the distribution of HPV types—individually and in coinfections—in cervical tissues of Mexican patients, the present study reports an analysis of the prevalence of type-specific HPV, and HPV coinfections, in the cervical epithelium of Mexican women without lesions (controls), in those with precancerous lesions, and in those with cervical cancer, by means of the Linear Array® HPV Genotyping Test (Roche Molecular Diagnostics, Mannheim, Germany).

MATERIALS AND METHODS

Nine hundred two women participated in this study. They were recruited at six gynecological clinics located in the following Mexican cities: Monterrey (in the northeastern region), Guadalajara and Tepic (both in the western region), and Mexico City, Metepec, and Tlaxcala (in the central region). Written informed consent was obtained from each of the women. This was followed by an interview, in which each of the participants responded to a questionnaire on reproductive history and sexual behavior, administered by research assistants. Control samples were obtained from women attending early cancer detection programs, precancerous lesions were collected from women attending dysplasia clinics, and cervical cancer samples were collected in dysplasia clinics and oncology services. Women without cervical lesions were diagnosed by conventional cytology (Papanicolaou or Pap staining) and colposcopy observations; in cases of precancerous lesions or cervical cancer, the diagnosis was confirmed by histopathology. Pap smears and biopsies were evaluated by the pathologist of each clinic, according to Bethesda diagnostic criteria [Solomon et al., 2002]. After confirmation of the diagnosis, the samples were classified as follows: control (without neoplastic alterations); preneoplastic lesions [Richart, 1990], including cervical intraepithelial neoplasia grade 1 and grade 3; and cervical cancer. From the 902 cervical samples initially obtained, only 822 were included in this study (those samples with sufficient quantity and quality of DNA). This study was approved by the Ethics and Research Committees of the Instituto Mexicano del Seguro Social (IMSS) (registration numbers R-2005–2106-0001, R-2008–1908-10, R-2008–3602-3, R-2009–785-086, and R-2009–3602-10).

Sample Collection

Cervical samples were collected with a cytobrush during gynecological examinations. It was inserted into the endocervical canal, rotated for 3–5 full turns, and then placed into the transport medium (PreservCyt solution; Hologic, Bedford, MA) and stored at 4°C until DNA extraction.

HPV Screening

Cervical samples diagnosed as precursor lesions or cancers were genotyped directly by the Linear Array® HPV Genotyping Test (Roche Molecular Diagnostics). Samples from control women without cervical lesions were first screened by conventional single-round PCR utilizing the following sets of primers independently: GP5+/GP6+ [Jacobs et al., 1997], MY09/MY11, and PGMY09/11 [Bauer et al., 1991]. Those samples that were positive for HPV with any of the primer sets were genotyped using the Linear Array® HPV Genotyping Test using single-round PCR with the primers included in the kit.

HPV Genotyping

The Linear Array® HPV Genotyping Test is based on four major processes: i) specimen preparation

TABLE I. Descriptive Characteristics of Women Enrolled in This Study

	Mean ± SD			
	Control	Cervical intraepithelial neoplasia grade 1	Cervical intraepithelial neoplasia grade 3	Cervical cancer
Mean age	45.9 ± 12.9	36.4 ± 11.7	33.5 ± 12.7	47.4 ± 14.5
Mean age at menarche	12.6 ± 1.6	12.5 ± 1.4	12.9 ± 1.4	12.6 ± 1.6
Mean age at 1rst intercourse	20.2 ± 4.6	19.6 ± 4.3	16.8 ± 2.5	18.3 ± 3.8
No. sexual partners	2.1 ± 1.7	1.9 ± 1.4	3.7 ± 3.6	2.1 ± 1.8
No. of pregnancies	2.8 ± 2.6	2.5 ± 2.1	3.7 ± 3.6	4.9 ± 3.5
Parity	1.8 ± 2.2	2.1 ± 2.0	3.2 ± 3.12	4.2 ± 2.7
No. of abortions	0.5 ± 1.0	0.4 ± 0.7	0.5 ± 0.9	0.6 ± 1.6

Characteristics of women are grouped by diagnosis. Mean ± Standard deviations (SD).

(DNA extraction by the AmpliLute Liquid Media Extraction Kit); ii) PCR amplification of target DNA using HPV primers; and iii) hybridization of the amplified products into oligonucleotide probes (Linear Array® HPV Genotyping Test); and iv) detection of probe-bound amplified products by colorimetric determination (Linear Array® Detection Kit). In each sample, the human beta globin gene was amplified as an internal control. After the hybridization reaction, the strips were read visually using a reference guide. All procedures were carried out following the manufacturer's instructions.

The Linear Array® HPV Genotyping Test is registered for use in the European Union for detecting 37 high- and low-risk HPV genotypes, including those considered to be a significant risk factor for cervical intraepithelial neoplasia grade 3 with progression to cervical cancer. The HPV genotypes include 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55 (HPV 44 subtype), 56, 58, 59, 61, 62, 64 (HPV 34 subtype), 66, 67, 68, 69, 70, 71, 72, 73 (MM9), 81, 82 (MM4), 83 (MM7), 84 (MM8), IS39 (HPV 84 variant), and CP6108 (HPV 89) [Coutlee et al., 2006; Stevens et al., 2006].

TABLE II. Association of Risk Factors With Cervical Lesions

	Control	Cervical intraepithelial neoplasia grade 1			Cervical intraepithelial neoplasia grade 3			Cervical cancer		
Risk Factors	n	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI
Age (years)										
≤25	25	57	1.0		8	1.0	1.0	1	1.0	
26–35	39	91	1.0	(0.5–1.9)	12	1.0	(0.34–2.68)	20	12.8	(1.61–101.62)*
36–45	100	67	0.3	(0.16–0.51)*	5	0.2	(0.04–0.51)*	27	6.8	(0.87–52.09)
46–55	97	43	0.2	(0.10–0.35)*	3	0.1	(0.02–0.39)*	17	4.4	(0.55–34.52)
≥56	80	20	0.1	(0.05–0.21)*	2	0.1	(0.01–0.39)*	28	8.8	(1.13–67.69)*
Age at menarche (years)										
>12	152	65	1.0		16	1.0		28	1.0	
≤12	161	81	1.2	(0.79–1.74)	10	0.6	(0.79–1.34)	22	0.7	(0.40–1.35)
Age at 1rst intercourse (years)										
>18	195	139	1.0		7	1.0	1.0	23	1.0	
≤18	144	129	1.3	(0.91–1.73)	22	4.3	(1.76–10.23)*	47	2.8	(1.60–4.76)*
Sexual partners										
0–2	243	154	1.0		12	1.0		52	1.0	
3–5	75	52	1.1	(0.72–1.64)	15	4.1	(1.81–9.03)*	14	0.9	(0.45–1.66)
≥6	10	4	0.6	(0.19–2.04)	3	6.1	(1.47–24.99)*	4	1.9	(0.56–6.19)
Pregnancies										
0–2	117	148	1.0		12	1.0		18	1.0	
3–5	134	96	0.6	(0.39–0.80)	12	0.9	(0.37–2.01)	29	1.4	(0.74–2.66)
≥6	34	26	0.6	(0.34–1.06)	6	1.7	(0.60–4.92)	26	5.0	(2.43–10.13)*
Parity										
0–2	259	178	1.0		14	1.0		21	1.0	
3–5	68	74	1.6	(1.08–2.31)*	11	3.0	(1.30–6.88)*	30	5.4	(2.93–10.09)*
≥6	18	17	1.4	(0.68–2.73)	5	5.1	(1.66–15.86)*	21	14.4	(6.65–30.90)*
Abortions										
0	234	202	1.0		19	1.0		51	1.0	
1–2	93	61	0.8	(0.52–1.10)	10	1.3	(0.59–2.95)	18	0.9	(0.49–1.59)
≥3	16	6	0.4	(0.16–1.13)	1	0.8	(0.09–6.12)	3	0.9	(0.24–3.06)

OR, Odds ratio with a P-value ≤ 0.05(*); 95% CI, 95% confidence interval; Control, women without cervical lesion. Smoking data were not analyzed.

Statistical Analyses

Descriptive statistics were calculated for clinical data. The crude prevalence and attribution rates were calculated. Crude prevalence was estimated for every group by analyzing all studied cases as the denominator. As defined previously, the attribution of each viral type was calculated considering the "crude prevalence of single-type infection" plus "crude prevalence of multiple-type infections × attribution factor." The attribution factor, in turn, was obtained by calculating "the number of samples with single-type infection of the HPV concerned divided by the number of samples with single-type infection of any HPV type in that disease category" [Insinga et al., 2008; Chan et al., 2012a].

The risk was estimated by calculating the odds ratio (OR) and 95% confidence interval (CI). Multinomial logistic regression was employed (comparing those women without cervical lesions with those having cervical cancer) to analyze HPV associations, adjusting for viral coinfection. The criteria used for inclusion in the model were to have an association in the bivariate analysis and to have a P-value ≤ 0.1. Data were analyzed using IBM SPSS Statistics version 20 software (IBM Corp., Armonk, NY) and P-values < 0.05 were considered significant.

RESULTS

Characteristics of the Study Patients

A total of 822 samples from all diagnostic groups of women (control, n = 356; cervical intraepithelial neoplasia grade 1, n = 315; cervical intraepithelial neoplasia grade 3, n = 30; and cervical cancer, n = 121) were genotyped. The demographic characteristics of the women enrolled, such as age, age at menarche, age at first intercourse, number of sexual partners, pregnancies, parity, and any abortions, are shown in Table I. The age range of all women enrolled was 18–87 years; age at menarche, 8–20 years; and age at first intercourse, 12–42 years. Regarding the number of sexual partners, some women reported having had only one sexual partner, while others reported having had > 10 or up to 20 in their lifetime. The ranges of the number of pregnancies, parity, and number of abortions were 0–27, 0–19, and 0–12, respectively.

ORs were calculated to identify factors that might be associated with cervical cancer. As can be seen in Table II, there were no significant differences in relation to age at menarche and number of abortions between the different diagnostic groups. However, age at first intercourse ≤18 years, >3 sexual partners, and >3 parities were statistically significant ($P < 0.05$) in women with cervical intraepithelial neoplasia grade 3. By contrast, in the cervical cancer group, only age at first intercourse ≤18 years, >6 pregnancies, and >3 parities were statistically significant ($P < 0.05$) when compared with women without cervical lesions.

As shown in Figure 1A, patients aged 26–35 years comprised the largest group with cervical intraepithelial neoplasia grades 1 and 3 (32.7% and 40%, respectively), although the respective ORs were not statistically significant (Table II). In contrast, in the cervical cancer group, patients aged 36–45 and >56 years showed the highest frequencies (around 30%), although only those >56 years old showed a significant OR (8.8; 95% CI, 1.13–67.7). Interestingly, more than 20% of patients with cervical cancer were under 36 years of age, and this group of patients showed a significant OR (12.8; 95% CI, 1.61–101.62).

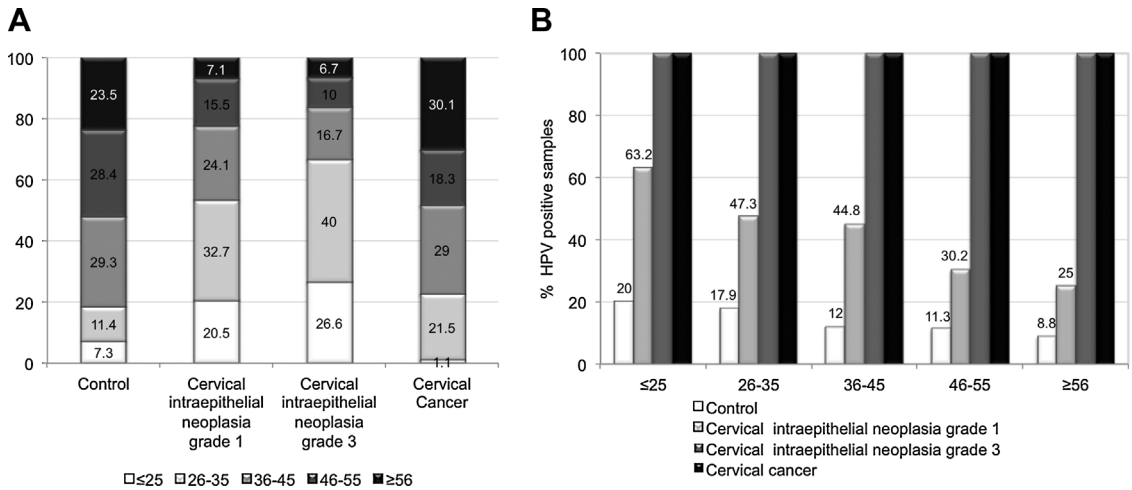

Fig. 1. Distribution of samples based on the diagnosis, presence of HPV, and age. **A**: Frequency of age groups according to the diagnosis, considering all samples. **B**: Frequency of HPV-positive samples within each age group according to the diagnosis. Values correspond to percentages, and ranges shown correspond to age. The control group included samples without cervical lesions.

HPV Prevalence According to Diagnosis and Age Groups

HPV infections were found in 12.4% of controls, 46.0% of cervical intraepithelial neoplasia grade 1 samples, and 100% of cervical intraepithelial neoplasia grade 3 and cervical cancer samples; a total of 35 different HPV types were detected. HPV type 16 was the most prevalent HPV type detected in all groups, being present in 3.1%, 9.8%, 40.0%, and 62.8% of the control, cervical intraepithelial neoplasia grade 1, cervical intraepithelial neoplasia grade 3, and cervical cancer samples, respectively. This was followed by HPV types 62, 51/84, 18, and 53/CP6108 in controls; 84, 58, 59, and 62 in the cervical intraepithelial neoplasia grade 1 group; 31, 18/70, and 6/51/59/66/CP6108 in the cervical intraepithelial neoplasia grade 3 group; and 18, 45, 52/58, and 39 in the cervical cancer group. The percentages of all HPV types detected in the different diagnostic groups are detailed in Table III.

Considering the oncogenic risk of HPV infections, it is noteworthy that even in samples from the control and cervical intraepithelial neoplasia grade 1 groups (taking into account only HPV-positive samples), at least 60% of the samples contained high-risk (HR) HPV types, increasing to 76.7% in the cervical intraepithelial neoplasia grade 3 group and to 96.7% in the cervical cancer group.

Regarding the HPV prevalence according to age group, independently of the diagnosis, women aged 25 years and younger had the highest percentage of HPV infection (54.9%), followed by women aged 26–35 (50.6%), and those aged 36–45 (37.2%). The lowest percentage of HPV infection was observed in women aged 46–55 (27.5%). Interestingly, in women older

TABLE III. Crude Prevalence of HPV Types in Control Women, and in Women With Precancerous Lesions or Cervical Cancer

HPV Type	Oncogenic risk		Control, % (n)	Cervical intraepithelial neoplasia grade 1, % (n)	Cervical intraepithelial neoplasia grade 3, % (n)	Cervical cancer, % (n)
	NM	IARC				
6	LR	3	0.6 (2)	2.2. (7)	10.0 (3)	2.5 (3)
11	LR	3	0.3 (1)	0.6 (2)	3.3 (1)	0.0 (0)
16	HR	1	3.1 (11)	9.8 (31)	40.0 (12)	62.8 (76)
18	HR	1	1.7 (6)	4.4 (14)	13.3 (4)	11.6 (14)
26	PHR	2B	0.0 (0)	0.0 (0)	3.3 (1)	0.0 (0)
31	HR	1	0.3 (1)	3.8 (12)	16.7 (5)	1.7 (2)
33	HR	1	0.0 (0)	1.3 (4)	3.3 (1)	2.5 (3)
35	HR	1	0.6 (2)	1.9 (6)	6.7 (2)	2.5 (3)
39	HR	1	0.3 (1)	4.1 (13)	3.3 (1)	5.8 (7)
40	LR		0.0 (0)	1.0 (3)	0.0 (0)	0.0 (0)
42	LR		0.6 (2)	2.2 (7)	6.7 (2)	0.8 (1)
45	HR	1	0.8 (3)	1.3 (4)	0.0 (0)	8.3 (10)
51	HR	1	2.0 (7)	3.8 (12)	10.0 (3)	2.5 (3)
52[a]	HR	1	1.1 (4)	3.2 (10)	3.3 (1)	6.6 (8)
53	PHR	2B	1.4 (5)	3.8 (12)	3.3 (1)	3.3 (4)
54	LR		1.1 (4)	1.0 (3)	0.0 (0)	0.8 (1)
55	UD		1.1 (4)	1.0 (3)	0.0 (0)	0.0 (0)
56	HR	1	0.8 (3)	3.2 (10)	6.7 (2)	1.7 (2)
58	HR	1	0.6 (2)	6.7 (21)	6.7 (2)	6.6 (8)
59	HR	1	0.6 (2)	5.7 (18)	10.0 (3)	0.8 (1)
61	LR		0.8 (3)	2.9 (9)	6.7 (2)	0.0 (0)
62	UD		3.1 (11)	5.1 (16)	6.7 (2)	0.8 (1)
66	PHR	2B	0.8 (3)	4.1 (13)	10.0 (3)	3.3 (4)
67	UD	2B	0.3 (1)	0.3 (1)	0.0 (0)	0.0 (0)
68	HR	2A	0.6 (2)	1.3 (4)	0.0 (0)	3.3 (4)
69	2B		0.3 (1)	1.3 (4)	3.3 (1)	1.7 (2)
70	LR	2B	1.1 (4)	3.8 (12)	13.3 (4)	2.5 (3)
71	UD		0.3 (1)	2.5 (8)	3.3 (1)	2.5 (3)
72	LR		0.0 (0)	1.0 (3)	0.0 (0)	0.0 (0)
73	HR	2B	0.3 (1)	2.5 (8)	0.0 (0)	0.0 (0)
81	LR		0.8 (3)	1.0 (3)	6.7 (2)	0.8 (1)
82	HR	2B	0.0 (0)	1.0 (3)	0.0 (0)	0.0 (0)
83	UD		0.6 (2)	1.0 (3)	0.0 (0)	0.8 (1)
84	UD		2.0 (7)	7.6 (24)	3.3 (1)	0.8 (1)
CP6108[b]	LR		1.4 (5)	3.2 (10)	10.0 (3)	0.0 (0)
			12.3 (44)	46.0 (146)	100.0 (30)	100.0 (121)

NM: Epidemiologic classification according to Nubia Muñoz et al. (2003). International Agency for Research on Cancer (IARC) classification (2009). LR, Low risk; HR, High risk; PHR, probably high risk; UD, undetermined risk. Control, without cervical lesion. 1, carcinogenic; 2A, probably carcinogenic; 2B, possibly carcinogenic to humans.
[a]The prevalence of HPV 52 could be underestimated due to possible coinfection with viral types 33, 35, and 58.
[b]HPV 89.

than 55 years, the HPV infection rate increased slightly (32.3%). All patients with cervical intraepithelial neoplasia grade 3 or with cervical cancer were positive for HPV, regardless of age. For those with cervical intraepithelial neoplasia grade 1, the percentage of HPV-positive patients showed a continuous decline according to age range, from 63.2% in patients under 25 years of age to 25% in patients 56 years and older. A similar trend—although at lower rates—was observed in the control group (Fig. 1B).

Prevalence of HPV Types as Single Infections or Coinfections

Because the genotyping test used allowed us to identify multiple infections in the same sample, it was of interest to determine the percentages of HPV coinfections in the different diagnostic groups. As illustrated in Figure 2, the rate of coinfections was very high in the control group (63.6%), as well as in the women with cervical intraepithelial neoplasia grade 1 (58.2%) and cervical intraepithelial neoplasia grade 3 (60.0%); however, a strong decrease was observed in the cervical cancer group (26.4%). Additionally, all HPV-positive samples were analyzed independently of the diagnostic group. As depicted in Figure 3, HPV types such as 68, 26, 40, 82, and 83 were only found in coinfections; other HPV types, such as 61, 70, 73, 89 (CP6108), 56, 69, 54, 52, and 66 (among others), were most commonly found in coinfections; and HPV types 45, 11, 67, and 16 were present in the same proportions in cases of both single infections and coinfections.

The crude prevalence rates of coinfection by HPV types were calculated for the control and cervical cancer groups. HPV types 6, 42, 54, 56, 66, 68, 81, and 83 were found in both diagnostic groups only as coinfections. On the other hand, types 62, 70, and 84 were always found as coinfections in cervical cancer samples, whereas types 71, 31, 69, 39, 52, 53, and 58 were found as coinfections in control samples. The main viral types, 16, 18, and 45, were detected in coinfections more frequently in control samples than in cervical cancer samples. Interestingly, HPV 33 was more frequently found as a single infection in women with cervical cancer, whereas it was not detected in any control samples. HPV types 11, 61, 67, 73, and CP6108 (HPV 89) were detected in 100% of control samples as coinfections (Fig. 4). Remarkably, HPV 16 was frequently found in coinfections with HPV 62, 51, and 84 in the control group, while it was often found in coinfections with HPV 18, 70, and 59 in women with cervical intraepithelial neoplasia grade 3, and with HPV 18, 39, and 70 in women with cervical cancer. Because of the multiple HPV types found in single lesions, the attribution of individual HPV types was also calculated as described [Insinga et al., 2008; Wentzensen et al., 2009; Chan et al., 2012a]. As depicted in Figure 5A, HPV 16 was the commonest HPV type for cases of cervical cancer at 57.2%, followed by 18 (7.9%), 45 (5.2%), 39 (2.6%), 52 and 58 (1.8% each), and 33 and 71 (1.7% each). All these HPV types were responsible for a total attribution rate of 79.9%.

The highest individual HPV attribution rates in cases of cervical intraepithelial neoplasia grade 3 were given by HPV types 16 (12.2%), 31 (8.3%), 6 (7.2%), and 66 and 89 (3.9% each; Fig. 5B). In contrast, the main attribution rates in cases of cervical intraepithelial neoplasia grade 1 for HPV types 84, 16, and 59 were 3.2%, 3.1%, and 1.9%, respectively (Fig. 5C). HPV types 62 (1.3%), 18 (1.0%), and 16 (0.9%) were attributable to control samples (Fig. 5D).

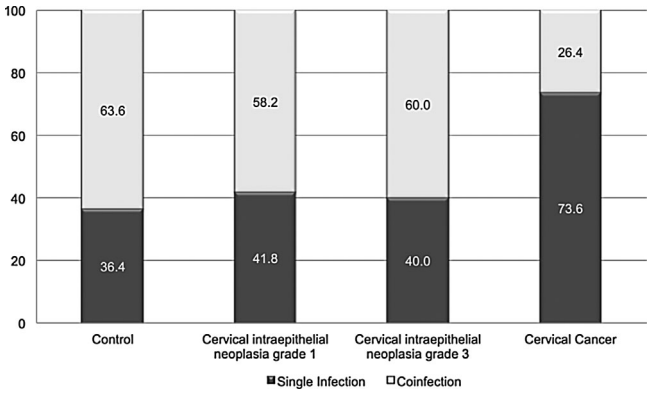

Fig. 2. Percentages of single infections or coinfections grouped by diagnosis among all HPV-positive samples.

DISCUSSION

Cervical cancer is a major public health problem in developing countries, including Mexico. There are many risk factors associated with the development of this cancer type, such as a woman's age at the initiation of sexual activity, a history of multiple sexual partners, high parity, smoking habit, and certain dietary deficiencies [Schiffman and Castle, 2003; Chelimo et al., 2013]. In this study, three factors were associated with cervical intraepithelial neoplasia 3 and with cervical cancer: age at first intercourse $\leq$18 years, having had >6 pregnancies, and parity $\geq$3. Other studies in Mexico did not identify multiple sexual partners as a risk factor for cervical cancer [Illades-Aguiar et al., 2009; Pina-Sanchez et al., 2011]. Here, smoking was not analyzed as a risk factor because not all of the patients included in the study responded to the questions regarding this habit. Thus, the information obtained on smoking was incomplete and not suitable to be considered for this study. It was found that 22% of women with cervical cancer were under 36 years of age. This is in keeping with a recent report by GLOBOCAN showing that in Mexico, the incidence of cervical cancer in women under 39 years of age is

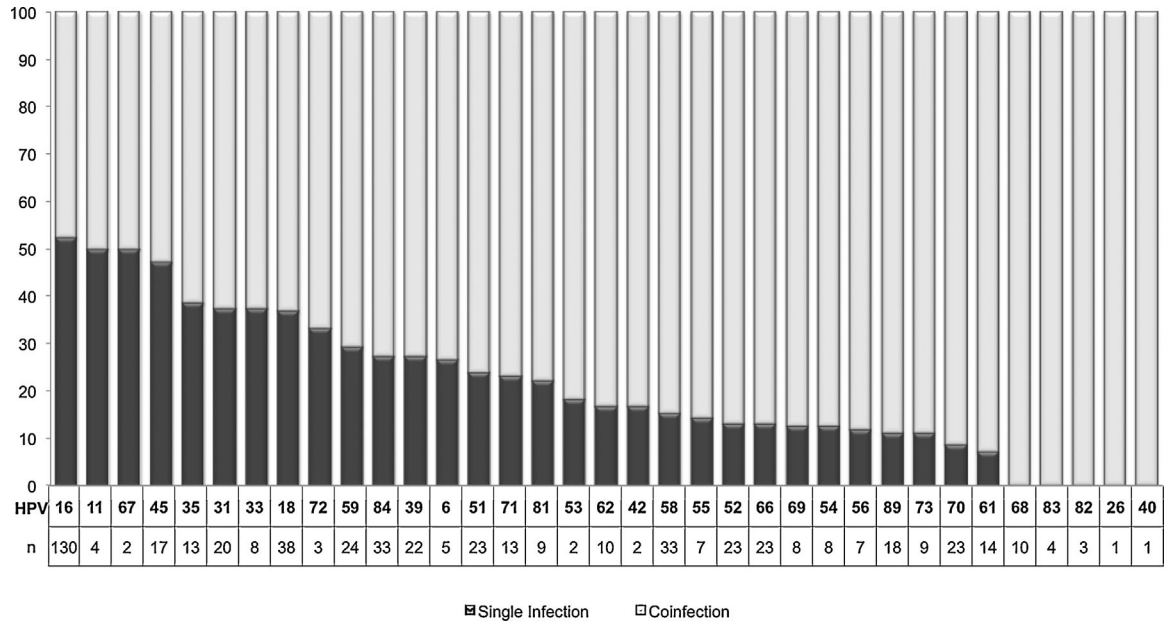

Fig. 3. Percentages of single infections or coinfections determined for each HPV type. Percentages were calculated considering only HPV-positive cases regardless of the diagnosis: n = number of samples in which a particular HPV type was detected.

16.7%, which is higher than in other developing and developed countries [Ferlay et al., 2013].

Infections with certain types of HPV have been considered the most important risk factors for developing cervical cancer. Thus, >99% of malignant samples are positive for the HPV genome [zur Hausen, 2009b; Alexander and Giuliano, 2012]. In the present study, all women with cervical cancer and cervical intraepithelial neoplasia grade 3 showed HPV infection, versus only 12.4% of women in the

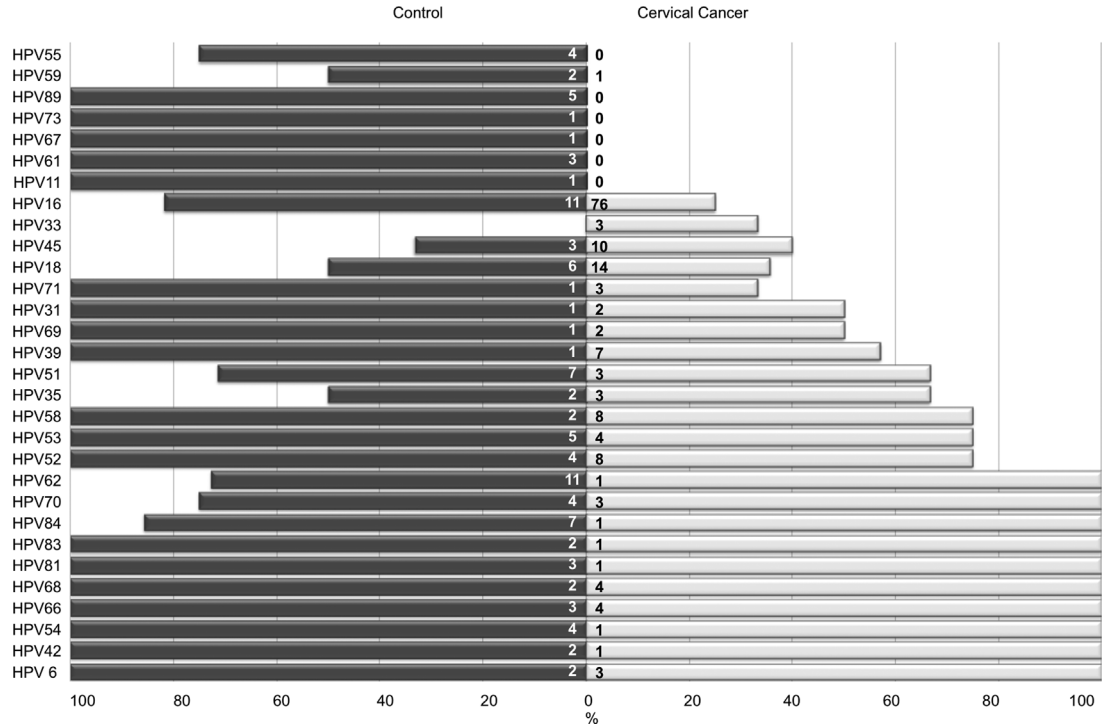

Fig. 4. Percentage of coinfections for each particular viral type in both control samples (women without cervical lesions) and women with cervical cancer. Numbers in the middle of the graphic indicate the total number of samples in which a particular HPV type was detected.

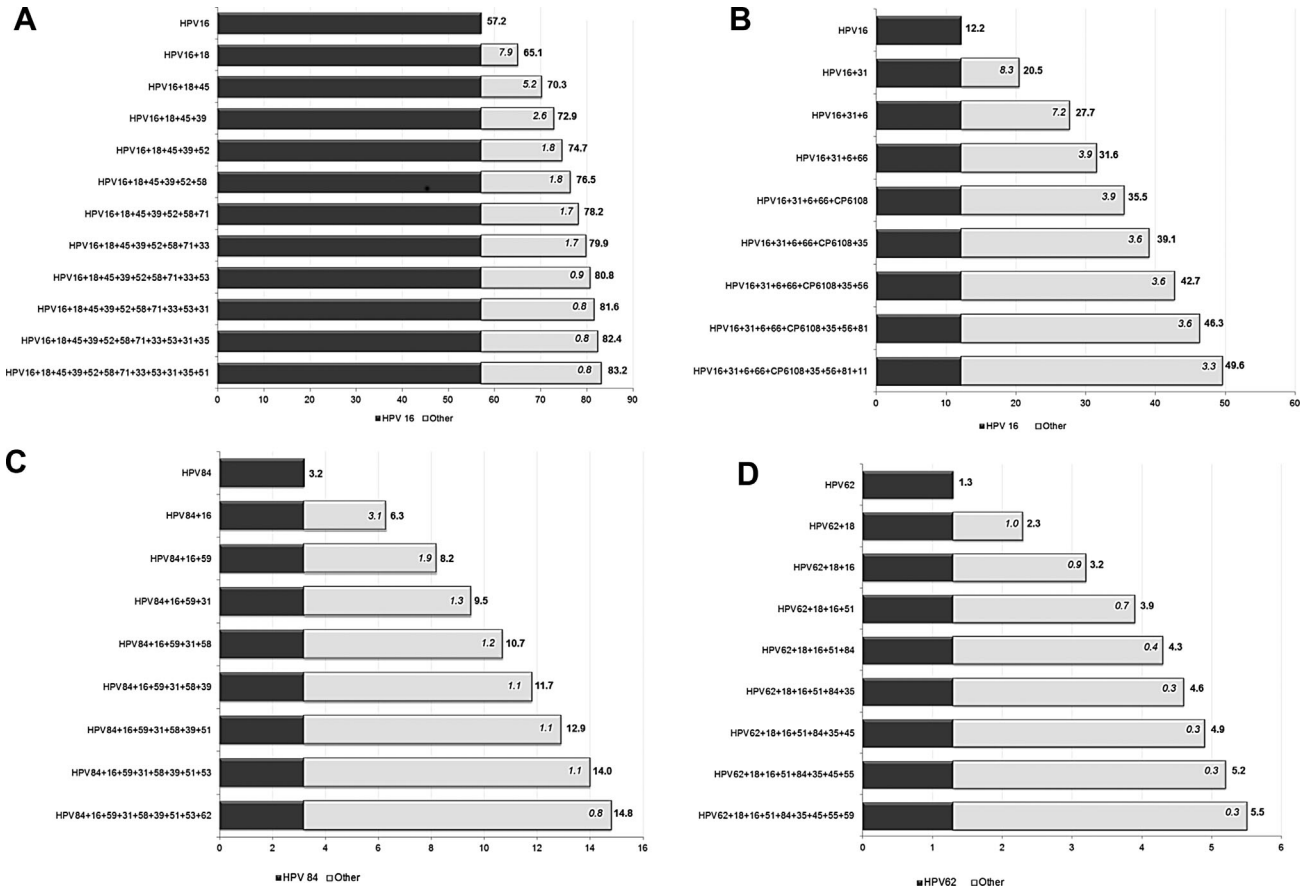

Fig. 5. Individual and cumulative attribution rates of HPV types. The percentages italicized represent individual attributions by viral type. Bolded percentages represent cumulative attribution rates in women with cervical cancer (**A**), with cervical intraepithelial neoplasia grade 3 (**B**), with cervical intraepithelial neoplasia grade 1 (**C**), or in control samples (**D**).

control group. The latter observation is consistent with results reported worldwide [de Sanjose et al., 2007; Bruni et al., 2010; Crow, 2012]. Previous studies conducted in Mexican patients reported an incidence of 10–12% for HPV infection in healthy women from Mexico City [Lopez Rivera et al., 2012], 16.7% in healthy women from Morelos State [Lazcano-Ponce et al., 2001], and 35–40% in healthy women from southern Mexico [Illades-Aguiar et al., 2010]. These differences could reflect actual epidemiological variability in the different regional areas analyzed and/or differences arising from the sensitivity of each study's diagnostic method.

Regarding HPV prevalence in relation to age irrespective of diagnosis, the major peak of HPV infection in this study was observed in women ≤25 years of age (54.9%) and this declined substantially in women aged 46–55 years (27.5%). Concerning HPV prevalence in relation to age and diagnosis group, the major peak of infection in control women and in those with cervical intraepithelial neoplasia grade 1 was observed in women ≤25 years, with 20% and 63.2%, respectively. It declined gradually with age, similar to previous reports (Fig. 1B) [Sargent et al., 2008; Brismar-Wendel et al., 2009; Ting et al., 2010]. However, no second peak of infection was detected in control women or in those with cervical intraepithelial neoplasia grade 1, in contrast to previous reports [Lazcano-Ponce et al., 2001].

HPV 16 was the most prevalent type found in all diagnostic groups, as has been reported worldwide by many authors [Woodman et al., 2001; Munoz et al., 2003; Smith et al., 2007; de Sanjose et al., 2010; Crow, 2012; Forman et al., 2012; Guan et al., 2012; IARC_-Working_Group, 2012] and also in Mexico [Peralta-Rodriguez et al., 2012]. It is noteworthy that whereas in women with cervical intraepithelial neoplasia grade 3 or cervical cancer the main attribution was HPV 16, in women with cervical intraepithelial neoplasia grade 1 and in control samples the main attributions were HPV 84 and HPV 62, respectively. These findings are consistent with previous report regarding attributions in women with cervical cancer and cervical intraepithelial neoplastic grade 3; however, they differ from those regarding women with cervical intraepithelial neoplasia grade 1 [Chan et al., 2012a]. The prevalence and attribution of the remaining genotypes differed depending on the severity of the lesion. Indeed, in the cervical

cancer group, HPV types 16, 18, and 45 were the most prevalent, followed by types 52, 58, and 39. HPV 52 has also been reported to fall among the top five places in prevalence in Asia [Quek et al., 2013; Wu et al., 2013], the USA [Wentzensen et al., 2009; Hariri et al., 2012], Thailand [Siriaunkgul et al., 2008], Canada [Coutlee et al., 2011], and Chile [Ferreccio et al., 2008]. However, the prevalence of this viral type might be underestimated because of cross-reaction with HPV types 33, 35, and 58 in the Linear Array® Genotyping Test. HPV 58 appears within the top five places only in Thailand [Siriaunkgul et al., 2008] and Chile [Ferreccio et al., 2008] and is common in East Asia [Chan et al., 2011, 2012b]. In fact, in Asia, researchers are currently developing vaccines that include protection against HPV 58 [Zhang et al., 2010]. Interestingly, this viral type is also frequently found in southeastern Mexico (Yucatan State) [Gonzalez-Losa Mdel et al., 2004]. There are fewer reports regarding HPV 39; however, this type has been considered to have significant prevalence in the USA and Canada [Wentzensen et al., 2009; Coutlee et al., 2011]. Interestingly, in India, HPV types 52, 58, and 39 are the most commonly found types in HIV-positive women (after types 18 and 16) [Sarkar et al., 2011]. The prevalence of HPV 71 in the cervical cancer group (2.5%) was similar to those of other oncogenic viral types such as 33, 35, and 51, but, interestingly, the attribution was greater. A preliminary multivariate analysis, adjusted for the most common viral types found in control and cervical cancer groups, showed an OR of 23.5 (95% CI, 1.42–386.6) for the risk of developing cervical cancer (Supplemental Table I). Additionally, HPV 71 E6 has been reported to degrade tumor suppressor protein p53 efficiently [Fu et al., 2010]. However, it will be necessary to increase the sample size to evaluate the possible carcinogenic role of this HPV type. It is important to mention that the attributable fraction of HPV 16 and 18 for cervical cancer is only 65%, so a significant proportion of women would not be protected by the current vaccines.

Concerning women with cervical intraepithelial neoplasia grade 3, there were high prevalence rates of HPV types 16, 31, 18, 70, and 51; but only HPV 16 and 31 had a major attribution. It is clear that the presence of HPV types 16, 31, and 18 is a global feature in this type of lesion [Castle et al., 2010; Sjoeborg et al., 2010; Wentzensen et al., 2010; Coutlee et al., 2011; Dobec et al., 2011; Mateos Lindemann et al., 2011; ; Hariri et al., 2012; Anderson et al., 2013; Pista et al., 2013]. It is noteworthy that there were some highly prevalent HPV types in the cervical intraepithelial neoplasia grade 3 group (HPV types 31, 70, and 59), but not in women with cervical cancer. These viral types could be associated with this kind of lesion, as was suggested previously [Quint et al., 2012].

Regarding the HPV types most commonly found in women with cervical intraepithelial neoplasia grade 1 and in control samples: besides HPV type 16, types 84 and 62 were also detected. Interestingly, HPV type 84 infections have also been observed frequently in Swedish [Froberg et al., 2012], Indian [Datta et al., 2010], and Chilean [Ferreccio et al., 2008] women. However, the prevalence rates of these types of virus might be underestimated because in most reports they are not taken into consideration. In a meta-analysis, HPV 84 was found to be equally or even more frequently detected than type 16 in male genital specimens, whereas type 16 was more commonly detected than type 84 in cervical and vaginal specimens [Castle, 2008]. It is noteworthy that the HPV genotypes that were found mainly in women without cervical lesions match those reported as being present in the external genitalia, glans penis/corona sulcus, shaft, and scrotum of men in the USA, Mexico, and Brazil; in one report, the most prevalent HPV types found were 62, 84, 16, CP6108, and 51 [Vaccarella et al., 2011b].

In this study, a preliminary multivariate analysis showed an inverse relation between the presence of HPV types 84 and 62 and the risk of developing cervical cancer, independently of the presence of other viral types (Supplemental Table I). In this regard, it has been determined previously that the clearance time for HPV 16 is longer (12–19 months) than that observed for HPV 84 (6–8 months) [Richardson et al., 2003; Moscicki et al., 2010]. Similar to HPV 84, HPV 62 has also been underdiagnosed in women; however, some reports from Chile [Ferreccio et al., 2008], Turkey [Demir et al., 2012], the USA [Hariri et al., 2011], and India [Datta et al., 2010] place it in the top ranks of low-risk HPV prevalence.

Interestingly, HPV 26 and 67 were not detected in cervical cancer samples, even though these HPV types have been classified as possibly carcinogenic (class 2B). On the other hand, HPV types 66 and 70 (also classified as 2B) were detected in women with cervical cancer, but only in coinfections with high-risk HPV [IARC_Working_Group, 2012].

Coinfection analysis showed that multiple infections were commonly observed in control samples and in preneoplastic lesions, particularly among young women. This prevalence was higher than that reported in other Latin American patients [Vaccarella et al., 2011a]. Otherwise, in cervical cancer samples there was a strong decrease in the prevalence of coinfection, similar to that found previously [Hariri et al., 2012]. In contrast, a high prevalence of confections has been reported in Japanese patients with a diagnosis of cervical cancer [Watari et al., 2011]. Additionally, HPV type 16 was more frequently found as a coinfection with types 18, 39, and 70 in women with cervical cancer, whereas in women without cervical lesions, it was most frequently accompanied by types 62, 51, and 84. Considering the high percentage of coinfections and the variety of HPV types found in the same sample, it is important to determine not only the crude prevalence of each HPV type, but also its individual attribution in cervical lesions [Insinga et al., 2008; Wentzensen et al., 2009; Chan et al., 2012a]. Comparing the crude prevalence of each HPV type with its

individual attribution in cervical cancer samples (Table IV), it seems that, besides HPV 16, HPV types 18, 45, 39, 52, 58, and 33 were responsible for most of the cases of cervical cancer in these Mexican patients. Interestingly, HPV 71, which is not considered a high-risk viral type, showed an individual attribution similar to that of HPV 33, suggesting that it also contributed to the development of this malignancy.

The role of coinfections in cervical carcinogenesis is still unclear, so it would be interesting to determine whether the presence of coinfections with certain HPV types modifies the time to progression and/or time to regression of the lesions. It has been reported that coinfection with HPV 34 is associated with a minor incidence of lymph node metastasis in patients with cervical cancer [Michimata et al., 2013]. Further studies are necessary to determine the biological contribution of HPV coinfections, especially those associated with immunogenic responses, which could have serious implications in treatment and/or prognosis [Bachtiary et al., 2002].

In conclusion, the data presented in this study show that in addition to HPV types 16 and 18, types 45, 52, 58, 39, 33, and 71 are also significant in Mexican women with cervical cancer. Therefore, since current vaccines only cover around 65% of Mexican

TABLE IV. Prevalence and Attribution of all HPV Types According to Diagnosis Status

	Control			Cervical intraepithelial neoplasia grade 1			Cervical intraepithelial neoplasia grade 3			Cervical cancer		
		95% confidence interval			95% confidence interval			95% confidence interval			95% confidence interval	
HPV type	%	Lower	Upper	%	Lower	Upper	%	Lower	Upper	%	Lower	Upper
6												
Prevalence	0.6	0.2	2.0	2.2	1.1	4.5	10.0	3.5	25.6	2.5	0.8	7.0
Attribution	0.0	0.0	1.1	0.7	0.2	2.4	7.2	2.1	22.1	0.0	0.0	3.1
11												
Prevalence	0.3	0.0	1.6	0.6	0.2	2.3	3.3	0.6	16.7	0.0	0.0	3.1
Attribution	0.0	0.0	1.1	0.3	0.1	1.8	3.3	0.6	16.7	0.0	0.0	3.1
16												
Prevalence	3.1	1.7	5.4	9.8	7.0	13.6	40.0	24.6	57.7	62.8	53.9	70.9
Attribution	0.9	0.3	2.5	3.1	1.7	5.6	12.2	4.7	28.3	57.2	48.3	65.6
18												
Prevalence	1.7	0.8	3.6	4.4	2.7	7.3	13.3	5.3	29.7	11.6	7.0	18.5
Attribution	1.0	0.4	2.7	0.8	0.2	2.5	0.0	0.0	11.4	7.9	4.3	14.0
26												
Prevalence	0.0	0.0	0.0	0.0	0.0	1.2	3.3	0.6	16.7	0.0	0.0	3.1
Attribution	0.0	0.0	0.0	0.0	0.0	1.2	0.0	0.0	11.4	0.0	0.0	3.1
31												
Prevalence	0.3	0.0	1.6	3.8	2.2	6.5	16.7	7.3	33.6	1.7	0.5	5.8
Attribution	0.0	0.0	1.1	1.1	0.4	3.0	8.3	2.6	23.5	0.8	0.1	4.5
33												
Prevalence	0.0	0.0	0.0	1.3	0.5	3.2	3.3	0.6	16.7	2.5	0.8	7.0
Attribution	0.0	0.0	0.0	0.3	0.1	1.8	0.0	0.0	11.4	1.7	0.5	5.9
35												
Prevalence	0.6	0.2	2.0	1.9	0.9	4.1	6.7	1.8	21.3	2.5	0.8	7.0
Attribution	0.3	0.1	1.6	0.7	0.2	2.3	3.6	0.7	17.1	0.8	0.2	4.6
39												
Prevalence	0.3	0.0	1.6	4.1	2.4	6.9	3.3	0.6	16.7	5.8	2.8	11.5
Attribution	0.0	0.0	1.1	1.1	0.4	3.0	0.0	0.0	11.4	2.6	0.9	7.2
40												
Prevalence	0.0	0.0	0.0	1.0	0.3	2.8	0.0	0.0	11.4	0.0	0.0	3.1
Attribution	0.0	0.0	0.0	0.0	0.0	1.2	0.0	0.0	11.4	0.0	0.0	3.1
42												
Prevalence	0.6	0.2	2.0	2.2	1.1	4.5	6.7	1.8	21.3	0.8	0.1	4.5
Attribution	0.0	0.0	1.1	0.7	0.2	2.4	0.0	0.0	11.4	0.0	0.0	3.1
45												
Prevalence	0.8	0.3	2.4	1.3	0.5	3.2	0.0	0.0	11.4	8.3	4.6	14.5
Attribution	0.3	0.1	1.6	0.3	0.1	1.8	0.0	0.0	11.4	5.2	2.4	10.7
51												
Prevalence	2.0	1.0	4.0	3.8	2.2	6.5	10.0	3.5	25.6	2.5	0.8	7.0
Attribution	0.7	0.2	2.3	1.1	0.4	3.0	0.0	0.0	11.4	0.8	0.2	4.6
52												
Prevalence	1.1	0.4	2.9	3.2	1.7	5.7	3.3	0.6	16.7	6.6	3.4	12.5
Attribution	0.0	0.0	1.1	0.4	0.1	1.9	0.0	0.0	11.4	1.8	0.5	6.0
53												
Prevalence	1.4	0.6	3.2	3.8	2.2	6.5	3.3	0.6	16.7	3.3	1.3	8.2
Attribution	0.0	0.0	1.1	1.1	0.4	3.0	0.0	0.0	11.4	0.9	0.2	4.6

TABLE IV. (*Continued*)

	Control			Cervical intraepithelial neoplasia grade 1			Cervical intraepithelial neoplasia grade 3			Cervical cancer		
		95% confidence interval			95% confidence interval			95% confidence interval			95% confidence interval	
HPV type	%	Lower	Upper	%	Lower	Upper	%	Lower	Upper	%	Lower	Upper
54												
Prevalence	1.1	0.4	2.9	1.0	0.3	2.8	0.0	0.0	11.4	0.8	0.1	4.5
Attribution	0.0	0.0	1.1	0.3	0.1	1.8	0.0	0.0	11.4	0.0	0.0	3.1
55												
Prevalence	1.1	0.4	2.9	1.0	0.3	2.8	0.0	0.0	11.4	0.0	0.0	3.1
Attribution	0.3	0.1	1.7	0.0	0.0	1.2	0.0	0.0	11.4	0.0	0.0	3.1
56												
Prevalence	0.8	0.3	2.4	3.2	1.7	5.7	6.7	1.8	21.3	1.7	0.5	5.8
Attribution	0.0	0.0	1.1	0.4	0.1	1.9	3.6	0.7	17.1	0.0	0.0	3.1
58												
Prevalence	0.6	0.2	2.0	6.7	4.4	10.0	6.7	1.8	21.3	6.6	3.4	12.5
Attribution	0.0	0.0	1.1	1.2	0.5	3.2	0.0	0.0	11.4	1.8	0.5	6.0
59												
Prevalence	0.6	0.2	2.0	5.7	3.6	8.9	10.0	3.5	25.6	0.8	0.1	4.5
Attribution	0.3	0.1	1.6	1.9	0.9	4.1	0.0	0.0	11.4	0.8	0.1	4.5
61												
Prevalence	0.8	0.3	2.4	2.9	1.5	5.3	6.7	1.8	21.3	0.0	0.0	3.1
Attribution	0.0	0.0	1.1	0.4	0.1	1.8	0.0	0.0	11.4	0.0	0.0	3.1
62												
Prevalence	3.1	1.7	5.4	5.1	3.2	8.1	6.7	1.8	21.3	0.8	0.1	4.5
Attribution	1.3	0.5	3.1	0.8	0.2	2.5	0.0	0.0	11.4	0.0	0.0	3.1
66												
Prevalence	0.8	0.3	2.4	4.1	2.4	6.9	10.0	3.5	25.6	3.3	1.3	8.2
Attribution	0.0	0.0	1.1	0.7	0.2	2.5	3.9	0.8	17.5	0.0	0.0	3.1
67												
Prevalence	0.3	0.0	1.6	0.3	0.1	1.8	0.0	0.0	11.4	0.0	0.0	3.1
Attribution	0.0	0.0	1.1	0.3	0.1	1.8	0.0	0.0	11.4	0.0	0.0	3.1
68												
Prevalence	0.6	0.2	2.0	1.3	0.5	3.2	0.0	0.0	11.4	3.3	1.3	8.2
Attribution	0.0	0.0	1.1	0.0	0.0	1.2	0.0	0.0	11.4	0.0	0.0	3.1
69												
Prevalence	0.3	0.0	1.6	1.3	0.5	3.2	3.3	0.6	16.7	1.7	0.5	5.8
Attribution	0.0	0.0	1.1	0.0	0.0	1.2	0.0	0.0	11.4	0.8	0.1	4.5
70												
Prevalence	1.1	0.4	2.9	3.8	2.2	6.5	13.3	5.3	29.7	2.5	0.8	7.0
Attribution	0.3	0.1	1.7	0.4	0.1	1.9	0.0	0.0	11.4	0.0	0.0	3.1
71												
Prevalence	0.3	0.0	1.6	2.5	1.3	4.9	3.3	0.6	16.7	2.5	0.8	7.0
Attribution	0.0	0.0	1.1	0.4	0.1	1.8	0.0	0.0	11.4	1.7	0.5	5.9
72												
Prevalence	0.0	0.0	0.0	1.0	0.3	2.8	0.0	0.0	11.4	0.0	0.0	3.1
Attribution	0.0	0.0	0.0	0.3	0.1	1.8	0.0	0.0	11.4	0.0	0.0	3.1
73												
Prevalence	0.3	0.0	1.6	2.5	1.3	4.9	0.0	0.0	11.4	0.0	0.0	3.1
Attribution	0.0	0.0	1.1	0.4	0.1	1.8	0.0	0.0	11.4	0.0	0.0	3.1
81												
Prevalence	0.8	0.3	2.4	1.0	0.3	2.8	6.7	1.8	21.3	0.8	0.1	4.5
Attribution	0.0	0.0	1.1	0.3	0.1	1.8	3.6	0.7	17.1	0.0	0.0	3.1
82												
Prevalence	0.0	0.0	0.0	1.0	0.3	2.8	0.0	0.0	11.4	0.0	0.0	3.1
Attribution	0.0	0.0	0.0	0.0	0.0	1.2	0.0	0.0	11.4	0.0	0.0	3.1
83												
Prevalence	0.6	0.2	2.0	1.0	0.3	2.8	0.0	0.0	11.4	0.8	0.1	4.5
Attribution	0.0	0.0	1.1	0.0	0.0	1.2	0.0	0.0	11.4	0.0	0.0	3.1
84												
Prevalence	2.0	1.0	4.0	7.6	5.2	11.1	3.3	0.6	16.7	0.8	0.1	4.5
Attribution	0.4	0.1	1.7	3.2	1.8	5.8	0.0	0.0	11.4	0.0	0.0	3.1
CP6108[2]												
Prevalence	1.4	0.6	3.2	3.2	1.7	5.7	10.0	3.5	25.6	0.0	0.0	3.1
Attribution	0.0	0.0	1.1	0.4	0.1	1.9	3.9	0.8	17.5	0.0	0.0	3.1

The attribution was calculated according previous reports, [Insigna et al., 2008; Chan et al., 2012a].

women, it will be necessary to implement new vaccines directed against such HPV types. It will also be important to investigate whether current vaccines induce cross-protection against other prevalent oncogenic types. The diagnostic method used here allowed us to detect a higher prevalence of some HPV types than previously reported in Mexican patients, such as types 62, 66, 70, 71, 84, and CP6108. It will be important to investigate more rigorously the specific HPV types found in women with coinfections, because to date it is unclear whether certain HPV types found in such cases could contribute to the development of precancerous lesions or cervical cancer, or whether the presence of particular viral types might contribute to regression of the lesions.

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IMSS RESEARCH NETWORK ON HPV

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