External Genital Human Papillomavirus Prevalence and Associated Factors Among Heterosexual Men on 5 Continents

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Background. We examined the baseline prevalence of penile, scrotal, and perineal/perianal human papillomavirus (HPV) in heterosexual men (HM). We also evaluated baseline characteristics of HM to assess factors associated with prevalent HPV detection.

Methods. We tested serum samples from 3463 HM aged 16–24 years with 1–5 lifetime female sexual partners for antibodies to HPV 6, 11, 16, and 18. We collected baseline swab specimens for the detection of DNA of HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 from 3 areas: penile, scrotal, and perineal/perianal. Risk factors for prevalent HPV DNA detection were evaluated.

Results. The prevalence of any tested HPV type was 18.7% at the penis, 13.1% at the scrotum, 7.9% at the perineal/perianal region, and 21.0% at any site. Having >3 lifetime female sexual partners had the greatest impact on HPV prevalence: odds ratio (OR) 3.2 (95% confidence interval (CI) 2.1–4.9) for HPV 6, 11, 16, and 18; and OR 4.5 (95% CI 3.3–6.1) for all HPV types tested. HPV DNA detection was highest in Africa. Neither condom usage nor circumcision was associated with HPV DNA prevalence.

Conclusion. Genital-HPV DNA detection is common in young, sexually active HM. We found HPV to be most prevalent in African men and least prevalent in men from the Asia-Pacific region. Increased numbers of sexual partners was an important risk factor for HPV DNA prevalence.

Infection with human papillomavirus (HPV) is common worldwide and contributes to disease in both men and women[1, 2]. HPV infection may be asymptomatic or benign (forming anogenital warts) or may manifest as various anogenital dysplastic lesions or cancers. Most commonly, these lesions appear on the cervix, vagina, or vulva in women; or the anus, penis, or oropharynx in men [2]. Because most HPV infections in men are asymptomatic and men are not routinely screened for HPV, heterosexual men (like women) may act as reservoirs of HPV infection, resulting in continued transmission of both high-risk and low-risk HPV types to women[3–5].

Now that prophylactic HPV vaccines are known to be efficacious in men [6], understanding the factors

associated with HPV acquisition in men is critical to the development of comprehensive preventative programs to control HPV infection [7, 8]. Few studies have examined the epidemiology and risk factors associated with HPV infection in heterosexual men (HM). Recent studies have enrolled specific cohorts of men from North America [9, 10], South America [9–11], or economically developed countries in Europe[12–15]. None has applied a standardized protocol across countries in multiple continents. Factors shown to increase the risk of anogenital HPV infection in men include the number of lifetime sexual partners [16, 17] and immune status, particularly as it relates to HIV status [18, 19]. Some studies have shown male circumcision to be protective, and associated it with a reduced risk of penile HPV infection and cancer [3, 20, 21].

We describe the prevalence of HPV DNA detection in heterosexual male subjects enrolled in a large international phase III clinical trial of quadrivalent HPV vaccine from multiple countries on 5 continents. We also evaluate the baseline characteristics of subjects to evaluate the factors associated with prevalent HPV DNA detection in this population.

METHODS

Subjects

Protocol 020 was designed to definitively evaluate the efficacy of quadrivalent HPV (types 6, 11, 16, and 18) L1 virus like particle vaccine in young men (Gardasil; Merck). The study enrolled 3463 HM aged 16–24 years and 602 men who have sex with men (MSM) aged 16–27 years from 71 sites in 18 countries in Africa, Asia-Pacific, Europe, Latin America, and North America. Although both HM and MSM were enrolled in the trial, only the HM data are presented here. Subjects were eligible if they were aged 16–24 years, if they were healthy, and if they agreed to refrain from sexual activity for 2 calendar days before scheduled visits (to avoid contamination with HPV DNA deposited during intercourse). Subjects also had to be nonvirgins who had from 1 to 5 female lifetime sexual partners (LSPs). Men with a history of, or current, clinically detectable anogenital warts or genital lesions suggesting other sexually transmitted diseases were excluded.

All enrolled subjects underwent external genital lesion inspection and swabbing for HPV DNA detection at baseline. If a lesion observed at baseline was judged by the investigator to be possibly HPV related or of unknown etiology, the subject was excluded from the study. Subjects with known immunodeficiency or HIV infection were also excluded. Subjects with HIV infection detected after enrollment were not excluded from the study.

Study Measurements

Subjects had serum samples collected for HIV and syphilis testing at baseline. Serum samples were also tested for the presence of antibodies to HPV 6, 11, 16, and 18, as described elsewhere [22]. Baseline external genital lesion inspection was conducted using a magnifying glass. Baseline swab specimens were collected separately from the penile, scrotal, and perineal/perianal areas with a wetted Dacron swab (anal canal swabs were not taken from HM subjects). All specimens were tested for the β-globin gene (positive control), and adequate samples were tested for a panel of 14 HPV types (HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), including the 4 HPV vaccine types. Swab, biopsy, and serum samples were tested at Merck Research Laboratories (Wayne, PA) and Pharmaceutical Product Development (PPD, Wilmington, DE).

HPV Testing

Multiplex polymerase chain reaction (PCR) based on real-time fluorescent PCR was used for the detection of HPV types 6, 11, 16, and 18 in swab samples and thin-section microtomy specimens [23–25]. This assay allowed for simultaneous detection of 3 gene products (L1, E6, and E7) for a given HPV type. DNA was purified using a QIAmp DNA kit (Qiagen, Germantown, MD). HPV type-specific primers based on published L1, E6, and E7 sequences were used to amplify specific portions of these genes simultaneously. Specific amplicons were detected in real time by fluorescently labeled oligonucleotide probes. The gene-specific oligonucleotide probes were each assigned a different fluorescent label. Similar PCR assays were used to ascertain HPV types not included in the vaccine in biopsy specimens using multiplex PCR for types 31, 45, 52, and 58, or biplex PCR for types 33, 35, 51, 52, 56, 58, and 59.

Specimens for serology were shipped on dry ice, and batched and stored at –20°C until testing. Anti-HPV 6, 11, 16, and 18 levels were measured using an experimental competitive Luminex-based immunoassay (cLIA) [26, 27]. Viruslike particles (VLP) derived from yeast were coupled to 4 distinct fluorescent cLIA microspheres. Antibody titers were determined in a competitive assay wherein type-specific phycoerythrin-labeled neutralizing monoclonal antibodies (mAbs) compete with the serum being tested to bind to conformationally sensitive neutralizing epitopes on the VLP. Fluorescent readings against a standardized curve provided the concentration of the specific anti-HPV being tested for in milli-Merck units per milliliter (mMU/mL).

Statistical Analysis

Univariate analysis was conducted to examine the association between putative risk factors and the detection of HPV DNA (for either HPV 6, 11, 16, and 18, or all 14 HPV types studied) on day 1 for initial assessment. Univariate analysis was performed to examine the individual association between the detection of HPV DNA on day 1 with geographic area of residence, age, tobacco use, condom use, age at first sexual intercourse with a female partner, number of LSPs, number of new partners in the past 6 months, and circumcision history. We also included these factors in multivariate logistic regression models, and

Table 1. Selected baseline characteristics and sexual history among heterosexual men

Subject characteristics	Subjects (N = 3463)
Age (years)	
Mean (Standard deviation)	20.2 (1.8)
Median	20
Range	15 to 24
Race/Ethnicity	
Asian	373 (10.8)
Black	763 (22.0)
Hispanic American	686 (19.8)
Native American	3 (.1)
White	1068 (30.8)
Other	570 (16.5)
Region	
Africa	538 (15.5)
Asia-Pacific	272 (7.9)
Europe	374 (10.8)
Latin America	1443 (41.7)
North America	836 (24.1)
Smoking Status	
Current smoker	1236 (35.7)
Ex-smoker	237 (6.8)
Never smoked	1960 (56.6)
Missing or unknown	30 (.9)
Circumcision	
Yes	1276 (36.8)
No	2185 (63.1)
Missing or unknown	2 (.1)
Subjects with female sexual history data at enrollment	3458
All virgins*	4 (.1)
Nonvirgins	3454 (99.9)
Age at first sexual intercourse among nonvirgins (years)	
Mean	16.7
Standard deviation	2.0
Median	17
Range	5–23
Lifetime number of female sexual partners at enrollment among non-virgins	
1	803 (23.2)
2	715 (20.7)
3	789 (22.8)
4	631 (18.2)
5	514 (14.9)
>5	2 (.1)
Lifetime condom usage with female sexual partners at enrollment among nonvirgins	
Unknown	2 (.1)
Never	344 (9.9)
Less than half the time	713 (20.6)
More than half the time	1123 (32.5)
Always	1272 (36.8)

Table 1. (Continued)

Subject characteristics	Subjects (N = 3463)
Number of new female sexual partners in the 6 mon prior to study start among nonvirgins	
Unknown	1 (.0)
0	2063 (59.7)
1	1121 (32.4)
2	222 (6.4)
3	42 (1.2)
4	5 (.1)
Condom usage with female sexual partners in the 6 mon prior to study start among nonvirgins	
Unknown	73 (2.1)
Never	955 (27.6)
Less than 50%	518 (15.0)
More than 50%	692 (20.0)
Always	1216 (35.2)

NOTE. * Virgins are defined as subjects who have had no vaginal intercourse with a female partner. Two virginal subjects were enrolled despite the study requirements of at least 1 lifetime sexual partner.

Percentages calculated as 100*(n/number of subjects with female sexual history data at enrollment).

Percentage calculated as 100*(n/N)

N = Number of subjects randomized.

adjusted for them accordingly. In the logistic regression models, odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated for the risks associated with the detection of HPV DNA on day 1, in relation to each of the possible risk factors included in the models, with adjustment for other possible risk factors in the models.

RESULTS

The mean age of participants was 20.2 years (range, 15–24 years). The majority of subjects were white (30.8%) (Table 1), and most were recruited from Latin America (41.7%) and North America (24.1%). More than half of the men in this cohort had never smoked (56.6%); 35.7% and 6.8% were current smokers and past smokers, respectively. The majority (63.1%) of men were not circumcised. The number of men reporting a history of non-HPV anogenital or sexually transmitted infections (STIs) was 2.1%. The most common STI reported was chlamydia (14 [.4%]), followed by gonorrhea (9 [.3%]), genital herpes (7 [.2%]), and hepatitis B (4 [.1%]). At enrollment, 23.2% of nonvirgins (n = 803) had 1 female LSP, and 43.5% (n = 1504) had either 2 or 3 LSPs. Overall, 36.8% of men reported a history of always using a condom, and 32.5% reported using a condom more than half the time; 9.9% of participants reported never using a condom. Although most study participants had 0 or 1 new sexual partner in the immediate 6 months prior to the study

start (59.7% and 32.4%, respectively), more risky sexual behavior was reflected in the assessment of condom use in the 6 months prior to the study start. At enrollment, 27.6% of men reported never using condoms, and only 20.0% reported using condoms more than half the time in the immediate 6 months prior to study start.

At enrollment, 171 subjects (5.0%) had serum antibodies to HPV 6, 11, 16, and/or 18 (Table 2A). Serum antibodies to HPV types 6 and 16 were most common, detected in 95 subjects (2.8%) and 51 subjects (1.5%), respectively. Serologic positivity to more than 1 tested HPV type (HPV 6, 11, 16, or 18) was uncommon, occurring in .3% of subjects ($n = 13$) (Table 2B).

The prevalence of HPV 6, 11, 16 or 18 DNA detection in any external genital swab sample was 8.8% ($n = 276$) (Table 2A). No subject was positive for all HPV-vaccine types 6, 11, 16, and 18 DNA, but detection of 1, 2, or 3 of these types was seen in 7.9% ($n = 249$), .8% ($n = 24$) and .1% ($n = 3$) subjects, respectively (Table 2B). HPV 6, 11, 16, and/or 18 DNA detection was most prevalent in swabs from the penis (7.0% [$n = 223$]), followed, by swab specimens from the scrotum (5.1% [$n = 156$]) and perineal/perianal area (2.9% [$n = 75$]). The combined prevalence of DNA detection for any tested HPV type (HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and/or 59) was 21.2% ($n = 664$) (Table 2A). Of the types tested, HPV 51, 16, and 56 were the most commonly detected (3.9% [$n = 124$], 3.8% [$n = 121$] and 3.6% [$n = 113$], respectively).

Table 3 presents the HPV DNA prevalence of individually tested HPV types in all HM subjects enrolled (with data available), stratified by geographic region. Although the study did not enroll equal numbers of subjects from all the regions, it is clear that the highest prevalence of HPV was seen in Africa and the lowest in the Asia-Pacific region. This is exemplified by the observed HPV 16 prevalence data. Whereas in the entire study HPV DNA prevalence was 3.8%, HPV 16 prevalence in Africa and the Asia-Pacific region were 4.4% and .8%, respectively. HPV 39 had the highest observed prevalence of any tested individual HPV type in the Asia-Pacific region (1.9%). The prevalence of HPV 6 in Africa was 5.6%, significantly higher than the combined study HPV 6 prevalence of 3.4%.

In multivariate analyses in which HPV DNA detection at any external genital site was considered, age was not associated with risk of being DNA positive for HPV 6, 11, 16, 18, or any tested HPV types (Table 4). Compared with men who reported always using condoms, men reporting condom-use rates of less than 50% experienced significant increased risk for both the 4 vaccine HPV types (OR, 1.5; 95% CI, 1.1–2.0) and all 14 HPV types tested (OR, 1.7; 95% CI, 1.4–2.2). Lifetime number of female sex partners was significantly associated with baseline HPV DNA prevalence. Compared with that of men who reported having 0 or 1 LSP; the OR for prevalent detection of HPV DNA in external genital swabs in men who reported having 2 LSPs was 1.6 (95% CI, 1.0–2.8) for HPV 6, 11, 16, and/or 18; and 2.2 (95% CI, 1.5–3.1) for any tested HPV type. The OR was greater for men with 3–6 female LSPs; 2.6 (95% CI, 1.7–4.2) for HPV 6, 11, 16, and/or 18; and 3.8 (95% CI, 2.8–5.3) for any tested HPV type. In addition, when compared with subjects from the Asia-Pacific region, subjects in all other regions except Europe were significantly more likely to have prevalent HPV DNA detected (both HPV-vaccine types and any HPV type). Residents of Africa had the highest risk for HPV detection with vaccine HPV types (OR, 5.19; 95% CI, 2.2–12.4), and for any HPV type (OR, 3.7; 95% CI., 2.3–6.1).

DISCUSSION

This study provides important data on prevalent HPV DNA detection and associated risk factors from a large, international cohort of young heterosexual men. Standardized clinical, sampling, and laboratory methods allow direct comparison of HPV DNA prevalence and risk factor data across the geographic regions examined. The data indicate that HPV is prevalent among young, heterosexual men and is significantly associated with their sexual behavior and the region in which they live.

In the current study, we observed a lower prevalence of HPV than did other published reports of male genital HPV. In the current study, only 14 HPV types were assessed, with only 2 of these belonging to the group of HPV types considered nononcogenic. Moreover, the study included only men with 1—to 5 sexual partners reported over their lifetimes. Previous studies have shown that infection with nononcogenic HPV types may account for about 50% of all HPV infections observed at the external genital skin in men[9]. When 37 HPV types are considered, the prevalence of any HPV infection was 30% at enrollment among men in a prospective follow-up study of slightly older (aged 18–44 years) HM from the United States[16]. A higher prevalence of HPV infection was also evident in another study conducted in men from the United States, Mexico, and Brazil. In that study, the age-specific HPV prevalence of any type (37 genotypes and unclassified infections) in young men (aged 20–24 years) was 61.3%, 58.5%, and 78.6% in each respective country [10]. Similarly, data from a large cohort of African men showed a high prevalence of HPV infection (38.1–37.1%) in men enrolled from Rakai [28]. The prevalence of HPV 6, 11, 16, and/or 18 DNA was also low (8.8%) in the current study, compared with 14.7% in other international cohorts [9], likely because men with >5 LSPs were excluded from the current trial.

We documented an almost 10% prevalence of HPV close to the anal canal in a group of subjects reporting prior sex exclusively with women. The presence of HPV DNA in this area could point to digital transmission either from a sex partner or by autoinoculation, as has been hypothesized by others [17, 29]. We did not test the intra-anal canal for HPV DNA in HM, but the relatively high prevalence of HPV close to the anus suggests the anal canal or perianal skin may act as a reservoir for HPV DNA in

Table 2. Summary of anogenital HPV serology and DNA status (A) and multiple HPV exposure (B) at enrollment among heterosexual men

A. HPV DNA positivity and seropositivity

| | HPV DNA positivity | | | | |
| | External genital anatomic sites | | | Any external genital site | Serum |
	Penile	Scrotal	Perineal/perianal		
HPV positivity					
Any tested type*	–	–	–	664 (21.2%)	171 (5.0%)
HPV 6/11/16/18	223 (7.0%)	156 (5.1%)	75 (2.9%)	276 (8.8%)	171 (5.0%)
HPV 16/18	159 (5.0%)	97 (3.2%)	49 (1.9%)	177 (5.6%)	66 (1.9%)
HPV 16	109 (3.4%)	60 (2.0%)	27 (1.0%)	121 (3.8%)	51 (1.5%)
HPV 18	58 (1.8%)	40 (1.3%)	23 (.9%)	64 (2.0%)	17 (.5%)
HPV 6/11	110 (3.4%)	69 (2.3%)	28 (1.1%)	118 (3.7%)	113 (3.3%)
HPV 6	98 (3.1%)	63 (2.1%)	26 (1.0%)	106 (3.4%)	95 (2.8%)
HPV 11	15 (.5%)	7 (.2%)	2 (.1%)	15 (.5%)	24 (.7%)
HPV 31	50 (1.6%)	30 (1.0%)	14 (.5%)	53 (1.7%)	–
HPV 33	21 (.7%)	10 (.3%)	10 (.4%)	22 (.7%)	–
HPV 35	31 (1.0%)	16 (.5%)	8 (.3%)	31 (1.0%)	–
HPV 39	64 (2.0%)	33 (1.1%)	14 (.5%)	70 (2.2%)	–
HPV 45	39 (1.2%)	28 (.9%)	16 (.6%)	44 (1.4%)	–
HPV 51	108 (3.4%)	72 (2.4%)	35 (1.3%)	124 (3.9%)	–
HPV 52	93 (2.9%)	49 (1.6%)	20 (.8%)	97 (3.1%)	–
HPV 56	99 (3.1%)	54 (1.8%)	24 (.9%)	113 (3.6%)	–
HPV 58	48 (1.5%)	31 (1.0%)	20 (.8%)	55 (1.7%)	–
HPV 59	69 (2.2%)	37 (1.2%)	23 (.9%)	79 (2.5%)	–

NOTE. * HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 for DNA detection, HPV 6, 11, 16, and 18 for serology.

B. Multiple HPV positivity (both DNA positivity and seropositivity)

| | HPV DNA positivity | | | | |
| | External genital anatomic sites | | | Any external genital site | Serum |
	Penile	Scrotal	Perineal/perianal		
Number of types detected (any tested types)*					
0	2597 (81.3%)	2661 (86.9%)	2419 (92.0%)	2503 (79.0%)	–
1	398 (12.5%)	305 (10.0%)	167 (6.4%)	449 (14.2%)	–
2	131 (4.1%)	72 (2.4%)	33 (1.3%)	139 (4.4%)	–
3	38 (1.2%)	14 (.5%)	7 (.3%)	45 (1.4%)	–
≥4	30 (.9%)	9 (.3%)	2 (.1%)	31 (1.0%)	–
Number of types detected (HPV 6, 11, 16, 18)					
0	2934 (92.2%)	2892 (94.9%)	2528 (97.1%)	2875 (91.2%)	3280 (95.0%)
1	223 (7.0%)	143 (4.7%)	72 (2.8%)	249 (7.9%)	158 (4.6%)
2	24 (.8%)	12 (.4%)	3 (.1%)	24 (.8%)	11 (.3%)
3	3 (.1%)	1 (.0%)	–	3 (.1%)	1 (.0%)
4	–	–	–	–	1 (.0%)

NOTE. * HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59

HM. Detection of HPV DNA at anatomic sites clearly not covered by condoms may account for the lack of a reduction in HPV prevalence among those using condoms in the current study.

As previous studies showed [16, 17], the number of LSPs had a strong influence on external genital HPV prevalence in men. After adjusting for sexual history, geographic region was

Table 3. HPV prevalence at any external genital site among HM enrolled from 5 different continents

HPV Type	Entire Study (N=4065) n/m	% (%95 CI)	Africa (N=538) n/m	% (95% CI)	Asia/Pacific (N=361) n/m	% (%95 CI)	Europe (N=496) n/m	% (95% CI)	Latin America (N=1575) n/m	% (%95 CI)	North America (N=1095) n/m	% (95% CI)
6	106/3146	3.4 (2.77-4.06)	29/518	5.6 (3.78-7.94)	2/263	0.8 (.09-2.72)	4/354	1.1 (.31-2.87)	43/1299	3.3 (2.41-4.43)	28/712	3.9 (2.63-5.63)
11	15/3143	0.5 (.27-.79)	5/518	1.0 (.31-2.24)	1/263	0.4 (.01-2.10)	0/354	-	6/1298	0.5 (.17-1.00)	3/710	0.4 (.09-1.23)
16	121/3146	3.8 (3.20-4.58)	23/518	4.4 (2.84-6.59)	2/263	0.8 (.09-2.72)	13/353	3.7 (1.98-6.22)	51/1301	3.9 (2.93-5.12)	32/711	4.5 (3.10-6.29)
18	64/3142	2.0 (1.57-2.59)	23/518	4.4 (2.84-6.59)	2/263	0.8 (.09-2.72)	9/354	2.5 (1.17-4.77)	17/1299	1.3 (.76-2.09)	13/708	1.8 (.98-3.12)
31	53/3131	1.7 (1.27-2.21)	7/513	1.4 (.55-2.79)	0/260	-	6/354	1.7 (.62-3.65)	30/1299	2.3 (1.56-3.28)	10/705	1.4 (.68-2.59)
33	22/3133	0.7 (.44-1.06)	8/515	1.6 (.67-3.04)	1/260	0.4 (.01-2.12)	6/354	1.7 (.62-3.65)	6/1298	0.5 (.17-1.00)	1/706	0.1 (.00-.79)
35	31/3133	1.0 (.67-1.40)	16/515	3.1 (1.79-5.00)	1/260	0.4 (.01-2.12)	1/354	0.3 (.01-1.56)	9/1298	0.7 (.32-1.31)	4/706	0.6 (.15-1.44)
39	70/3134	2.2 (1.75-2.81)	11/514	2.1 (1.07-3.80)	5/260	1.9 (.63-4.43)	2/354	0.6 (.07-2.03)	29/1300	2.2 (1.50-3.19)	23/706	3.3 (2.08-4.85)
45	44/3132	1.4 (1.02-1.88)	15/514	2.9 (1.64-4.77)	0/260	-	3/354	0.8 (.18-2.46)	17/1297	1.3 (.77-2.09)	9/707	1.3 (.58-2.40)
51	124/3131	4.0 (3.30-4.70)	22/513	4.3 (2.71-6.42)	3/260	1.2 (.24-3.33)	15/354	4.2 (2.39-6.89)	51/1299	3.9 (2.94-5.13)	33/705	4.7 (3.24-6.51)
52	97/3131	3.1 (2.52-3.77)	27/516	5.2 (3.48-7.52)	4/260	1.5 (.42-3.89)	10/354	2.8 (1.36-5.13)	46/1297	3.5 (2.61-4.70)	10/704	1.4 (.68-2.60)
56	113/3127	3.6 (2.99-4.33)	21/514	4.1 (2.55-6.18)	4/260	1.5 (.42-3.89)	5/353	1.4 (.46-3.27)	58/1296	4.5 (3.42-5.75)	25/704	3.6 (2.31-5.20)
58	55/3133	1.8 (1.33-2.28)	18/515	3.5 (2.08-5.47)	2/260	0.8 (.09-2.75)	2/354	0.6 (.07-2.03)	26/1298	2.0 (1.31-2.92)	7/706	1.0 (.40-2.03)
59	79/3137	2.5 (2.00-3.13)	17/515	3.3 (1.93-5.23)	2/260	0.8 (.09-2.75)	7/354	2.0 (.80-4.03)	35/1301	2.7 (1.88-3.72)	18/707	2.5 (1.52-3.99)

NOTE. N = number of subjects randomized; n = number of subjects positive for HPV type at baseline; m = number of subjects with available data for HPV type.

significantly associated with HPV detection where men in Asia and the Pacific Islands have the lowest risk of HPV detection. This is consistent both with low prevalence of genital HPV reported in studies conducted in Korea and China, and with international studies that have found reduced risk of HPV infection among men reporting a race of Asian or Pacific Islander [9]. The reasons for regional differences may be due to other factors, such as partners' sexual histories, which were not captured in this study.

Male circumcision has been shown to protect men from acquiring various STIs, including HIV [30, 31], HSV-2, and HPV [28]. The current study was unable to confirm those findings for HPV, as male circumcision was not associated with HPV DNA detection. Similarly, there was no association between non-HPV anogenital infections (chlamydia, gonorrhea, genital herpes, and hepatitis B infection) and HPV detection in this study, although this may have been because the overall prevalence of non-HPV STI was very low (2.1%).

A limitation to the current study is its exclusion of men with more than 5 LSPs and men with a history of, or current, clinically detectable anogenital warts or genital lesions suggesting other sexually transmitted diseases. Additionally, the influence of genital hygiene was not considered and may play a role in HPV prevalence and transmission. Moreover, this clinical-trial population was not specifically selected to be representative of all men, and so it may not be. Factors for selection include recruitment and enrollment strategies, as well as decisions made by trial investigators who may prefer to enroll those with a higher probability of completing the trial. Moreover, we did not test for intra-anal HPV prevalence and tested for only 14 HPV types; therefore, this study may have missed additional prevalent HPV types. These limitations are likely to result in an underestimate of the HPV prevalence in relation to other studies, and may explain the discrepancy between these HM HPV-prevalence data and other data in the published literature.

In conclusion, this study shows that there is a substantial global burden of HPV in young, heterosexual men and that the prevalence of HPV in men differs across geographical regions.

Acknowledgments

Table 4. Risk factors for prevalent detection of HPV DNA in external genital swabs at enrollment in heterosexual men

Risk factor	Prevalent detection of HPV 6/11/16/18 DNA in external genital swabs		Prevalent detection of any tested HPV DNA in external genital swabs*	
	% (no. with infection/ no. of subjects)	Odds Ratio* (95% CI)	% (no. with infection/ no. of subjects)	Odds Ratio* (95% CI)
Age				
15-20	7.9% (139/1758)	.9 (.7-1.1)	19.4% (341/1758)	0.91 (.76-1.10)
21-27	9.7% (137/1409)	1.0	22.9% (323/1409)	1.0
Tobacco use on day 1				
Never used	8.1% (148/1822)	1.0	19.5% (356/1822)	1.0
Ex-users	9.0% (18/200)	1.0 (.6-1.8)	19.0% (38/200)	.9 (.6-1.3)
Current user	9.6% (110/1145)	1.1 (0.8-1.4)	23.6% (270/1145)	1.1 (.9-1.3)
Sexual history on day 1				
Age at 1st intercourse				
< 15	13.5% (53/392)	.7 (.5-.9)	30.6% (120/392)	.7 (.6-.9)
15-19	8.2% (207/2521)	.8 (.4-1.5)	20.2% (510/2521)	.8 (.5-1.2)
⩾ 20	6.4% (16/249)	1.0	13.7% (34/249)	1.0
Lifetime sex partners				
⩽ 1	3.4% (25/734)	1.0	7.4% (54/734)	1.0
2	6.6% (43/647)	1.6 (1.0-2.8)	16.7% (108/647)	2.2 (1.5-3.1)
3-6	11.7% (208/1781)	2.6 (1.7-4.2)	28.2% (502/1781)	3.8 (2.8-5.3)
Frequency of lifetime condom use				
Never	4.1% (13/317)	0.8 (0.4-1.5)	15.1% (48/317)	1.4 (1.0-2.1)
Less than half of the time	9.2% (59/643)	1.3 (0.9-2.0)	23.8% (153/643)	1.7 (1.3-2.2)
More than half of the time	11.5% (118/1028)	1.5 (1.1-2.0)	26.8% (276/1028)	1.7 (1.4-2.2)
Always	7.3% (86/1173)	1.0	15.9% (187/1173)	1.0
Circumcision				
No	8.0% (161/2015)	1.0	20.7% (417/2015)	1.0
Yes	10.0% (115/1152)	1.1 (0.8-1.5)	21.4% (247/1152)	0.9 (0.7-1.2)
Region				
Asia-Pacific	2.3% (6/263)	1.0	8.4% (22/263)	1.0
Africa	13.5% (70/520)	5.2 (2.2-12.4)	29.2% (152/520)	3.7 (2.3-6.1)
Europe	6.8% (24/354)	2.4 (1.0-6.2)	17.8% (63/354)	1.6 (1.0-2.8)
Latin America	8.2% (108/1312)	3.1 (1.3-7.2)	21.3% (280/1312)	2.2 (1.4-3.5)
North America	9.5% (68/718)	3.4 (1.4-8.1)	20.5% (147/718)	2.2 (1.4-3.7)

NOTE. *HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. Multivariate logistic regression model was adjusted for geographic area of residence, age, tobacco use, condom use, age at first sexual intercourse with a male partner, number of lifetime sexual partners, number of new partners in the past 6 months, and circumcision history.

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