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Condom Use and Other Factors Affecting Penile Human Papillomavirus Detection in Men Attending a Sexually Transmitted Disease Clinic

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Background and Objectives: **Human papillomavirus (HPV) is the primary cause of cervical, anal, and other anogenital cancers, but risk factors for penile HPV detection in men have not been well-characterized.**

Goal: **The goal of this study was to identify correlates of penile HPV detection in ethnically diverse men attending a sexually transmitted disease clinic.**

Study: **A cross-sectional investigation was conducted among 393 men. Participants completed a risk-factor questionnaire and underwent testing for penile HPV DNA. Presence of HPV DNA was assessed using polymerase chain reaction with PGMY primers and reverse line blot genotyping. Logistic regression analyses were conducted to identify variables associated with any-type, oncogenic, and nononcogenic HPV.**

Results: **Circumcision was associated with reduced risk for oncogenic, nononcogenic, and overall HPV. Regular condom use was associated with reduced risk for oncogenic and overall HPV.**

Conclusion: **These findings, if confirmed by other studies, could impact public health practices and messages regarding HPV.**

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HUMAN PAPILLOMAVIRUS (HPV) has been identified as the necessary, sexually transmitted etiologic agent of cervical cancer, cervical intraepithelial neoplasia (CIN), and other squamous cell-based anogenital cancers in women and men. In U.S. women, HPV causes 13,000 cases of cervical cancer each year.[1] HPV is also associated with 4000 cases of anal cancer each year in the United States, as well as many of the 4800 incident vulvar and vaginal cancers and 1000 penile cancers.[1–4]

Although much data exist on HPV infection in women, knowledge about penile HPV in men is limited. However, most recent studies suggest that prevalence of penile HPV in men is at least as high as cervical HPV prevalence in women.[5–12] Moreover, several studies have demonstrated that the sexual behavior of men impacts rates of HPV infection, CIN, and cervical cancer in female sex partners, even after adjusting for female sexual behavior.[14–18] The epidemiologic characteristics of men that contribute to the risk of cervical carcinogenesis in women have been termed the "male factor"[13]; we now recognize that these characteristics are markers for male HPV infection.

Despite the important role men play in the pathogenesis of cervical disease, little is known about the prevalence and natural history of HPV in men. HPV lesions in men are overwhelmingly subclinical, resulting in a large number of asymptomatic carriers. More data are needed on the epidemiology of genital HPV in men to elucidate the mechanism of sexual transmission and improve our understanding of the initiation of carcinogenesis.

The purpose of our investigation was to identify factors associated with HPV detection in men. Prevalence and HPV typing data from this study are presented elsewhere.[12] In this article, we present the results of the risk factor analysis. We specifically focused on determining whether sexual behaviors, including condom use as reported by study participants, are associated with HPV detection.

Materials and Methods

A detailed description of the study methods is presented elsewhere.[12] The project was a descriptive, cross-sectional investigation of high-risk men attending a public sexually transmitted disease clinic in Tucson, Arizona, between July 2000 and January 2001. Men aged 18 and over presenting to the clinic for any reason were invited to participate in the study, resulting in the enrollment of 443 participants, of whom 393 had complete HPV DNA analyses.

All study materials were available in both English and Spanish. An informed consent document, approved by the University of Arizona Human Subjects Committee and by the Pima County

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Health Department, was reviewed with each subject and signed. Trained interviewers then administered a 50-item questionnaire assessing sexual history, risk factors for sexually transmitted infections, and sociodemographic information. The questionnaire used in this study was developed based on 2 previously validated instruments: a questionnaire used by our research group in the binational study of HPV infection in women along the Arizona, U.S.–Sonora, Mexico border, and a questionnaire that assesses sexual beliefs, practices, and condom use among unmarried Latino men and women.[19,20] Questions were modified and/or eliminated to suit the assessment needs of this project.

We specifically aimed to determine whether condom use, as reported by study participants, influenced the prevalence of HPV. To this end, 12% of the participant risk factor questionnaire consisted of condom-related questions. A 5-point Likert scale was used to evaluate frequency of condom use, with the categories "always," "more than half the time," "half the time," "less than half the time," and "never." (The 3 midrange categories were combined into "sometimes" for statistical analyses.) Other items addressed in the instrument were sexual history, sexual behavior, and sociodemographic characteristics. In this population, men were described as Hispanic, white non-Hispanic, or "other" ethnicity, which included black men, Native American men, and men of Asian and South Asian descent.

All completed interviews were carefully reviewed before being entered into computer files. Data entry was completed using the Epi Info version 6.0 program (CDC, Atlanta, GA). Ten percent of the surveys were randomly selected and verified for coding and entry errors.

Trained clinicians performed clinical examination of study participants and collected samples for routine laboratory tests for chlamydia and gonorrhea (Gen-Probe PACE system; Gen-Probe Inc., San Diego CA) and for other infections as was clinically indicated. For HPV sampling, a Dacron swab was brushed 360° around the coronal sulcus and then another 360° around the glans penis, and was inserted into a vial containing 300 μL of STM (Digene Corp., Gaithersburg, MD). Specimens were refrigerated until the end of the workday and were then maintained at −80°C until analysis.

Clinicians documented several clinical findings for each participant, which included evidence of genital warts/condyloma on examination, circumcision status, and presence of nongonococcal urethritis (NGU) on Gram stain. All subjects' charts were reviewed for assessment of clinical diagnoses and laboratory test results.

HPV detection was conducted using polymerase chain reaction (PCR). All reagents were provided by Roche Molecular Systems, Inc. (Alameda, CA). Genomic DNA was extracted following standard techniques.[21] Aliquots of 50 μL were digested with 5 μL Proteinase K for 1 hour at 65°C, followed by 5 mol/L ammonium acetate and ethanol precipitation. The crude DNA pellet was dried and resuspended in 50 μL 10 mmol/L 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 and Ampli*Taq* Gold polymerase (Perkin-Elmer Applied Biosystems, Foster City, CA). Each amplification contained 1X PCR Buffer II, 4 mmol/L MgCl2, 200 μmol/L (each) dCTP, dGTP, and dATP, 600 μmol/L dUTP, 7.5 U of Ampl*Taq* Gold, 1 μmol/L PGMY09 primer blend, 1 μmol/L PGMY11 primer blend, 25 nM B PC04, 25 nM B GH20, and 5 μL of the template DNA extract. 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 Cell Line American Type Culture Collection, Manassas, VA) 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 minutes, 95°C denaturation for 1 minute, 55°C annealing for 1 minute, and 72°C extension for 1 minute ×40 cycles, followed by a 5 minutes. terminal extension at 72°C and a hold step at 4°C.

HPV genotyping was conducted using the reverse line blot method on all samples that were positive by PCR.[22] This detection method used the HPV L1 consensus PCR products labeled with biotin to detect 27 HPV types. The HPV genotype strip contained 29 probe lines detecting 27 individual HPV genotypes and 2 concentrations of the β-globin control probe. Coamplification and detection of human DNA with GH20/PC04 human β-globin primers served as the control for sample adequacy and PCR amplification. Poor or no β-globin amplification indicated lack of sufficient cellular material for PCR or the presence of polymerase inhibitors. When adequate sample material was available, HPV genotyping was conducted on specimens that tested β-globin negative to avoid false-negative results caused by high HPV copy numbers competing with β-globin amplification.

The PCR products were labeled with biotin and 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 mol/L sodium citrate. Color development was activated by incubation in a mixture of hydrogen peroxide in sodium citrate buffer and tetramethylbenzidine in dimethylformamide for 5 minutes 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 for the line blot assay whereby HPV types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 55, 56, 58, 59, 68, 73, 82, and 83 are considered oncogenic, and HPV types 6, 11, 40, 42, 53, 54, 57, 66, and 84 are considered nononcogenic.[22]

We have defined the presence of HPV DNA in penile skin samples as HPV detection, rather than infection, because the cross-sectional study design inherently limited our ability to distinguish HPV carriage on the penis from true HPV infection.

STATA/SE 7.0 (Stata Statistical Software: Release 7.0, College Station, TX: Stata Corp., 2001) was used for all data analyses. Comparisons of categorical variables were analyzed by chi-squared tests. Odds ratios to determine univariate and multivariate associations with oncogenic, nononcogenic, and overall HPV detection were calculated. To ascertain those factors independently associated with HPV detection in a multivariate model, all variables listed in Tables 1 and 2 were examined. Backward stepwise logistic regression analyses were conducted using the method of maximum-likelihood estimation of the models, with the significance level for removal from the model set at $P > 0.10$. Statistical interactions between variables were examined, but none were found to be statistically significant.

Results

Table 1 contains sociodemographic data of 393 study participants and the univariate associations between these factors and oncogenic, nononcogenic, and any-type (overall) HPV detection. Overall HPV prevalence was 28.2% (data not shown).[12] Detection of HPV overall was significantly associated with ethnicity (odds ratio [OR] = 1.79 for Hispanic compared with white,

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TABLE 1. Male HPV Detection: Age-Adjusted Association With Socio-Demographic & Sexual History Variables (n = 393)

	Any Type HPV			Non-Oncogenic HPV			Oncogenic HPV		
	HPV+ (%)	OR	(95% CI)	HPV+ (%)	OR	(95% CI)	HPV+ (%)	OR	(95% CI)
Age (years)									
18–24	42 (33.6)	1.00		19 (15.2)	1.00		23 (18.4)	1.00	
25–29	19 (19.8)	0.49	(0.26–0.91)	12 (12.5)	0.80	(0.37–1.73)	7 (7.3)	0.35	(0.14–0.85)
30–39	22 (25.0)	0.66	(0.36–1.21)	14 (15.9)	1.06	(0.50–2.24)	8 (9.0)	0.44	(0.19–1.04)
40–70	27 (32.5)	0.95	(0.53–1.72)	18 (21.7)	1.54	(0.76–3.16)	9 (10.8)	0.54	(0.24–1.23)
Race/ethnicity									
White, non-Hispanic	35 (21.3)	1.00		20 (12.2)	1.00		15 (9.2)	1.00	
Hispanic	50 (32.7)	1.79	(1.07–2.98)	28 (18.3)	1.71	(0.91–3.22)	22 (14.4)	1.54	(0.76–3.13)
Other	25 (34.3)	1.86	(1.01–3.46)	15 (20.6)	1.95	(0.93–4.09)	10 (13.7)	1.39	(0.58–3.35)
Country of birth									
US	76 (26.0)	1.00		45 (15.4)	1.00		31 (10.6)	1.00	
Mexico	24 (39.3)	1.72	(0.95–3.11)	12 (19.7)	1.44	(0.70–2.93)	12 (19.7)	1.71	(0.79–3.73)
Other	10 (27.8)	1.17	(0.53–2.55)	6 (16.7)	1.16	(0.45–2.97)	4 (11.1)	1.11	(0.37–3.37)
Marital status									
Married/cohabiting	21 (29.7)	1.00		9 (12.5)	1.00		12 (16.7)	1.00	
Single	89 (28.0)	0.99	(0.55–1.75)	54 (17.0)	1.44	(0.67–3.07)	35 (11.0)	0.64	(0.31–1.35)
Educational level									
≤HS completed	68 (35.2)	1.00		37 (19.2)	1.00		31 (16.1)	1.00	
Some college or above	42 (21.3)	0.51	(0.33–0.81)	26 (13.2)	0.63	(0.36–1.08)	16 (8.1)	0.51	(0.26–0.97)
Currently employed									
No	31 (32.6)	1.00		17 (17.9)	1.00		14 (14.7)	1.00	
Yes	79 (26.9)	0.78	(0.47–1.30)	46 (15.7)	0.86	(0.46–1.59)	33 (11.2)	0.76	(0.38–1.53)
Jail (ever)									
No	58 (28.7)	1.00		33 (16.3)	1.00		25 (12.4)	1.00	
Yes	51 (27.6)	0.89	(0.57–1.40)	29 (15.7)	0.94	(0.55–1.64)	22 (11.9)	0.87	(0.46–1.63)
Age at 1st intercourse									
≤13	21 (30.4)	1.00		6 (8.7)	1.00		15 (21.7)	1.00	
14–16	50 (32.3)	1.18	(0.63–2.20)	33 (21.3)	2.96	(1.17–7.49)	17 (11.0)	0.47	(0.21–1.02)
17–19	27 (21.4)	0.65	(0.33–1.28)	15 (11.9)	1.45	(0.53–3.94)	12 (9.5)	0.38	(0.16–0.90)
>20	12 (30.0)	1.05	(0.44–2.48)	9 (22.5)	2.95	(0.96–9.10)	3 (7.5)	0.33	(0.09–1.25)
Sexual orientation									
Heterosexual	99 (28.1)	1.00		56 (15.9)	1.00		43 (12.2)	1.00	
Homosexual	5 (19.2)	0.61	(0.22–1.66)	4 (15.4)	0.93	(0.31–2.81)	1 (3.9)	0.30	(0.04–2.27)
Bisexual	6 (50.0)	2.53	(0.79–8.07)	3 (25.0)	1.60	(0.42–6.17)	3 (25.0)	2.68	(0.69–10.48)
Lifetime no. of female partners									
≤5	22 (32.4)	1.65	(0.48–5.66)	14 (16.5)	1.00		12 (17.7)	1.00	
6–10	25 (27.5)	1.20	(0.36–4.06)	10 (11.0)	0.62	(0.26–1.49)	15 (16.5)	1.08	(0.47–2.49)
>10	58 (27.8)	1.26	(0.39–4.02)	38 (18.2)	1.10	(0.56–2.16)	20 (9.6)	0.62	(0.29–1.36)
No. new female partners past 3 mos.									
None	55 (35.0)	1.00		32 (20.4)	1.00		23 (14.7)	1.00	
1	28 (23.5)	0.57	(0.33–0.97)	15 (12.6)	0.57	(0.29–1.17)	13 (10.9)	0.71	(0.35–1.48)
2	16 (26.2)	0.68	(0.34–1.30)	8 (13.1)	0.59	(0.26–1.38)	8 (13.1)	0.88	(0.37–2.09)
≥3	7 (21.9)	0.58	(0.23–1.45)	4 (12.5)	0.63	(0.20–1.94)	3 (9.4)	0.60	(0.17–2.14)
Steady partner									
No	38 (27.3)	1.00		26 (18.7)	1.00		12 (8.6)	1.00	
Yes	72 (28.6)	1.04	(0.65–1.66)	37 (14.7)	0.76	(0.44–1.32)	35 (13.9)	1.60	(0.79–3.21)
Sexual frequency per month/past 3 mos									
0	9 (23.7)	1.00		7 (18.4)	1.00		2 (5.3)	1.00	
1–5	29 (23.2)	0.96	(0.41–2.29)	20 (16.0)	0.87	(0.34–2.26)	9 (7.2)	1.26	(0.26–6.20)
6–30	55 (28.7)	1.33	(0.59–3.00)	29 (15.1)	0.82	(0.33–2.05)	26 (13.5)	2.81	(0.64–12.40)
>30	16 (51.6)	3.82	(1.33–11.00)	6 (19.4)	1.28	(0.37–4.35)	10 (32.3)	8.29	(1.62–42.67)
Insertive anal sex									
Never	65 (26.5)	1.00		37 (15.1)	1.00		28 (11.4)	1.00	
Ever	44 (30.8)	1.24	(0.79–1.97)	25 (17.5)	1.15	(0.66–2.01)	19 (13.3)	1.27	(0.68–2.41)
Time since anal sex									
Never	55 (25.0)	1.00		30 (13.6)	1.00		25 (11.4)	1.00	
1–22 yrs	14 (26.4)	1.07	(0.54–2.13)	8 (15.1)	1.04	(0.44–2.44)	6 (11.3)	1.09	(0.42–2.84)
3 mos <1 yr	14 (35.0)	1.63	(0.79–3.35)	11 (27.5)	2.35	(1.06–5.20)	3 (7.5)	0.67	(0.19–2.34)
<3 mos	21 (31.3)	1.41	(0.77–2.57)	11 (16.4)	1.22	(0.57–2.59)	10 (14.9)	1.48	(0.66–3.30)

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TABLE 1. (Continued)

	Any Type HPV			Non-Oncogenic HPV			Oncogenic HPV		
	HPV+ (%)	OR	(95% CI)	HPV+ (%)	OR	(95% CI)	HPV+ (%)	OR	(95% CI)
Current relationship									
Monogamous	39 (31.0)	1.00		20 (15.9)	1.00		19 (15.1)	1.00	
Steady partner and others	33 (26.2)	0.79	(0.45–1.38)	17 (13.5)	0.85	(0.42–1.73)	16 (12.7)	0.79	(0.38–1.65)
No steady partner	38 (27.3)	0.86	(0.50–1.47)	26 (18.7)	1.22	(0.64–2.31)	12 (8.6)	0.56	(0.26–1.21)
Circumcised									
No	46 (41.1)	1.00		25 (22.3)	1.00		21 (18.8)	1.00	
Yes	46 (19.8)	0.35	(0.21–0.57)	28 (12.1)	0.47	(0.26–0.85)	18 (7.8)	0.36	(0.18–0.71)
Genital warts									
No	92 (26.5)	1.00		49 (14.1)	1.00		43 (12.4)	1.00	
Yes	17 (46.0)	2.36	(1.16–4.80)	13 (35.1)	3.21	(1.49–6.90)	4 (10.8)	0.92	(0.31–2.76)
Chlamydia trachomatis									
No	88 (27.2)	1.00		49 (15.1)	1.00		39 (12.04)	1.00	
Yes	9 (33.3)	1.45	(0.62–3.39)	4 (14.8)	1.06	(0.35–3.24)	5 (18.5)	1.72	(0.61–4.89)

n varies due to missing data.

non-Hispanic; OR = 1.86 for "other" race/ethnicity compared with white, non-Hispanic). After adjustment for circumcision status, ethnicity was no longer associated with detection of HPV.

Men who had some college education had decreased risk for any-type and oncogenic-type HPV detection. Increased risk for any-type HPV and for oncogenic HPV was noted among men who reported 30 or more episodes of vaginal or anal sexual intercourse per month. Circumcised participants had decreased risk for all measures of HPV detection. Participants diagnosed with genital warts at their clinic visit were at increased risk for any-type and nononcogenic HPV.

Table 2 presents the associations between condom use and risk for HPV detection. Thirty-nine percent of participants reported never using a condom in the past 3 months, whereas 15.2% reported using a condom every time they had sexual intercourse; all others used condoms "sometimes" (data not shown). In univariate analyses, any-type and oncogenic HPV detection risk was significantly decreased with some use of condoms compared with "never" use during the past 3 months. Condom use with a steady partner was significantly associated with a decreased risk for overall HPV detection. For those with a steady partner, the use of condoms "always" also was associated with a nearly significant decrease in risk for oncogenic HPV detection. Condom use during most recent episode of anal sex was

TABLE 2. Male HPV Detection: Association with Condom Use (n = 393)

	Any Type HPV			Non-Oncogenic HPV			Oncogenic HPV		
	HPV+ (%)	OR	(95% CI)	HPV+ (%)	OR	(95% CI)	HPV+ (%)	OR	(95% CI)
Condom use-past 3 mos.									
Never	51 (36.7)	1.00		28 (20.1)	1.00		23 (16.6)	1.00	
Sometimes	40 (24.5)	0.56	(0.34–0.92)	19 (11.7)	0.53	(0.28–1.00)	21 (12.9)	0.76	(0.39–1.47)
Always	12 (22.2)	0.49	(0.24–1.02)	10 (18.5)	0.96	(0.43–2.18)	2 (3.7)	0.20	(0.05–0.89)
Condom use-last vaginal sex									
No	76 (30.9)	1.00		41 (16.7)	1.00		35 (14.2)	1.00	
Yes	29 (23.6)	0.69	(0.42–1.13)	18 (14.6)	0.89	(0.48–1.64)	11 (8.9)	0.60	(0.29–1.24)
Condom use-last anal sex									
No	47 (40.5)	1.00		29 (25.0)	1.00		18 (15.5)	1.00	
Yes	7 (14.0)	0.24	(0.10–0.58)	4 (8.0)	0.24	(0.08–0.73)	3 (6.0)	0.39	(0.11–1.40)
Condom use with steady partner									
Never	42 (40.0)	1.00		21 (20.0)	1.00		21 (20.0)	1.00	
Sometimes	24 (23.5)	0.46	(0.25–0.84)	12 (11.8)	0.52	(0.24–1.14)	12 (11.7)	0.56	(0.26–1.23)
Always	5 (14.7)	0.26	(0.09–0.72)	4 (11.8)	0.54	(0.17–1.71)	1 (2.9)	0.13	(0.02–1.00)
Condom use 1st time with steady partner									
No	42 (30.9)	1.00		17 (12.5)	1.00		25 (18.4)	1.00	
Yes	29 (26.6)	0.81	(0.46–1.42)	19 (17.4)	1.56	(0.76–3.23)	10 (9.2)	0.47	(0.21–1.04)
Condom use with extrarelational partners									
Never	14 (29.8)	1.00		8 (17.0)	1.00		6 (12.8)	1.00	
Sometimes	10 (22.2)	0.67	(0.26–1.73)	4 (8.9)	0.48	(0.13–1.75)	6 (13.3)	0.97	(0.29–3.32)
Always	9 (33.3)	1.18	(0.43–3.25)	5 (18.5)	1.15	(0.33–3.98)	4 (14.8)	0.82	(0.19–3.63)

n varies due to missing data.

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TABLE 3. Male HPV Detection: Independent Risk Factors

	Any Type HPV		Non-Oncogenic HPV		Oncogenic HPV	
	OR*	(95% CI)	OR**	(95% CI)	OR***	(95% CI)
Sexual frequency per month/past 3 months						
0–5	**1.00**		1.00		**1.00**	
6–30	**1.57**	**0.89–2.78**	0.73	0.40–1.34	**1.91**	**0.87–4.14**
>30	**3.65**	**1.49–8.97**	0.84	0.30–2.38	**5.01**	**1.81–13.92**
p-trend		0.006		0.449		0.003
Circumcised						
No	**1.00**		**1.00**		**1.00**	
Yes	**0.34**	**0.20–0.57**	**0.44**	**0.23–0.81**	**0.44**	**0.22–0.90**
Genital warts						
No	**1.00**		**1.00**		1.00	
Yes	**2.48**	**1.17–5.25**	**4.35**	**1.97–9.62**	0.86	0.28–2.70
Condom use-past 3 months						
Never	**1.00**		1.00		**1.00**	
Sometimes	**0.60**	**0.35–1.02**	0.66	0.34–1.29	**0.80**	**0.41–1.55**
Always	**0.41**	**0.18–0.93**	1.42	0.58–3.48	**0.21**	**0.05–0.96**
Steady partner						
No	**1.00**		1.00		1.00	
Yes	**0.58**	**0.32–1.03**	0.56	0.31–1.01	0.76	0.34–1.70
Condom use-last anal sex						
No	1.00		**1.00**		1.00	
Yes	0.27	0.10–0.73	**0.25**	**0.08–0.79**	0.58	0.15–2.28

Independent risk factors for HPV are shown in **bold type**; all other ORs are included in table for comparison only.
*Odds ratio adjusted for sexual frequency per month, circumcised, genital warts, condom use in past 3 months, and steady partner.
**Odds ratio adjusted for circumcised, genital warts, and condom use with last anal sex.
***Odds ratio adjusted for sexual frequency per month, circumcised, and condom use in past 3 months.

associated with decreased risk of any-type and nononcogenic type HPV compared with participants who had not used a condom.

Logistic regression analyses identified variables independently associated with overall, nononcogenic, and oncogenic HPV detection (Table 3). Risk for any type of HPV was significantly increased among participants reporting greater frequency of sexual intercourse (vaginal or anal) during the last 3 months (*P* trend = 0.006) and among those with current genital warts (adjusted odds ratio [AOR] = 2.48). Reduced risk for any-type HPV detection was associated with circumcision (AOR = 0.34), having a steady sexual partner (AOR = 0.58), and regular condom use during the previous 3 months (AOR = 0.41 and AOR = 0.60 for men who always and sometimes used condoms vs. never).

Risk for nononcogenic HPV detection was significantly associated with circumcision (AOR = 0.44), current genital warts (AOR = 4.35), and use of condoms with last episode of anal sex (AOR = 0.25).

Risk for oncogenic HPV detection was significantly associated with greater frequency of sexual intercourse (vaginal or anal) during the last 3 months (*P* trend = 0.003), and was inversely associated with circumcision (AOR = 0.44), condom use (AOR = 0.21 for always use vs. never), and reporting a steady sexual partner (AOR = 0.76).

Discussion

This study is one of a few that have analyzed the correlates of HPV detection in men and the first to investigate risk factors for HPV among men in the United States. Our results suggest that "classic" risk factors for HPV do not apply in men. In females, risk for HPV infection has been consistently increased among young women and in women who report a greater number of lifetime sexual partners. In some studies, HPV has been associated with the number of recent sexual partners or with an early age at first coitus. In this male study of HPV detection, no clear age-related association was identified, and HPV was not associated with number of lifetime female sexual partners or the number of female sexual partners in the last 3 months. These results differ from the findings of a Danish study and those of a large multinational study by the International Agency for Research on Cancer (IARC), both of which reported that HPV DNA detection in men was associated with the number of lifetime female sexual partners.[7,9,11] Our findings, however, do replicate those of a study of HPV DNA among Mexican men, among whom number of female partners did not correlate with the presence of penile HPV. Although the Danish study identified young age as a strong predictor of HPV DNA in men, the IARC study, the Mexican study, and our own investigation have not confirmed this association. Notably, none of these male HPV studies has reported an association between HPV DNA in men and age of first coitus.

Our results confirm published data that demonstrate a reduction in HPV detection among men who are circumcised.[8,11] This association was robust in our study, with statistically significant risk reduction occurring across HPV type categories. The significance of circumcision as a modifying factor in penile HPV infection, and perhaps as a strong determinant of the risk of cervical cancer conferred to the female sexual partner, has profound implications for public health practice. In developing nations where circumcision is uncommonly performed and incidence of cervical cancer is high, increased rates of circumcision could potentially play a role in anogenital cancer prevention.

In designing this study, we specifically addressed the question of whether condom use would impact the risk of HPV detection in men. Although most past investigations have failed to demonstrate a decreased risk for HPV among women or men who used con-

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doms,[9,11,23–25], other studies have reported reduction of risk for cervical neoplasia in the female partners of men who used condoms[17,26] or among women who used barrier contraceptive methods such as the diaphragm.[27,28] Our hypothesis that condoms would decrease the risk for HPV in men was based on these positive findings and was also grounded in results from in vitro experiments showing that latex condoms are normally impervious to the passage of small virus particles,[29] as well as in vitro and in vivo studies in which latex condoms have prevented transmission of cytomegalovirus (CMV), a herpesvirus 10 to 20 nm smaller the papillomaviruses.[30–32].

Viral STDs can infect genital skin beyond the area covered by a condom, so condom use does not afford complete protection against these infections. However, condom use has been previously demonstrated to decrease the incidence of genital herpes infection among both men and women.[33,34] In this study, we sampled only the tip of the penis and therefore cannot draw conclusions about HPV infection in other areas of the male genitalia, for which condom use may not reduce risk. Because we have not accounted for the presence of virus at other anatomic sites, our analysis may overestimate the protective benefit of condom use. Nonetheless, we were encouraged to find that in multivariate analyses, consistent condom use was associated with a significantly decreased risk for overall and oncogenic HPV detection on the penis. Because penile contact with the cervix could be an important mechanism for HPV transmission from men to women, particularly in the development of cervical neoplasia, reduction of penile HPV through condom use may have important implications for public health and for public education messages regarding HPV.

A strength of our study was its focus on assessment of condom use as it relates to HPV detection. Participants' diverse responses to questionnaire items regarding condom use provided us with ample data on this issue. However, investigation of condom use in a research population is inherently difficult, and our data would have been more precise had we queried participants with specific questions about not only when they use condoms, but how they use them. To serve as effective barriers to disease, condoms must be used consistently and correctly with every sexual encounter. Potential exposure to semen occurs when condoms are used improperly, as when withdrawal is delayed after ejaculation or when an oil-based lubricant is used in conjunction with a condom[35]; such errors have been reported by a high percentage of condom users.[36] Assessment of condom use is also limited by the difficulty in determining the true consistency of use among subjects.[37,38] However, if participants overestimated their condom use, or if those who used condoms "sometimes" or "always" used them improperly, the benefit of proper condom use would be underestimated in our analysis.

Another finding with potential public health implications is that men who reported having a steady sexual partner had a lower risk of overall HPV detection. One explanation for this finding is that men in a steady relationship are less likely to have other sexual partners and therefore may have less exposure to HPV. (In our study, 47.2% of men in a steady relationship reported having other partners.) Another explanation is that if HPV infection in men is short-term, as has been suggested in previous studies,[39,40] men with a steady sexual partner may have had time to mount an immune response and clear their HPV infection.

Our logistic regression analyses indicate that increased frequency of sexual contact is associated with detection of oncogenic and any-type HPV in men. This finding may simply reflect that the risk of sexually transmitted disease acquisition, in general, is a function of exposure to an infectious agent and as such increases with multiple or repeated sexual encounters. Alternatively, the association between penile HPV and frequent sexual intercourse could be the result of a bias created by our sampling method, which entailed collection of superficial penile skin cells. Some of the HPV detected may therefore originate from cellular material such as dried secretions on the surface of the penis.[12] HPV DNA identified in these samples may reflect carriage of the virus rather than true infection and could be increased in men who had more numerous sexual encounters. However, if detection of HPV in men reflected transient carriage, we would expect risk for HPV to be increased in participants who reported more recent sexual encounters; we observed no such association between HPV detection and days elapsed since last vaginal or anal intercourse (data not shown). We did not collect data on frequency of genital washing or most recent penile cleansing, and so could not control for this potentially confounding variable.

Our study has another limitation, in that the STD clinic population participating in this investigation was an especially high-risk group.[12] Results are therefore not necessarily applicable to the general male population. Nonetheless, this report is the first to document risk factors for HPV detection in a diverse population of U.S. men, and as such, represents an important contribution to basic HPV epidemiology. The enrollment of many Hispanic/Mexican American men in this study, nearly 40% of participants, allows us to contribute to the nascent body of information about this subgroup, a rapidly growing segment of the U.S. population that has been underrepresented in most health-related research. Identifying risk factors for HPV among Hispanic men has special public health significance because in the United States, cervical cancer and cervical dysplasia incidence are disproportionately high among Hispanic women.

The increasing incidence of cervical dysplasia, anal cancer, and HPV-related vulvar cancer in the United States attests to the importance of understanding HPV not only in women, but in men, who serve as vectors of this ubiquitous virus and potentially as reservoirs. For prophylactic HPV vaccine efforts, targeted education campaigns, and other future cancer prevention endeavors to be successful, comprehensive knowledge about the epidemiology of HPV in men must be acquired through further studies.

References

1. Cancer Facts and Figures 2002. Atlanta: American Cancer Society; 2002.
2. Griffiths TRL, Mellon JK. Human papillomavirus and urogenital tumours I: basic science and role in penile cancer. BJU Int 1999; 84:579–586.
3. Melbye M, Frisch M. The role of human papillomaviruses in anogenital cancers. Semin Cancer Biol 1998; 8:307–313.
4. Frisch M, Glimelius B, van den Brule AJ, et al. Sexually transmitted infection as a cause of anal cancer. N Engl J Med 1997; 337:1386–1388.
5. Hippelainen MI, Syrjanen S, Hippelainen MJ, et al. Prevalence and risk factors of genital human papillomavirus infections in healthy males: A study on Finnish conscripts. Sex Transm Dis 1993; 20: 321–328.
6. Wikstrom A, Popescu C, Forslund O. Asymptomatic penile HPV infection: A prospective study. Int J STD AIDS 2000; 11:80–84.
7. Lazcano-Ponce E, Herrero R, Munoz N, et al. High prevalence of human papillomavirus infection in Mexican males. Sex Transm Dis 2001; 28:277–280.
8. Castellsagué X, Bosch FX, Munoz N, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med 2002; 346:1105–1112.
9. Franceschi S, Castellsagué X, Dal Maso L, et al. Prevalence and

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determinants of human papillomavirus genital infection in men. Br J Cancer 2002; 86:705–711.
10. Svare EI, Kjaer SK, Worm AM, et al. Risk factors for HPV infection in women from sexually transmitted disease clinics: Comparison between two areas with different cervical cancer incidence. Int J Cancer 1998; 75:1–8.
11. Svare EI, Kjaer SK, Worm AM, et al. Risk factors for genital HPV DNA in men resemble those found in women: A study of male attendees at a Danish STD clinic. Sex Transm Infect 2002; 78:215–218.
12. Baldwin S, Wallace D, Papenfuss M, et al. Human papillomavirus infection among men attending a sexually transmitted disease clinic. J Infect Dis 2003; 187:1064–1070.
13. Skegg DCG, Corwin PA, Paul C, Doll R. Importance of the male factor in cancer of the cervix. Lancet 1982; 2:581–583.
14. Zunzunegui MV, King MC, Coria CF, Charlet J. Male influences on cervical cancer risk. Am J Epidemiol 1986; 123:302–307.
15. Buckley JD, Doll R, Harris RWC, Vessey MP, Williams PT. Case–control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. Lancet 1981; 2:1010–1015.
16. Agarwal SS, Sehgal A, Sardana S, Kumar A, Luthra UK. Role of male behavior in cervical carcinogenesis among women with one lifetime sexual partner. Cancer 1993; 72:1666–1669.
17. Thomas DB, Ray RM, Pardthaisong T, et al. Prostitution, condom use, and invasive squamous cell cervical cancer in Thailand. Am J Epidemiol 1996; 143:779–786.
18. Bosch FX, Castellsagué X, Muñoz N, et al. Male sexual behavior and human papillomavirus DNA: Key risk factors for cervical cancer in Spain. J Natl Cancer Inst 1996; 88:1060–1067.
19. Giuliano AR, Denman C, Guernsey de Zapien J, et al. Design, methods, and results of the US-Mexico border binational human papillomavirus, cervical dysplasia, and *Chlamydia trachomatis* infection study. Pan Am Health Organization Journal 2001; 9:172–181.
20. Marin G, Sabogal F, VanOss MB, et al. Short acculturation scale for Hispanics. In: Quadagno D, Sly DF, Harrison DF, Eberstein IW, Soler HR, eds. Ethnic Differences in Sexual Decisions and Sexual Behavior. Arch Sex Behav 1998; 27:57–75.
21. Gravitt P, Peyton C, Alessi T, et al. Improved amplification of genital human papillomaviruses. J Clin Microbiol 2000; 38:357–361.
22. Gravitt, PE, Payton CL, Apple RJ, Wheeler CM. Genotyping of 27 human papillomavirus types by using L1 consensus PCR products by a single hybridization, reverse line blot detection method. J Clin Microbiol 1998; 36:3020–3027.
23. Kjaer SK, Engholm G, Teisen C, et al. Risk factors for cervical human papillomavirus and herpes simplex virus infections in Greenland and Denmark: A population based study. Am J Epidemiol 1990; 131: 669–682.
24. Young TK, McNichol P, Beauvais J. Factors associated with human papillomavirus infection detected by polymerase chain reaction among urban Canadian aboriginal and non-aboriginal women. Sex Transm Dis 1997; 24:293–298.
25. Jamison JH, Kaplan DW, Hamman R, Eager R, Beach R, Douglas JM. Spectrum of genital human papillomavirus infection in a female adolescent population. Sex Transm Dis 1995; 22:236–243.
26. Kjaer SK, de Villiers EM, Dahl C, et al. Case control study of risk factors for cervical neoplasia in Denmark. I. Role of the 'male factor' in women with one lifetime sexual partner. Int J Cancer 1991; 48:39–44.
27. Cuzick J, Singer A, DeStavola BL, Chomet J. Case–control study of risk factors for cervical intraepithelial neoplasia in young women. Eur J Cancer 1990; 26:684–690.
28. Parazzini F, Negri E, LaVecchia C, Federle L. Barrier methods of contraception and the risk of cervical neoplasia. Contraception 1989; 40:519–530.
29. Lytle CD, Rouston LB, Seaborn GB, et al. An in vitro evaluation of condoms as barriers to a small virus. Sex Transm Dis 1997; 24:161–164.
30. Katznelson S, Drew WL, Mintz L. Efficacy of the condom as a barrier to the transmission of cytomegalovirus. J Infect Dis 1984; 150:155–157.
31. Robain M, Carre N, Dussaix E, et al. Incidence and sexual risk factor of cytomegalovirus seroconversion in HIV-infected subjects. Sex Transm Dis 1998; 25:476–480.
32. Drew LW. Condoms and the transmission of cytomegalovirus. Sex Transm Dis 1998; 25:481–482.
33. Wald A, Langenberg AG, Link K, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. JAMA 2001; 285:3100–3106.
34. Wald A, Langenberg A, Kexel E, et al. Condoms protect men and women against herpes simplex virus type 2 acquisition. Presentation B9E, National STD Prevention Conference 2002; San Diego, CA.
35. Warner L, Clay-Warner J, Boles J, Williamson J. Assessing condom use practices: implications for evaluating method and user effectiveness. Sex Transm Dis 1998; 25:273–276.
36. Sanders SA, Graham CA, Yarber WL, Crosby RA. Condom use errors and problems among young women who put condoms on their male partners. JAMWA 2003; 58:95–98.
37. Zenilman JM, Weisman CS, Rompalo AM, et al. Condom use to prevent incident STDs: The validity of self-reported condom use. Sex Transm Dis 1995; 22:15–20.
38. Sabogal F, Faigeles B, Catania JA. Multiple sex partners among Hispanics in high-risk cities. Fam Plann Perspect 1993; 25:257–262.
39. Van Doornum GJV, Prins M, Juffermans LHJ, et al. Regional distribution and incidence of human papillomavirus infections among heterosexual men and women with multiple sexual partners: A prospective study. Genitourin Med 1994; 70:240–246.
40. Svare EI, Kjaer SK, Nonnenmacher B, et al. Seroreactivity to human papillomavirus type 16 virus-like particles is lower in high-risk men than in high-risk women. J Infect Dis 1997; 176:876–883.

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