MAJOR ARTICLE

Human Papillomavirus Infection in Men Attending a Sexually Transmitted Disease Clinic

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Human papillomavirus (HPV) is the main etiologic agent of anogenital cancers, including cervical cancer, but little is known about the type-specific prevalence of HPV in men. Participants were men aged 18–70 years attending a sexually transmitted disease clinic. Penile skin swabs were assessed for HPV DNA using polymerase chain reaction with reverse line-blot genotyping. Of 436 swabs collected, 90.1% yielded sufficient DNA for HPV analysis. Men with inadequate swab samples were significantly more likely to be white and circumcised than men with adequate swab samples. The prevalence of HPV was 28.2%. Oncogenic HPV types were found in 12.0% of participants, nononcogenic types were found in 14.8% of participants, multiple types were found in 6.1% of participants, and unknown types were found in 5.9% of participants. The most prevalent subtypes were nononcogenic 6, 53, and 84. HPV positivity was not associated with age. These results indicate that HPV infection among men at high risk is common but that characteristics of male HPV infection may differ from those of female infection.

Human papillomavirus (HPV) infection is the necessary, sexually transmitted cause of invasive cervical cancer and its precursor lesion, cervical intraepithelial neoplasia [1–3]. HPV has also been closely linked with other anogenital cancers, including anal cancer and certain penile cancers [4–6]. HPV infection in men is overwhelmingly subclinical, which has resulted in a potentially large number of asymptomatic carriers who serve as reservoirs and vectors for the virus.

Although HPV has been studied extensively in women, data on male infection are limited. Studies of HPV in men are necessary to improve our understanding of HPV transmission and HPV-related carcinogenesis and to prevent disease in both men and women. The success of future cancer prevention strategies, such as prophylactic HPV vaccination, will be limited without a basic epidemiological understanding of HPV in men.

Earlier studies of papillomavirus infection in men used a variety of clinical and histological techniques to establish a diagnosis of HPV, but polymerase chain reaction (PCR) has emerged as the most sensitive method available for the detection of latent HPV [7–9]. Among studies that have used PCR to detect penile HPV DNA in healthy men, sampling methodologies have been inconsistent. Nonetheless, results from these diverse investigations have suggested that penile HPV in sexually active men is at least as prevalent as cervical HPV is among women [10–15].

HPV prevalence in men has been shown to vary by

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Informed consent was obtained from all participants in the study, in accordance with guidelines of the University of Arizona Human Subjects Committee and the Pima County Health Department.

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country [16]. To date, none of the published studies has investigated penile HPV among men in the United States. The purpose of our investigation was to assess the prevalence and type distribution of HPV in an ethnically diverse group of men attending a sexually transmitted disease (STD) clinic in the southwestern United States.

MATERIALS AND METHODS

The present study was a descriptive, cross-sectional investigation of men self-referring to an STD clinic in Tucson, Arizona, between July 2000 and January 2001. Study personnel were present at the clinic on regularly scheduled days, and all men aged ⩾18 years who registered at the clinic on those days were invited to participate in the study.

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 Health Department, was reviewed and signed by each participant. Trained interviewers then administered a 50-item questionnaire that assessed sexual history, risk factors for STDs, and demographic information. The questionnaire was developed on the basis of 2 previously validated instruments: a questionnaire used by our research group in the binational study of HPV infection in women along the Arizona–Sonora, Mexico border [17] and a questionnaire that assessed sexual beliefs, practices, and condom usage among unmarried Latino men and women [18]. Questions were modified and/or eliminated to suit the assessment needs of our project and were pilot tested.

Because the significance of a positive HPV test in men is unknown, study personnel spent a considerable amount of time educating men about HPV and explaining that a positive test for the virus did not necessarily put them at any risk for disease. Participants were notified of their HPV results by phone or by mail, depending on their preference, and all men who tested positive for HPV were instructed to have their female partners screened with a Pap smear.

Clinical examinations were performed by physicians and midlevel clinicians experienced in the detection of STDs. All clinicians working on the study were trained in specimen collection. Participants first underwent a routine examination that included a visual inspection of genitalia, Gram stain of penile secretions, and sampling for chlamydia, gonorrhea, and other infections, as clinically indicated. Chlamydia and gonorrhea testing was conducted using the PACE system (Gen-Probe), to limit urethral sampling prior to the collection of research specimens. With the PACE system, laboratory analyses for chlamydia and gonorrhea were conducted using a single swab.

Three research specimens were collected from each participant. First, a narrow Dacron-tipped urethral swab was inserted 1 cm into the urethral meatus, rotated, and removed. A second, cervical-sized swab was swept 360° around the coronal sulcus and then another 360° around the glans penis. Both swabs were prewetted with normal saline, and each swab was inserted into a vial that contained 300 μL of Specimen Transport Medium (Digene). Seven hundred microliters of medium was removed from each 1-mL Digene vial, to achieve a higher concentration of cells and a better yield of DNA.

For each participant, clinicians documented clinical findings as follows: (1) evidence of genital warts/condyloma on examination, (2) circumcision status, (3) the presence of nongonococcal urethritis (NGU) on Gram stain, (4) the quantity of polymorphonuclear leukocytes on gram stain, and (5) the presence of gonococci on gram stain. After the clinical examination, each subject provided a urine sample for HPV testing. All medical charts were reviewed for the assessment of clinical diagnoses and laboratory test results.

HPV detection was conducted using PCR. Genomic DNA was extracted according to standard techniques [19]. 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 m*M* 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 [19] and Ampli*Taq* Gold polymerase (Perkin-Elmer Applied Biosystems). Each amplification contained 1× PCR Buffer II (Roche Molecular Systems), 4 m*M* $MgCl_2$, 200 μM each dCTP, dGTP, and dATP, 600 μM dUTP, 7.5 U of Ampli*Taq* Gold, 1 μM PGMY09 primer blend, 1 μM PGMY11, 25 n*M* B_PC04, 25 n*M* B_GH20, and 5 μL of the template DNA abstract. For the 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 (ATCC CaSki cell line) were run to control for contamination and accuracy. The samples were amplified using the Perkin-Elmer GeneAmp PCR System 9700. 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 a 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 [20] on all samples that were positive according to PCR. 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, which detected 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 con-

trols for sample adequacy and PCR amplification. Poor or no β-globin amplification indicated a 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.

All reagents were provided by Roche Molecular Systems. The following HPV types were detected: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51–59, 66, 68, 73, 82, 83, and 84. The PCR products were labeled with biotin, denatured, and added to the probe strip in a hybridization buffer. After the strips were washed, streptavidin–horseradish peroxidase was added, to facilitate the detection of the various HPV types. After a final wash, the 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.

Intercooled Stata 7.0 for Windows 2000 (Stata) statistical application was used for all statistical analyses. Differences in the distributions of categorical variables were ascertained using Pearson's χ^2 tests of significance.

RESULTS

Approximately 69% of the 645 patients who were approached elected to participate, resulting in the enrollment of 443 participants. Men who declined participation most commonly cited time constraints and lack of interest as reasons for not participating. Compared with nonparticipants, study participants were more likely to be of "other" race/ethnicity, a category that included Native Americans, Pacific Islanders, and men of Asian or South Asian descent ($P = .011$) and were more likely to fall in the age category 25–29 years (compared with 18–24 years and ⩾30 years; $P = .043$). Study participants also had a significantly higher prevalence of several STDs than did nonparticipants, including NGU ($P = .000$), chlamydia ($P = .045$), genital warts ($P = .000$), and genital herpes ($P = .003$) (data not shown).

Prevalence results are based on HPV analysis of penile skin swabs (samples collected from the coronal sulcus and glans penis) from 393 participants. Urethral samples yielded adequate DNA in only 65.6% of participants, and our laboratory was unable to develop an adequate methodology for the detection of HPV in urine. Therefore, only penile skin HPV results are presented in the present article.

Of the 443 participants, HPV DNA analysis was performed for 393 (88.7%). For 50 men (11.3%), penile skin samples either were not available for testing ($n = 7$) or did not yield enough DNA for analysis ($n = 43$). Overall, 90.1% of 436 samples analyzed yielded sufficient DNA for HPV detection. Men whose specimens did not yield adequate DNA for analysis were significantly more likely to be white ($P = .029$) and circumcised ($P = .029$) than were men with adequate penile skin specimens. Adequate samples were obtained from 86.6% (232/268) of circumcised men and 93.3% (112/120) of uncircumcised men.

Table 1. Human papillomavirus (HPV) infection: association with sociodemographic factors.

Characteristic	No. (%) of subjects	HPV positive,[a] %
Age, years		
18–24	125 (31.9)	33.6
25–29	96 (24.5)	19.8
30–39	88 (22.5)	25.0
40–70	83 (21.2)	32.5
Race/ethnicity[b]		
White, non-Hispanic	164 (42.1)	21.3
Hispanic	153 (39.2)	32.7
Other	73 (18.7)	34.3
Country of birth		
United States	292 (75.1)	26.0
Mexico	61 (15.7)	39.3
Other	36 (9.3)	27.8
Marital status		
Married	37 (9.5)	24.3
Single	246 (63.1)	26.8
Cohabitating	35 (9.0)	34.3
Divorced/separated/widowed	72 (18.5)	31.9
Educational level[b]		
High school not completed	96 (24.6)	33.3
High school completed	97 (24.9)	37.1
Some college	109 (28.0)	19.3
College or above	88 (22.6)	23.9
Currently employed		
No	95 (24.4)	32.6
Yes	294 (75.6)	26.9
Ever in jail		
No	202 (52.2)	28.7
Yes	185 (47.8)	27.6
Sexual orientation		
Heterosexual	353 (90.3)	28.1
Homosexual	26 (6.7)	19.2
Bisexual	12 (3.1)	50.0

NOTE. The no. of subjects varies because of missing data.

[a] HPV DNA positive on penile skin swab.

[b] $P < .05$ for differences in distribution of HPV by Pearson χ^2 tests of significance.

Men who enrolled in the study reported that the primary reason for their clinic visit was a complaint of genitourinary symptoms (e.g., penile discharge or burning with urination) (49.6%), "exposure to a partner with an STD" (18.4%), or "just wanting to get checked" (37.9%). (Percentages add to >100% because some participants cited >1 reason for their clinic visit.)

Selected sociodemographic characteristics of participants, along with prevalence of infection, are shown in table 1. The mean ($\pm$SD) age of participants was 30.9 ($\pm$10.3) years, with a range of 18–70 years. The majority of participants were either white (42.1%) or Hispanic (39.2%), with 75.1% born in the United States and 15.7% born in Mexico. More than 47% of participants reported having spent at least 1 night in jail. Most study participants were single (63.1%), 75.6% were currently employed, and 90.3% were heterosexual. Neither age nor marital status was significantly associated with HPV infection in men. Men who reported bisexual behaviors had a higher prevalence of HPV (50%) than did men who reported having sex with only women or only men, but this difference was not statistically significant.

Statistically significant associations with HPV infection were observed with ethnicity and educational level. Participants of Hispanic or "other" nonwhite race/ethnicity and those reporting fewer years of education had higher HPV prevalence.

Table 2 shows the prevalence of genital HPV in penile skin swabs, with the classification of HPV into oncogenic, nononcogenic, and unclassified types. One hundred eleven (28.2%) of the men participating in the study tested positive for any type of HPV, whereas 24 subjects (6.1%) were positive for multiple types. Among the subjects who tested positive for multiple HPV types, the majority were infected with both oncogenic and nononcogenic strains. Overall, the most prevalent types of HPV were the nononcogenic types 6 (3.8%), 53 (3.1%), and 84 (2.8%). Among oncogenic types, the most common were 16 (2.3%), 52 (1.8%), and 59 (2.3%). In addition, there were 23 men with unclassified types of HPV (5.9%).

Table 3 presents the association between prevalent HPV infection and other concurrent STDs, as detected by clinicians at the clinic. NGU was the most commonly diagnosed STD, with a prevalence of 47.5%. The only significant association was found between HPV infection and the current presence of genital warts ($P = .013$). A fairly strong correlation was noted between the detection of HPV types 6 or 11 and the presence of genital warts. Of the 15 men positive for HPV type 6, 7 (46.9%) had genital warts at their clinic visit. Of the 2 men positive for HPV 11, both had genital warts (100%). Overall, 9 (52.9%) of 17 men with types 6 or 11 HPV had genital warts at their clinic visit. Conversely, of 37 men diagnosed with genital warts, 24.3% tested positive for HPV type 6 or 11, whereas 21.6% tested positive for other HPV types.

DISCUSSION

Ours is the first study to examine penile HPV prevalence among US men using PCR and is one of few studies to report on HPV type distribution in men. Our sampling method, which involved the collection of cells from the skin of the glans penis and coronal sulcus, is a noninvasive method that enables easy sampling of male participants. The DNA yield from these penile samples, at 90.1%, falls within the range reported in other studies of HPV in men [10, 15]. However, we were unable to obtain adequate DNA from most urethral and urine samples.

Other authors have reported adequate DNA yields with urethral sampling, which suggests that our mechanism of specimen collection or processing was flawed. Ninety-nine percent of par-

Table 2. Prevalence of human papillomavirus (HPV) types.

HPV type	No. (%) of subjects
Any HPV type	111 (28.2)
Oncogenic	47 (12.0)
16	9 (2.3)
18	4 (1.0)
31	3 (0.8)
33	3 (0.8)
35	1 (0.3)
39	5 (1.3)
45	3 (0.8)
51	3 (0.8)
52	7 (1.8)
56	1 (0.3)
58	3 (0.8)
59	9 (2.3)
68	1 (0.3)
Nononcogenic	58 (14.8)
6	15 (3.8)
11	2 (0.5)
26	0 (0.0)
40	1 (0.3)
42	5 (1.3)
53	12 (3.1)
54	5 (1.3)
55	4 (1.0)
57	0 (0.0)
66	4 (1.0)
73	0 (0.0)
82	6 (1.5)
83	3 (0.8)
84	11 (2.8)
Unclassified	23 (5.9)
Multiple	24 (6.1)

Table 3. Male human papillomavirus (HPV) infection concurrent with other sexually transmitted diseases (STDs).

STD	No. (%) of subjects	HPV positive,[a] %
Nongonococcal urethritis		
No	196 (52.8)	25.5
Yes	175 (47.2)	31.4
Gonorrhea		
No	325 (91.0)	27.7
Yes	32 (9.0)	31.3
Chlamydia trachomatis		
No	324 (92.3)	27.2
Yes	27 (7.7)	33.3
Herpes		
No	343 (96.9)	31.5
Yes	11 (3.1)	27.3
Warts[b]		
No	347 (90.4)	26.5
Yes	37 (9.6)	46.0
Folliculitis		
No	331 (93.8)	31.1
Yes	22 (6.2)	36.4

NOTE. No. of subjects varies because of missing data.
[a] HPV DNA positive on penile skin swab.
[b] $P = .013$.

ticipants described here provided urethral specimens. A prewetted urethral swab was inserted 1 cm into the urethral meatus and rotated 360°, consistent with methods described in previous studies of male HPV that described sampling the "distal meatus" [15, 21, 22]. However, a study of HPV in Mexican men published after our study was under way described a urethral sampling technique in which the swab was inserted 2 cm into the meatus; those authors reported a high yield of human DNA from the urethra [10]. Our low β-globin yield may also have been the result of inadequate laboratory techniques for DNA extraction.

We were unable to obtain adequate DNA samples from participants' urine samples, many of which were cloudy with infectious or inflammatory material. Our laboratory did not fully develop the methodology to adequately assess HPV DNA in urine. Most attempts at using urine for HPV testing in men have been unsuccessful [10, 23, 24]. The majority of studies that have successfully detected HPV in urine have been conducted in women [25–28], in whom cervicovaginal shedding likely increases the presence of cellular material in urine.

The HPV prevalence in this ethnically mixed population, 28.2% (95% confidence interval, 23.8–33.0), falls within the range reported by investigators in other countries. In STD clinics in Greenland and Denmark, HPV prevalence among men was 45%–49%, whereas, in a Swedish STD clinic, HPV prevalence was 13% [12, 29, 30]. In an international case-control study that investigated the HPV prevalence among the male partners of women with and without cervical cancer, International Agency for Research on Cancer (IARC) investigators found penile HPV DNA in 3.5%–39.0% of the control husbands and 12.0%–36.0% of husbands of the case patients, with prevalence varying significantly by country [15, 16]. Among military men, HPV DNA detection ranged from 16.5% in Finnish military conscripts to 36% among Danish military recruits [11, 14]. Most recently, penile HPV was detected in 42.7% of sexually active college students and industrial workers in Mexico [10]. Comparison across these male HPV studies is difficult, however, because study populations, sampling methods, and molecular techniques have varied widely.

Our data show that nononcogenic HPV types occur more frequently in men than do oncogenic types. These data differ greatly from reports of HPV infection in women, in whom oncogenic HPV types, specifically type 16, are more common [31–34]. In some previous studies on male HPV, the majority of men who tested positive for HPV had oncogenic subtypes [10, 12, 30], but, in the IARC 5-nation study, unspecified HPV types were most common [16]. In our population, in which we probed for 27 HPV types, the prevalence of unknown HPV types was 5.9%.

Infection with multiple HPV types occurred in 6.1% of the participants. Among women, multiple HPV infection has commonly been reported and, in some studies, has been found to be a risk factor for HPV persistence or for cervical neoplasia [1, 35]. To determine the significance of multiple HPV types in men, prospective studies of men are needed.

In the present study, as in others [10, 13, 16, 36], age was not associated with HPV prevalence among men. In women, HPV infection declines with increasing age, with a smaller postmenopausal peak observed in some populations [37–40]. In contrast, we did not identify a linear association between age and HPV infection in our study. It has been suggested that age-associated changes in HPV prevalence among women are linked to the development of immune responses to HPV. The lack of age association we observed in the present study of men likely reflects a sex-based variation in immune response to the virus. Men have been shown to promulgate less of a humoral response to HPV than do women [41–43].

Genital warts were the only STD to be associated with penile HPV detection. Only 46% of men with genital warts tested positive for HPV, demonstrating a low sensitivity for this method of collection. However, condylomatous areas of the penis were not specifically sampled. Some false-negative results are expected, because HPV DNA may be present within condyloma but not in skin on other areas of the penis. Concordance between genital warts and the presence of HPV on the penis likely would have

been higher if study clinicians had been instructed to swab any warts identified on the glans or shaft.

The use of penile skin swabs to detect HPV infection raises the question of whether detection of HPV DNA indicates true HPV infection. Because the sampling technique involved collection of superficial cells, some of the HPV detected may originate from cellular material, such as dried secretions, on the surface of the penis. Men with inadequate DNA in skin samples were more likely to be circumcised, which suggests that the presence of cellular material from secretions under the foreskin facilitated DNA-based testing in uncircumcised participants.

Our study is limited, in that the STD clinic population participating in the study was a higher risk group than the general male population; therefore, results cannot be generalized to other US men. Nor can our results be generalized to the general population with STDs, because our participants had a significantly higher prevalence of several STDs than did nonparticipants. As a cross-sectional study, we were unable to provide information about the persistence of HPV infection or about the relationship between HPV and the onset of disease in men or their sex partners.

Nonetheless, the present article is the first to document the prevalence of penile HPV among US men, as determined by a sensitive type-specific PCR. Our population was ethnically and socioeconomically diverse and included men of all ages. Results reveal that HPV is highly prevalent in this population—a finding that has implications for public health and cancer prevention. Both prevalence and natural history data are needed to ensure the success of HPV vaccine efforts and other future public health endeavors; more research, especially prospective cohort studies of HPV in men, is needed.

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