Short Communication

Differences in Factors Associated with Oncogenic and Nononcogenic Human Papillomavirus Infection at the United States-Mexico Border[1]

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Abstract

Previous studies have shown that risk factors for oncogenic (high-risk) and nononcogenic (low-risk) human papillomavirus (HPV) infection differ. To determine the risk factors for oncogenic and nononcogenic HPV infection in women residing along the United States-Mexico border, a cross-sectional study of type-specific HPV prevalence was conducted. Women (N=2246) ages 15–79 years, living in communities on both sides of the United States-Mexico border and attending family planning clinics were recruited. Women were screened for HPV and cytology and were asked to complete a health questionnaire. HPV status was determined by PCR, and HPV genotyping was performed using a reverse line blot hybridization assay (Roche Molecular Systems, Inc., Alameda, CA). Logistic regression analysis was conducted to determine factors independently associated with oncogenic and nononcogenic HPV infection in separate analyses. Similar to previous studies, lifetime number of sexual partners was only associated with oncogenic HPV infection. In contrast, nononcogenic HPV infection appeared to be associated with recent sexual activity, suggesting that nononcogenic infections may be more transient. Results from this study add to the growing literature suggesting that transmission and persistence of HPV differs by oncogenicity.

Introduction

It is now well established that infection with HPV[3] is the cause of cervical neoplasia (1–5). A recent epidemiological study reported a worldwide HPV prevalence in cervical carcinomas of 99.7% (6). As laboratory techniques have improved, evidence of the association between HPV and cervical cancer has strengthened. Incidence of cervical cancer differs greatly throughout the world, yet it remains the second most common cancer in women worldwide. Each year, 500,000 new cases of cervical cancer are reported, 80% of which occur in women living in developing countries (7). In the United States, the rate of invasive cervical cancer is 7.8 of 100,000, whereas in Mexico the incidence is 40.5 of 100,000 (8). Although HPV infection is considered necessary for the development of invasive cervical cancer, HPV alone may be insufficient requiring the presence of other factors such as smoking, oral contraceptive use, immunological status, and genetic predisposition (9–13).

HPV is the most common sexually transmitted infection in women, with prevalence ranging from 10 to 40%, depending on the population studied and method of detection (12). The majority of HPV infections are asymptomatic and remain clinically undetected making it difficult to ascertain prevalence in the general population. Higher prevalence of infection occurs in young women and in women with higher numbers of lifetime sexual partners (9, 11, 12). More than 100 HPV genotypes have been identified, with >40 types found to be associated with cervical infection (14). Most epidemiological studies have reported risk factors for overall HPV infection and do not distinguish between oncogenic and nononcogenic HPV types. Recent studies (11, 12, 15, 16) indicate that oncogenic and nononcogenic HPV types vary in their degree of association with sexual factors. In this cross-sectional study conducted along the United States-Mexico border, we examine the factors independently associated with oncogenic and nononcogenic HPV infections.

Materials and Methods

From January 1997 to June 1998, we conducted a cross-sectional study examining HPV prevalence and HPV genotypes. Details of the methodology of this study have been published elsewhere (17). Briefly, 2246 women 15 years and older were recruited from family planning clinics in three pairs of contiguous communities at the Arizona (United States)-Sonora (Mexico) border and in Tucson, Arizona, and Hermosillo, Sonora, Mexico. Women were excluded from the study if they were currently pregnant, <2 months postpartum, or had a hysterectomy. Participants completed an interviewer-administered questionnaire and a gynecological examination, during which a Pap smear was collected followed by a sample of exfoliated cervical cells to determine HPV status. The overall participation rate in this study was 92.8% (17).

Laboratory Testing. The methodology for collection and detection of HPV samples has been published elsewhere (17). Cervical cells were collected for HPV analysis from the ectocervix and endocervix using the Cone Brush Cytosoft and immediately suspended in 0.6 ml of Digene Diagnostics Sample Transport Medium (Digene Corporation, Gaithersburg, MD).

HPV DNA analyses were conducted using PCR. Genomic DNA was extracted following standard techniques. In brief, 50

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[3] The abbreviations used are: HPV, human papillomavirus; OR, odds ratio; CI, confidence interval.

μl of 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). DNA extracts were stored at −80°C until amplification. Specimens were tested for the presence of HPV using the PGMY09/11 L1 consensus primer system and Ampli*Taq* Gold polymerase (Perkin-Elmer, Foster City, CA). Each amplification contained 10× PCR Buffer II, 25 mM $MgCl_2$, 200 μl (each) dCTP, dGTP, and dATP, 600 μl of dUTP, 5 units of Ampli*Taq* Gold polymerase, 50 μM PGMY09, 50 μM PGMY11, 50 μM B PC04, and 50 μM B GH20 globin primers, and 5 μl of the template. To determine specimen adequacy, the GH20/PC04 human β-globin target was coamplified with the HPV consensus primers. The following amplification profile was used: 95°C hot start 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 using Perkin-Elmer GeneAmp PCR System 9700. HPV genotyping was conducted using the reverse line blot method (18) on samples positive by PCR. This detection method uses the HPV L1 consensus PCR products labeled with biotin to detect 27 HPV types. All reagents were provided by Roche Molecular Systems, Inc. Strip interpretation was performed with a labeled overlay, with lines indicating the position of each probe relative to the reference mark. Oncogenic HPV types detected were 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; nononcogenic HPV types detected were 6, 11, 26, 40, 42, 53, 54, 55, 57, 66, 73, 82, 83, and 84.

Chlamydia trachomatis testing of the endocervical and ectocervical specimens collected for HPV detection was conducted using the Digene CT-ID Hybrid Capture II test (Digene Corporation). This test is similar to the Digene Hybrid Capture II test for HPV detection in that it is a signal-amplified hybridization microplate assay that uses chemiluminescence for qualitative detection of *Chlamydia trachomatis* DNA (17).

Statistical Analysis. To minimize misclassification, women infected with multiple HPV types ($n = 83$) were categorized using the following schema. Participants positive for any oncogenic HPV infection were included in the oncogenic group, although they may also have been simultaneously positive for a nononcogenic HPV. Participants infected with only nononcogenic HPV types were included in the nononcogenic HPV group. Samples testing positive for HPV by the PGMY09/11 consensus primer with no specific HPV type detected using the line blot method (6 from Mexico and 2 from the United States) were considered to be nononcogenic.

Differences between the distribution of selected participant characteristics were assessed using Pearson's χ^2. Logistic regression analysis, where the OR provided an estimate of the relative risk, was used to determine factors independently associated with oncogenic and nononcogenic HPV infection separately. In all analyses, women free of an HPV infection comprised the control group. Analyses were conducted using Intercooled Stata (Stata Statistical Software: release 6.0; Stata Corp., College Station, TX).

Results

The mean age of study participants was 33.1 ± 10.2 years. The majority of study participants was married (56.8%), had one male sexual partner in their lifetime (57.1%), and did not have any new sexual partners within the past 3 months (93.5%). A complete description of the study population has been published previously (17, 19).

Overall, HPV DNA was detected in 324 women (14.4%). Of these women, 259 (79.9%) tested positive for any oncogenic HPV type, 57 (17.6%) were infected with only nononcogenic HPV types, and 8 women (2.5%) were infected with unclassified types of HPV that were considered nononcogenic infections in these analyses. Multiple infections were detected in 83 (26.6%) of 324 women positive for HPV, and 33 (10.2%) women were infected with both oncogenic and nononcogenic HPV types. An oncogenic HPV infection was detected in 11.5% (259 of 2246) of all study participants, whereas 2.9% (65 of 2246) tested positive for only nononcogenic or unclassified HPV types.

Table 1 shows the age-adjusted OR for both oncogenic and nononcogenic HPV infection with potential risk factors. Oncogenic infection significantly decreased with increasing age. Oncogenic infection was significantly higher with younger age at first intercourse, increasing numbers of lifetime sexual partners, any new sexual partners in the past 3 months, unmarried women, concurrent infection with *Chlamydia trachomatis*, and ever use of injectable contraceptives.

In age adjusted analyses, nononcogenic HPV infection was associated with young age, ≥10 lifetime sexual partners, with a marital status of single, ever use of Norplant, and current smoking.

In multivariate models, the factors that predict oncogenic infection were young age ($P_{trend} < 0.001$), higher number of lifetime male partners ($P_{trend} < 0.001$), marital status of single (OR = 1.79, 95% CI = 1.28–2.51), concurrent *Chlamydia trachomatis* infection (OR = 2.07, 95% CI = 1.35–3.16), current use of injectable contraceptives (OR = 2.23, 95% CI = 1.39–3.57), and ever use of Norplant (OR = 2.37, 95% CI = 0.94–5.97; Table 2). The factors that predicted infection with nononcogenic HPV types were two or more new partners in the past 3 months (OR = 3.56, 95% CI = 1.02–12.43), current injectable contraceptive use (OR = 2.51, 95% CI = 1.09–5.82), and ever use of Norplant (OR = 4.22, 95% CI = 1.21–14.72).

Discussion

Results from this study add additional evidence that the sexual behaviors that are associated with oncogenic and nononcogenic HPV infections differ (11, 12, 15, 16). The finding that oncogenic and nononcogenic HPV infections were associated with different sexual behaviors was first shown by Franco *et al.* (11) among northeastern Brazilian women. Since this publication, other studies conducted in Denmark (12) and Montreal (15) have also shown that number of lifetime or number of male partners in the past several years were associated with only oncogenic HPV infection. Our study is the first to also show that recent sexual activity (*i.e.*, number of male partners in the past 3 months) is only associated with nononcogenic HPV infections. As this was a cross-sectional study, incident and prevalent or persistent cases of HPV infection were included in the analysis. The fact that nononcogenic infections are exclusively associated with recent sexual activity suggests that these infections may be more transient than oncogenic infections. The potential transient nature of nononcogenic infections is supported by prospective natural history studies of HPV infection (20, 21). However, caution must be taken when interpreting results from this study as there were few women reporting new sexual partners in the past 3 months.

Recent reports suggested that the association between age and risk of HPV infection was not linear (22, 23). Our results demonstrated a strong linear decrease in risk with increasing

Table 1 Oncogenic and nononcogenic HPV infection: association with selected risk factors[a]

	Oncogenic HPV		Nononcogenic HPV	
	HPV +(%)	OR[b] (95% CI)	HPV +(%)	OR[b] (95% CI)
Country of clinic				
Mexico	129 (10.5)	1.00	34 (3.0)	1.00
United States	130 (13.6)	1.16 (0.89–1.53)	31 (3.6)	1.03 (0.62–1.73)
Age (yrs)				
15–19	24 (20.5)	1.00	7 (7.0)	1.00
20–24	70 (20.1)	0.97 (0.58–1.63)	13 (4.5)	0.62 (0.24–1.60)
25–34	91 (11.6)	0.51 (0.31–0.84)	22 (3.1)	0.42 (0.18–1.01)
35–44	42 (7.5)	0.32 (0.18–0.55)	18 (3.4)	0.46 (0.19–1.14)
45–79	19 (6.8)	0.28 (0.15–0.54)	3 (1.1)	0.15 (0.04–0.60)
P_{trend}		$P < 0.001$		$P = 0.008$
Age at first intercourse				
≥20	52 (7.7)	1.00	16 (2.5)	1.00
18–19	58 (11.4)	1.28 (0.85–1.91)	16 (3.4)	1.05 (0.50–2.20)
16–17	76 (14.6)	1.51 (1.02–2.24)	13 (2.9)	0.93 (0.43–2.00)
6–15	62 (15.7)	1.53 (1.00–2.33)	20 (5.7)	1.78 (0.87–3.66)
P_{trend}		$P = 0.032$		$P = 0.158$
Lifetime no. of male partners				
1	75 (6.3)	1.00	26 (2.3)	1.00
2–3	92 (16.5)	2.86 (2.06–3.96)	21 (4.3)	1.80 (0.99–3.25)
4–9	43 (21.9)	3.57 (2.35–5.43)	7 (4.4)	1.77 (0.75–4.16)
≥10	35 (28.5)	5.39 (3.39–8.59)	11 (11.1)	4.75 (2.21–10.19)
P_{trend}		$P < 0.001$		$P < 0.001$
No. of new partners in past 3 mos				
0	216 (10.7)	1.00	55 (3.0)	1.00
1	26 (25.5)	2.37 (1.46–3.85)	3 (3.8)	1.10 (0.33–3.63)
≥2	12 (31.6)	2.87 (1.38–5.97)	3 (10.3)	3.15 (0.91–10.84)
P_{trend}		$P < 0.001$		$P = 0.124$
Marital status				
Married/cohabiting	126 (8.3)	1.00	32 (2.2)	1.00
Single/divorced/separated	122 (20.8)	2.54 (1.92–3.36)	32 (6.4)	2.75 (1.63–4.63)
No. of live births				
0	63 (18.9)	1.00	12 (4.2)	1.00
1–2	109 (12.1)	0.77 (0.53–1.13)	25 (3.1)	0.66 (0.32–1.39)
3–4	67 (9.3)	0.83 (0.53–1.32)	25 (3.7)	1.16 (0.51–2.66)
5–13	20 (8.7)	1.06 (0.55–2.04)	3 (1.4)	0.56 (0.13–2.35)
Chlamydia trachomatis infection				
No	212 (10.6)	1.00	58 (3.2)	1.00
Yes	45 (25.9)	2.60 (1.78–3.81)	6 (4.4)	1.07 (0.42–2.73)
Injectable contraceptive history				
Never	173 (10.3)	1.00	42 (2.7)	1.00
Past	45 (14.2)	1.45 (1.01–2.07)	13 (4.6)	1.68 (0.89–3.19)
Current	35 (26.7)	2.66 (1.74–4.09)	7 (6.8)	2.27 (0.98–5.25)
Norplant history				
Never	240 (11.5)	1.00	62 (3.3)	1.00
Ever	7 (23.3)	2.15 (0.91–5.08)	3 (11.5)	3.70 (1.08–12.68)
Oral contraceptive use				
Never	68 (11.3)	1.00	17 (3.1)	1.00
Past	106 (11.5)	1.22 (0.87–1.70)	27 (3.2)	1.16 (0.61–2.21)
Current	60 (13.6)	1.15 (0.79–1.69)	19 (4.8)	1.54 (0.78–3.05)
Smoking history				
Never	164 (10.7)	1.00	40 (2.8)	1.00
Past	25 (10.8)	1.15 (0.73–1.83)	5 (2.4)	0.94 (0.36–2.41)
Current	59 (17.1)	1.76 (1.27–2.45)	20 (6.5)	2.23 (1.26–3.95)

[a] Note: *n* varies because of missing data.
[b] Age adjusted OR.

age for both oncogenic and nononcogenic infection. The association between age and oncogenic and nononcogenic infections appears to differ by population studied as associations have been noted in studies conducted in Denmark (12) and Sao Paolo, Brazil (16), but not in Montreal (15).

Current injectable contraceptive use, most commonly reported as Depo-Provera, was independently associated with both oncogenic and nononcogenic HPV infection, and Norplant use was related to an oncogenic HPV infection. As has been discussed previously, hormonal contraceptives may influence persistence and perhaps progression of HPV infections to clinically significant lesions (20, 21, 24–27).

Concurrent *Chlamydia trachomatis* infection was associated with increased risk of oncogenic HPV infection, in agreement with a previously published study (12). Kjaer *et al.* observed that self-reported history of *Chlamydia trachomatis*

Table 2 Independent risk factors for oncogenic and nononcogenic HPV infections

	Oncogenic HPV	Nononcogenic HPV
	OR (95% CI)[a]	OR (95% CI)[b]
Age (yrs)		
15–19	1.00	1.00
20–24	1.19 (0.68–2.10)	0.55 (0.21–1.48)
25–34	0.70 (0.40–1.21)	0.38 (0.15–0.94)
35–44	0.52 (0.26–0.96)	0.39 (0.15–1.02)
45–79	0.43 (0.21–0.87)	0.17 (0.04–0.69)
P_{trend}	$P < 0.001$	$P = 0.012$
Lifetime no. of male partners		
1	1.00	1.00
2–3	2.33 (1.64–3.32)	1.84 (1.00–3.39)
4–9	2.36 (1.47–3.78)	1.64 (0.65–4.16)
≥10	3.94 (2.34–6.64)	3.58 (1.37–9.32)
P_{trend}	$P < 0.001$	$P = 0.008$
No. of new partners in past 3 mos		
0	1.00	1.00
1	1.16 (0.68–1.98)	0.77 (0.18–3.23)
≥2	0.82 (0.35–1.93)	3.56 (1.02–12.43)
P_{trend}		
Marital status		
Married/cohabiting	1.00	1.00
Single/divorced/separated	1.79 (1.28–2.51)	2.69 (1.55–4.68)
Chlamydia trachomatis infection		
No	1.00	1.00
Yes	2.07 (1.35–3.16)	1.24 (0.48–3.22)
Injectable contraceptive history		
Never	1.00	1.00
Past	1.34 (0.92–1.96)	1.52 (0.77–3.00)
Current	2.23 (1.39–3.57)	2.51 (1.09–5.82)
Norplant history		
Never	1.00	1.00
Ever	2.37 (0.94–5.97)	4.22 (1.21–14.72)

[a] Adjusted for age, lifetime no. of male partners, marital status, injectable contraceptives, Norplant use, and concurrent Chlamydia infection.
[b] Adjusted for new partners in past 3 months, injectable contraceptives, and Norplant use.

infection was associated with increased risk of oncogenic HPV infection but not with nononcogenic HPV infection. Since our study was a cross-sectional study, we cannot ascertain whether *Chlamydia trachomatis* promotes HPV persistence or if it is an independent risk factor for new infection. However, because *Chlamydia trachomatis* has been found to play a role in the development of cervical neoplasia this association warrants further study (1, 3, 28).

In conclusion, results from this study indicate that different factors are associated with oncogenic compared with nononcogenic HPV infection and may relate to differences in acquisition and persistence of these viral types. As oncogenic infections constitute increased risk for cervical neoplasia it is particularly important to further evaluate the factors that determine acquisition and persistence of these infections among diverse populations and regions.

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