Human Papillomavirus Infection at the United States-Mexico Border: Implications for Cervical Cancer Prevention and Control[1]

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Abstract

The United States-Mexico border is a region comprised of a country with one of the highest rates of invasive cervical cancer (Mexico) and a country with one of the lowest rates (United States). Recent evidence clearly indicates that human papillomavirus (HPV) infection is the cause of cervical cancer. The distribution of specific types of HPV is known to vary in different regions of the world, as do the cofactors that may inhibit or promote HPV carcinogenesis. Estimating the prevalence of oncogenic HPV is needed for guiding vaccine development. The purpose of this study was to determine the prevalence of oncogenic and nononcogenic HPV types and risk factors for HPV among women residing along the United States-Mexico border. A cross-sectional study of 2319 women, ages 15–79 years, self-referring for gynecological care was conducted between 1997 and 1998. HPV was detected by PCR using the PYGMY 09/11 L1 consensus primer, and HPV genotyping was conducted using the reverse line blot method. Overall, the HPV prevalence was 14.4% with no significant differences observed by country after adjustment for age. HPV 16 was the most commonly detected HPV type in both the United States and Mexico. Among women with high-grade squamous intraepithelial lesions, HPV types 58, 45, 51, 31, 35, 55, and 73 were most common in Mexico, and HPV types 18, 31, 35, 51, 52, and 58 were most common in the United States. In both countries, HPV prevalence declined linearly with age from 25% among women ages 15–19 years to 5.3% among women 56–65 years. Factors significantly independently associated with HPV infection were older age [adjusted odds ratio (AOR) = 0.15 for ages 56–65 years compared with those 15–19 years], a marital status other than married (AOR = 1.58–3.29), increased numbers of lifetime male partners (AOR = 3.8 for ≥10 partners compared with 1 partner), concurrent infection with *Chlamydia trachomatis* (AOR = 1.79), ever use of Norplant (AOR = 2.69), and current use of injectable contraceptives (AOR = 2.29). Risk factors for HPV infection did not differ by country. Results from this study suggest that in addition to HPV 16 and 18, HPV types 31, 45, 51, and 58 should be considered for inclusion in an HPV prevention vaccine for distribution in Mexico.

Introduction

Cervical cancer is the second most common cancer among women globally with 400,000 cases of invasive cervical cancer diagnosed yearly (1). Mexico has one of the highest rates of invasive cervical cancer in the world (44.4/100,000) with approximately one death from cervical cancer occurring every 2 h (2). In the United States, Hispanic women have a significantly elevated rate of invasive cervical cancer (17.1/100,000) compared with non-Hispanic white women (7.5/100,000; Ref. 3). The disproportionate rate of invasive cervical cancer observed in Hispanics nationally is also observed in Arizona.

Evidence from epidemiological studies conducted worldwide clearly indicates that HPV[3] infection is the cause of cervical cancer (4–6). Whereas cervical cancer prevention currently relies on screening and treatment of precancerous lesions, new technologies such as HPV testing (7) and the development of HPV prophylactic vaccines (8) will offer alternatives for prevention and control in the near future. HPV prevention vaccines are currently under development and testing in Phase II and III trials (8, 9).

The distribution of specific types of HPV is known to vary in different regions of the world, as do the cofactors that may inhibit or promote HPV carcinogenesis. HPV 16 is the predominant HPV type, found in ~50% of all tumors assessed (4). The potential to reduce invasive cervical cancer with a vaccine will depend on the distribution of the other HPV types in the population and the dissemination of the vaccine to the target population. The prevalence of oncogenic HPV types among women both with and without cervical abnormalities is needed for guiding vaccine development and for estimating the impact these vaccines may have on cervical disease burden. First generation vaccines will not eliminate the need for cervical

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[3] The abbreviations used are: HPV, human papillomavirus; OR, odds ratio; SIL, squamous intraepithelial lesion.

cancer screening as they currently include a limited number of oncogenic HPV types (8, 9). Therefore, data are also needed to guide development of coordinated screening, treatment, and public health programs to prevent and control cervical cancer.

Despite the high rate of invasive cervical cancer in Mexico, there are only three (to our knowledge) published papers documenting rates of HPV infection and associations with cervical cancer (10–12). Recently, we completed a cross-sectional study at the United States-Mexico border examining the prevalence of HPV and *Chlamydia trachomatis* (13, 14). In this study, we present the prevalence of 27 different HPV types, risk factors for HPV, and associations with abnormal cytology in this population.

Materials and Methods

Study Design. A cross-sectional survey was conducted from January 1997 to June 1998, recruiting women ≥15 years living at the Arizona, United States-Sonora, Mexico border. A detailed description of the study design and methods of the United States-Mexico Border Binational HPV, Cervical Dysplasia, and *C. trachomatis* Infection Study has been published previously (14). Briefly, a total of eight sites were chosen for this study: three pairs of contiguous communities (Arizona, United States-Sonora, and Mexico) directly on the United States-Mexico border and two metropolitan areas, Hermosillo, Sonora and Tucson, Arizona each ~100 km from the United States-Mexico border. The sites chosen on the United States-Mexico border are the population centers of this region (100% sample of communities). Hermosillo, Sonora and Tucson, Arizona are the large metropolitan areas closest to the border which services the border communities. As the United States-Mexico border region is predominantly rural, there are few clinics which serve these populations. Among the United States-Mexico border communities, we included all of the public health and family planning clinics. In addition, in one region of the Arizona border, the only clinic providing family planning services was Planned Parenthood; therefore, this clinic was also included in the study. In Mexico, only Secretaria de Salud Publica de Sonora clinics were included. Participants were women who self-referred to Community Health Centers, County Health Departments, and Planned Parenthood clinics in Arizona and Public Health Clinics in Sonora for routine gynecological care. Women who: (*a*) were ≥15 years; (*b*) were residents of Arizona-Sonora border communities, Hermosillo, Sonora, or Tucson, Arizona; (*c*) were nonpregnant or a minimum of 2 months postpartum; and (*d*) had no history of hysterectomy were invited to participate in this study. Study participants completed an interviewer-administered risk factor questionnaire that assessed reproductive, sexual and medical histories, and demographic data. Overall, the study participation rate was 92.8%. Reasons for nonparticipation are given in a previous publication (14).

After a Pap smear was obtained for routine clinical purposes, two additional samples of exfoliated cervical cells were obtained for the analysis of HPV DNA and for *C. trachomatis* determination. Specimens for *C. trachomatis* analysis were collected from the endocervical os or the cervical canal. A major focus of the study was the development of a detailed cytological coding system and quality control system that was used by study pathologists to ensure the consistency of Pap smear diagnoses across countries (14).

Cervical cells were collected for HPV analysis from the ectocervix and endocervix using the Cone Brush Cytosoft and were immediately suspended in 0.6-ml Digene Diagnostics Sample Transport Medium (Digene Corp., Gaithersburg, MD). After collection, samples were placed and maintained in 4°C until shipment for a maximum of 2 weeks, at which point they were transported on ice. Samples were then maintained at −70°C until analysis. A total of 2319 women provided cervical cell samples for HPV detection. Of these, 2246 were evaluable by PCR and comprise the final sample for this study.

HPV detection was conducted using PCR among all of the cervical cell samples collected. Genomic DNA was extracted following standard techniques (15). In brief, 50-μl aliquots were digested with 5 μl of Proteinase K for 1 h at 65°C, followed by 5 M Ammonium Acetate and Ethanol precipitation. The crude DNA pellet was dried and resuspended in 50 μl of 10 mM Tris (pH 7.5). The DNA extracts were then stored at −80°C until amplification. Specimens were tested for the presence of HPV by amplifying 5 μl of the DNA extracts with the PGMY09/11 L1 consensus primer system (15) and AmpliTaq Gold polymerase (Perkin-Elmer, Foster City, CA). In brief, each amplification contained 10 × PCR Buffer II; 25 mM MgCl2; 200 μl (each) of dCTP, dGTP, and dATP; 600 μl of dUTP; 5 units of AmplTaq Gold; 50 μM PGMY09; 50 μM PGMY11; 50 μM B_PC04; 50 μM B_GH20; and 5 μl of the template. For eventual inclusion of uracil-*N*-glycosylase to prevent product carryover, dTTP was replaced with dUTP. To determine specimen adequacy, the GH20/PC04 human β-globin target was coamplified with the HPV consensus primers. For every 10 samples, a negative control (H_2O) and a positive control (CaSki cells) were run to control for contamination and accuracy. The samples were amplified using Perkin-Elmer GeneAmp PCR System 9700. The following amplification profile was used: 95°C hotstart for 9 min, 95°C denaturation for 1 min, 55°C annealing for 1 min, and 72°C extension for 1 min for 40 cycles, followed by a 5-min terminal extension at 72°C and a hold step at 4°C. HPV genotyping was conducted using the reverse line blot method (16) on all samples that were positive by PCR. This detection method uses the HPV L1 consensus PCR products labeled with biotin to detect 27 HPV types. The HPV genotype strip contains 29 probe lines, detecting 27 individual HPV genotypes and two concentrations of the β-globin control probe. All reagents were kindly provided by Roche Molecular Systems, Inc. (Alameda, CA). The following types were detected: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51–59, 66, 68, 73, 82, 83, and 84. Briefly, the PCR products labeled with biotin were denatured and added to the probe strip in a hybridization buffer. After strips were washed, streptavidin-horseradish peroxidase was added to facilitate detection of the various HPV types. After final wash, buffer was removed by vacuum aspiration, and strips were rinsed in 0.1 M sodium citrate. Color development was activated by incubation in a mixture of hydrogen peroxide in sodium citrate buffer and tetramethylbenzidine in dimethylformamide for 5 min on a rotating platform (70 rpm). Developed strips were interpreted and photographed for future reference. Strip interpretation was performed with a labeled overlay, with lines indicating the position of each probe relative to the reference mark.

Grouping of HPV types by oncogenicity was based on the classification adopted by Roche, whereby HPV types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 55, 56, 58, 59, 68, 82, 83, and 73 are considered oncogenic, and HPV types 6, 11, 40, 42, 53, 54, 57, 66, and 84 are considered nononcogenic.

Testing for *C. trachomatis* infection was conducted using the Digene CT-ID Hybrid Capture II (Digene Corp.) test, a signal-amplified hybridization microplate assay which uses chemiluminescence for qualitative detection of *C. trachomatis* DNA (14).

Statistical Analysis. To control for statistical differences in ages of Mexican and United States women, age-adjusted prevalence was calculated by the direct method using the population distribution of the entire study sample as an estimate of the standard population. To investigate the relationship between predictor variables and HPV infection, we looked at the magnitude of the statistical association by calculating the OR for each variable. To additionally evaluate which of these variables were independently associated with HPV infection, the method of weighted least squares was used to estimate maximum-likelihood logistic models. Multivariate regression with backward stepwise elimination ($P < 0.20$) determined the best model and yielded the final adjusted ORs and their corresponding 95% confidence intervals to determine significance. All analyses were conducted using Intercooled Stata (Stata Statistical Software: Release 7.0; Stata Corp., College Station, TX).

Results

Study participants were primarily Mexican or Mexican-American (90%) and ranged in age from 15 to 79 years (mean 33.1 ± 10.2 years) with significantly fewer young women participating in Mexico compared with the United States (Table 1). Significant differences were observed by country in the distribution of factors potentially associated with HPV infection and cervical cancer. In this sample, a higher percentage of Mexican women were married, had fewer lifetime and recent numbers of sexual partners, had never smoked, had never used oral contraceptives, and were older at first sexual intercourse.

A total of 324 (14.4%) study participants tested positive for HPV by PCR, with a significantly higher overall crude prevalence in the United States (16.3%) compared with Mexico (13%). Oncogenic HPV type infections were significantly more prevalent among United States women (13.9%) compared with Mexican women (10.9%). However, after adjusting for age, no significant difference in HPV prevalence was observed by country (Table 2).

In both the United States and Mexico, HPV 16 was the most common type detected and varied by category of cervical cytology (Table 2). Among cytologically normal women, 1.2% of women in Mexico and 2.6% of women in the United States were HPV 16 positive. Among women with high-grade SIL, 27.3% of women in Mexico and 12.5% of women in the United States were positive for HPV 16. In addition to HPV 16 in Mexico, types 58, 45, 51, 31, 35, 55, and 73 were detected in women with high-grade SIL, in descending order of prevalence. In the United States, HPV 16, 18, 31, 35, 51, 52, and 58 were equally distributed among women with high-grade SIL. In the United States and Mexico combined, 1.9% of women tested positive for only nononcogenic HPV types, and 8 (0.4%) were positive for unknown HPV types. Multiple HPV infections were detected among 51 women (2.3%).

Abnormal Pap smears were detected in 9.3% of study participants with 5.7% having atypical squamous cells of unknown significance/atypical glandular cells of unknown significance, 2.1% low-grade SIL, and 1.4% high-grade SIL. HPV prevalence was significantly, positively, associated with cytopathology outcome (Table 2). Overall, 10.7% of women with normal cytology was positive for HPV compared with 63.3% of women with high-grade SIL. Compared with Mexican women, the prevalence of HPV was higher among United States women for each cytology outcome assessed, *e.g.*, 75% of United States women diagnosed with high-grade SIL were HPV positive, compared with 59.1% of Mexican women.

The frequency distribution of selected risk factors and their association with HPV infection (any type) is shown in Table 3. Risk for HPV positivity decreased with increasing age (p-trend < 0.001). The proportion of women positive for HPV decreased from 25% among women ages 15–19 years to 5.3% among women 56–65 years. No women >65 years ($n = 9$) tested positive for HPV. The relative frequency of HPV types did not vary by age group (data not shown). Ethnicity, marital status, employment status, age at first sexual intercourse, lifetime number of male partners, number of new partners in the past 3 months, smoking history, *C. trachomatis* infection, Norplant use, and current injectable contraceptive use were significantly associated with HPV infection in age-adjusted analyses (Table 3).

Multivariate logistic regression analyses were conducted to determine factors independently associated with HPV infection (Table 4). Young age; marital status of single and divorced, separated, or widowed; increased numbers of lifetime male

Table 1 Selected socio-demographic characteristics of study participants by country of residence

	Mexico %	US %	$P\ \chi^2$
Age (yrs)			
15–19	1.8	10.6	
20–24	14.3	19.8	
25–34	40.4	34.0	
35–44	29.3	23.7	
45–79	14.3	11.9	
Mean age (SD)	34.3 (9.8)	31.7 (10.4)	<0.001
Age at first intercourse			
≥20	34.2	29.2	
18–19	24.7	23.8	
16–17	23.0	25.6	
6–15	18.2	20.5	0.033
Lifetime no. of sex partners			
1	63.0	50.0	
2–3	27.3	26.9	
4–9	4.7	15.4	
>10	5.0	7.8	<0.001
No. of new partners in past 3 mos.			
0	94.7	91.9	
1	3.4	6.4	
2	0.4	1.3	
3–60	1.5	0.4	<0.001
Norplant history			
Never	99.5	97.2	
Ever	0.5	2.8	<0.001
Injectable contraceptive history			
Never	79.2	78.0	
Past	15.7	14.2	
Current	5.1	7.7	0.036
Marital status			
Married	62.1	50.4	
Single	10.1	27.9	
Cohabitating	20.1	8.1	
Divorced/separated/widowed	7.7	13.6	<0.001
OC history[a]			
Never	33.8	26.1	
Past	50.5	41.8	
Current	15.7	32.2	<0.001
Smoking history			
Never	75.6	68.5	
Past	8.8	13.4	
Current	15.6	18.1	<0.001
Chlamydia trachomatis			
Negative	91.3	92.7	
Positive	8.7	7.3	0.218

[a] OC, oral contraceptive.

Table 2 Prevalence of HPV types by country and grade of cytology[a]

	Mexico					United States					Total
	Normal (n = 995) %	ASCUS/AGUS (n = 64) %	LGSIL (n = 33) %	HGSIL (n = 22) %	Total (n = 1258) %	Normal (n = 881) %	ASCUS/AGUS (n = 99) %	LGSIL (n = 7) %	HGSIL (n = 8) %	Total (n = 988) %	(n = 2246) %
Any type HPV	8.8	21.9	60.6	59.1	13.6[b]	12.8	42.9	71.4	75	15.1[b]	14.4
Oncogenic types					11.4[b]					12.9[b]	12.2
16	1.2	4.7	15.2	27.3	2.4	2.6	6.1	14.3	12.5	3.2	2.8
18	0.8		3.0		0.8	0.8	6.1		12.5	1.1	0.9
26	0.1				0.1					0.0	0.04
31	0.9	1.6		4.6	1.2	0.6	4.1		12.5	0.9	1.1
33		1.6			0.2	0.1	2.0			0.2	0.2
35	0.1		3.0	4.6	0.3	0.3	2.0		12.5	0.5	0.4
39	0.5	1.6	12.1		0.8	2.2	6.1			2.2	1.4
45	0.7	3.1	3.0	9.1	1.0	0.7				0.7	0.9
51	0.6	3.1	6.1	9.1	1.0	0.3	2.0	14.3	12.5	0.7	0.9
52	0.7	3.1	6.1		1.2	1.8	2.0	14.3	12.5	2.0	1.4
55	0.3			4.6	0.4	0.3				0.3	0.4
56	0.3		6.1		0.5	0.9	2.0			1.0	0.7
58	0.5	1.6	6.1	13.6	1.0	0.6	6.1		12.5	1.2	1.1
59	1.2	1.6	9.1		1.4	0.5	2.0			0.8	1.2
68	0.6	1.6			0.6	0.5	2.0			0.6	0.6
82			6.1		0.3	0.1	2.0	14.3		0.3	0.3
83	0.4		3.0		0.6	0.5	2.0			0.5	0.5
73	0.1			4.6	0.2	0.1				0.3	0.2
Nononcogenic types					1.8[b]					2.1[b]	1.9
6	0.3				0.2	0.2		14.3		0.4	0.3
11	0.2		3.0		0.2	0.1	2.0			0.2	0.2
40					0.0					0.0	0.0
42	0.3	1.2			0.3	0.6	2.0			0.7	0.5
53	0.3	4.7	3.0		0.7	0.9	4.1			1.1	0.9
54			3.0		0.2	0.5				0.4	0.3
57					0.0					0.0	0.0
66	0.2	1.2	3.0	4.6	0.4	0.8	2.0	14.3		1.3	0.8
84	0.6		3.0	9.1	0.8	0.6				0.5	0.7
Unknown types					0.5[b]					0.2[b]	0.4[b]

[a] Because of missing data totals for HPV results and cytology results vary. Blanks indicate type not detected. AGUS, atypical glandular cells of unknown significance; ASCUS, atypical squamous cells of unknown significance; HGSIL, high-grade SIL; LGSIL, low-grade SIL.
[b] Adjusted for age in country-specific analysis.

partners; *C. trachomatis* infection; ever use of Norplant; and current use of injectable contraceptives were independently associated with HPV infection. No interactions with country of residence (United States *versus* Mexico) were observed, indicating that the risk factors for HPV infection did not differ by country.

Discussion

This is the first study to compare and contrast the prevalence of HPV infection and risk factors at the United States-Mexico border. Our results indicate that the overall age-adjusted prevalence of HPV is similar in Mexico (13.6%) and the United States (15.1%) and that the risk factors for HPV infections were not different by country. These findings are consistent with previous work conducted among Mexican-American women, where a prevalence of 13.2% was observed (17), and among women residing in various regions of Mexico and Latin America (11, 18, 19). Other investigators have found comparable rates of HPV infection and risk factors for these infections when contrasting countries with high and low cervical cancer disease burdens (20). However, studies comparing the HPV prevalence in Spain and Colombia found the prevalence of HPV to be significantly lower in Spain, the country with the lower rate of cervical cancer incidence (21, 22). In this study, whereas the overall HPV prevalence was similar in Mexico and the United States, a significantly lower rate of HPV was detected among Mexican women for any given category of cytology compared with United States women. These results add to the growing literature, suggesting that other factors, such as HPV type variant (23), genetics (24), diet (25, 26), smoking (27–29), and cervical cancer screening rates (30), are influencing the divergent rates of the disease internationally.

In Mexico and other Latin-American countries, HPV 16 is the most prevalent type of infection detected (4, 11, 12, 18, 31, 32). Consistent with the literature, in this study, HPV 16 was the predominant HPV type detected in the United States and Mexico among both cytologically normal and abnormal women. In order of decreasing prevalence, HPV types 16, 59, 31, 18, 45, and 52 were the most common in Mexico, whereas in the United States, HPV types 16, 39, 52, 56, 18, and 45 were most prevalent. Reports from other regions of Latin America and Mexico suggest that there is heterogeneity in the distribution of oncogenic HPV types both within Mexico and between countries. Overall, it appears that HPV 16, 51, 33, 53, 31, 58, 18, and 56 are the most prevalent types found in Mexico (11, 12, 33).

As expected, the prevalence of oncogenic HPV types was significantly higher among women with cytological abnormalities compared with normal women (34, 35). HPV type 16 was the most common type detected in high-grade SIL with a rate

Table 3 HPV infection: association with socio-demographic and selected risk factor variables ($n = 2246$)[a]

	n[b]	HPV+	%	OR[c] (95% CI)
Age (yrs)				
15–25	560	127	22.7	1.00
26–35	809	107	13.2	0.52 (0.39–0.69)
36–45	540	58	10.7	0.41 (0.29–0.57)
46–55	178	14	7.9	0.29 (0.16–0.52)
56–65	57	3	5.3	0.19 (0.06–0.62)
66–79	9	0	0.0	
P-trend				$P < 0.001$
Race/ethnicity				
Mexican	1258	163	13.0	1.00
Mexican American	742	102	13.8	1.00 (0.77–1.32)
White, non-Hispanic	205	47	22.9	1.49 (1.01–2.19)
Other	27	8	29.6	2.08 (0.88–4.91)
Country of birth				
Mexico	1722	221	12.8	1.00
US	437	86	19.7	1.18 (0.88–1.59)
Other	26	6	23.1	1.78 (0.70–4.54)
Marital status				
Married	1239	107	8.6	1.00
Single	394	97	24.6	2.30 (1.65–3.21)
Cohabitating	321	51	15.9	1.62 (1.12–2.34)
Divorced/separated/widow	226	57	25.2	4.49 (3.09–6.53)
Educational level				
<Primary	254	35	13.8	1.00
Primary completed	539	72	13.0	0.83 (0.53–1.31)
Middle school completed	691	95	13.8	0.66 (0.42–1.04)
HS completed	302	41	13.6	0.69 (0.41–1.15)
>HS	312	62	19.9	1.06 (0.65–1.71)
P-trend				$P = 0.707$
Currently employed				
No	1296	145	11.2	1.00
Yes	881	166	18.8	1.76 (1.37–2.25)
Country of clinic				
Mexico	1258	163	13.0	1.00
US	988	161	16.3	1.14 (0.89–1.45)
Clinic site				
Nonborder	544	74	13.6	1.00
Border	1702	250	14.7	1.18 (0.88–1.58)
Geographic site				
Hermosillo	326	38	11.7	1.00
Mexico border	932	125	13.4	1.19 (0.79–1.79)
US border	770	125	16.2	1.34 (0.89–2.03)
Tucson	218	36	16.5	1.15 (0.69–1.93)
Age at first intercourse				
≥20	691	68	9.8	1.00
18–19	525	74	14.1	1.22 (0.85–1.76)
16–17	532	89	16.7	1.38 (0.97–1.97)
6–15	416	82	19.7	1.58 (1.09–2.30)
P-trend				$P = 0.014$
Lifetime no. of male partners				
1	1224	101	8.3	1.00
2–3	580	113	19.5	2.59 (1.93–3.47)
4–9	203	50	24.6	3.10 (2.11–4.56)
≥10	134	46	34.3	5.19 (3.41–7.91)
P-trend				$P < 0.001$
No. of new partners in past 3 mos.				
None	2081	271	13.0	1.00
1	105	29	27.6	2.12 (1.34–3.36)
2–60	41	15	36.6	2.92 (1.49–5.72)
P-trend				$P < 0.001$
No. of live births				
0	346	75	21.7	1.00
1–2	924	134	14.5	0.74 (0.53–1.06)
3–4	743	92	12.4	0.89 (0.59–1.35)
5–13	233	23	9.9	0.94 (0.52–1.72)
P-trend				$P = 0.989$
STD history				
No	1280	177	13.8	1.00
Yes	783	120	15.3	1.10 (0.85–1.42)
Smoking history				
Never	1580	204	12.9	1.00
Past	237	30	12.7	1.11 (0.72–1.69)
Current	365	79	21.6	1.85 (1.38–2.49)
Chlamydia trachomatis				
Negative	2052	270	13.2	1.00
Positive	180	51	28.3	2.26 (1.57–3.25)
OC history				
Never	621	85	13.7	1.00
Past	951	133	14.0	1.20 (0.88–1.63)
Current	459	79	17.2	1.23 (0.87–1.73)
Norplant history				
Never	2146	302	14.1	1.00
Ever	33	10	30.3	2.45 (1.15–5.23)
Injectable contraceptive history				
Never	1726	215	12.5	1.00
Past	330	58	17.6	1.49 (1.08–2.06)
Current	138	42	30.4	2.57 (1.72–3.84)
Current condom use				
No	999	145	14.5	1.00
Yes	233	37	15.9	0.86 (0.57–1.31)
IUD[a] history				
Never	1547	233	15.1	1.00
Past	413	51	12.4	0.90 (0.64–1.25)
Current	225	30	13.3	0.74 (0.48–1.12)

[a] CI, confidence interval; STD, sexually transmitted disease; OC, oral contraceptive; IUD, intrauterine device.
[b] n varies because of missing data.
[c] Age-adjusted OR.

of 27.3 and 12.5% in Mexico and the United States, respectively. The prevalence of HPV 16 among women with high-grade SIL appears to vary by region within Latin America, with a prevalence of HPV 16 reported from 27.5 to 58.3%. Despite individual HPV type variability, HPV 16, 58, 18, 33, and 31 were the most consistently detected in high-grade SIL of published Latin-American studies (12, 19, 31, 33). As a whole, the variability in oncogenic HPV type distribution will significantly impact vaccine efficacy in Latin America. These data suggest a need for inclusion of multiple HPV types in a vaccine designed to prevent the majority of high-grade SIL and cancer lesions observed in this region. Others have suggested that inclusion of HPV types 18, 31, and 45 in addition to HPV 16 would additionally increase vaccine efficacy to 70–80% (8). Our study suggests that HPV types 58, 45, and 51 (occurring in 31.8% of high-grade SIL) should also be considered.

In this study, both oncogenic and nononcogenic HPV infections declined linearly with age. HPV prevalence peaked in the age group 15–19 years (25%) and declined linearly to 5.3% among women ages 56–65 years, with no women >65 years HPV positive. Recent reports indicate that a second HPV peak might occur in older women (11, 19), where the second peak is associated with infection with nononcogenic HPV types in some studies and both oncogenic and nononcogenic types in other studies. The small number of women in the oldest age group (≥65 years) in this study may have limited our ability to detect a second HPV peak with increasing age.

Similar to other HPV studies, we found age, marital status,

Table 4 Independent risk factors for HPV infection

	AOR[a]	95% CI[b]
Age		
15–25	1.00	
26–35	0.51	0.36–0.71
36–45	0.45	0.30–0.67
46–55	0.28	0.14–0.55
56–79	0.15	0.04–0.53
(P-trend)	($P < 0.001$)	
Marital status		
Married	1.00	
Single	1.58	1.06–2.30
Cohabitating	1.24	0.83–1.85
Divorced/separated/widowed	3.29	2.15–5.03
Lifetime no. of male partners		
1	1.00	
2–3	2.01	1.45–2.80
4–9	1.87	1.20–2.91
≥10	3.80	2.34–6.17
(P-trend)	($P < 0.001$)	
Chlamydia trachomatis		
Negative	1.00	
Positive	1.79	1.20–2.68
Norplant		
Never	1.00	
Ever	2.69	1.17–6.19
Injectable contraceptive history		
Never	1.00	
Past	1.28	0.91–1.82
Current	2.29	1.49–3.53

[a] Adjusted OR mutually adjusted for all variables in table.
[b] CI, confidence interval.

and sexual history to be significant independent predictors of HPV infection (17, 36–40). Risk for HPV infection as estimated by the OR increased 2-fold when comparing monogamous women with those who have had two to three sexual partners in this binational population. As discussed previously (17), an elevation in HPV infection risk with a low-risk profile suggests that the sexual behavior of the male partner strongly influences a woman's risk for infection, independent of her own sexual behavior (41, 42).

To our knowledge, this is the first report of an independent association between HPV infection and use of Norplant and injectable contraceptives, most commonly reported as Depo-Provera by study participants. It is important to note that in cross-sectional studies, HPV prevalence is a mixture of incident infections and persistent, prevalent infections. Unfortunately, with this design, the temporal relationship of exposure and new *versus* persistent infections cannot be disentangled. Given that sexual history, the primary behavior resulting in new infections, was accounted for in the final model predicting HPV infection, it is reasonable to assume that these progesterone-based hormonal contraceptives exert an effect primarily on persistence of the virus in this prevalence study. This effect appears to be limited to progesterone-based contraceptives compared with combination estrogen/progesterone contraceptives, as an association between HPV detection and oral contraceptive use was not observed in this study. Recent studies implicate progesterone in viral persistence and progression to SIL; however, the mechanism of action remains elusive (43). *In vitro,* progesterone and its synthetic derivatives increase HPV 16 transformation of cultured cells (44, 45), enhance colony formation efficiency (46), and increase HPV E6/E7 oncogene transcription (46, 47). These observations are supported mechanistically by the finding of a steroid-responsive element within the promoter region of HPV 16 (48, 49). Evaluation of the effect of progesterone-based contraceptive formulations warrants additional investigation in large prospective cohort studies.

Recent studies have observed significant associations between *C. trachomatis* infection and risk for dysplasia and invasive cervical cancer (50). In this study, we found a significantly elevated risk for HPV infection among women concurrently infected with *C. trachomatis*. Similar findings of elevated risk for HPV detection were observed by Kjaer *et al.* (39) among women with a self-reported history of *C. trachomatis* infection and by Munoz *et al.* (36) among women with antibodies against *C. trachomatis*. Because we did not measure presence of other sexually transmitted infections, it remains unclear whether this association with *C. trachomatis* is specific or occurs with other sexually transmitted infections. In this study, *C. trachomatis* infection could either be associated with acquisition of HPV or HPV persistence. On the basis of reports from prospective and case-control studies of invasive cervical cancer, *C. trachomatis* infection may be exerting an effect on HPV persistence and progression through various mechanisms, such as inhibiting cell apoptosis, increasing cell oxidant load, and increasing host cell genetic damage (51).

Results presented in this manuscript represent participation from women self-referring for Pap smears in each country. As such, these women may have a different overall prevalence of HPV and risk profile for HPV infection and SIL compared with the underlying population in each country. To examine this question specifically, we are currently investigating the prevalence of HPV in a population-based random sample of women residing at the United States-Mexico border. In addition, only women from northern Mexico and southern Arizona were included in this study, thereby limiting the generalizability of these findings to other populations in each respective country.

In conclusion, comparable rates of HPV infection were observed in the United States and Mexico, and the factors contributing to these infections were similar. HPV 16 was the most common type of infection regardless of cytology status. However, differences in other oncogenic HPV type distribution in Mexico and United States were observed, suggesting that the efficacy of prevention vaccines under current development will vary depending on the HPV type. Results from this study suggest that in addition to age, marital status, and sexual history, infection with *C. trachomatis* and progesterone-based contraceptives are associated with HPV infection detection. Only large population-based studies can determine whether these factors are associated with the acquisition or persistence of HPV infection. To model vaccine effectiveness for any given region, more studies determining HPV type distribution and risk factors for these infections need to be conducted, with emphasis placed on type distribution in high-grade SIL and cancer. These data are also essential to inform development of other prevention and control methods coordinated with vaccine deployment, such as cervical cancer screening, and possibly control of other sexually acquired infections.

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