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Circumcision and Sexual Behavior: Factors Independently Associated with Human Papillomavirus (HPV) Detection among Men in The *HIM* Study

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Abstract

There is growing interest in understanding HPV infection and related disease among men. To date there have been numerous studies reporting HPV DNA prevalence among men from several different countries, however, few have incorporated multivariable analyses to determine factors independently associated with male HPV detection. The purpose of this study was to assess the factors independently associated with HPV detection in men ages 18–70 years residing in Brazil (n=343), Mexico (n=312), and the United States (US) (n=333). In samples combined from the coronal sulcus, glans penis, shaft, and scrotum we evaluated factors associated with any, oncogenic, and non-oncogenic HPV infections. In multivariable analyses, detection of any HPV infection was significantly associated with reported race of Asian/Pacific Islander, lifetime and recent number of sexual partners, and having sex in the past three months. Oncogenic HPV detection was independently associated with lifetime and recent number of sexual partners, and having sex in the past three months. Non-Oncogenic HPV infection was independently associated with lifetime number of sexual partners. Circumcision, assessed by clinical examination, was associated with reduced risk of HPV detection across all categories of HPV evaluated. HPV detection in men in the current study was strongly related to sexual behavior and circumcision status. Interventions such as circumcision may provide a low cost method to reduce HPV infection.

Keywords

HPV prevalence; males; international

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INTRODUCTION

There is growing interest in understanding HPV infection and related disease among men. To date there have been numerous studies reporting HPV DNA prevalence among men from several different countries [1]. However, only seven studies have incorporated multivariable analyses to determine factors independently associated with male HPV detection [2–8]. In these studies detection of HPV in men has been independently associated with sexual behavior [3, 4, 7], circumcision status [2, 5–8], condom use [4, 7], and smoking status [2, 4]. In one report [3], young age (18–24 vs. ≥35) was associated with increased risk of HPV detection. Each of these studies sampled from different anatomic sites and specimens, utilized different sampling methods, and utilized different instruments for assessing behaviors, making direct comparisons of study results difficult. Hence the need for a study that utilizes a standardized protocol for interviewing and sampling men, as well as for the laboratory detection of HPV among men from diverse communities.

The purpose of this study was to assess the factors independently associated with HPV detection in men ages 18–70 years residing in Brazil, Mexico, and the US. This international study utilized a common protocol for HPV sampling, molecular detection of HPV, and assessment of behavioral factors across a broad age range of men.

MATERIALS AND METHODS

Men enrolled from 2005 through 2006 in the on-going HPV in Men (*HIM*) Study were included in this analysis. Participants were recruited from Sao Paulo, Brazil, Cuernavaca, Mexico, and Tampa, Florida, US. To encourage compliance with follow-up, men received compensation for their participation. Prior to study initiation, the Human Subjects Committees of the University of South Florida, the CRT-DST/Aids, Brazil, the Instituto Mexicano del Seguro Social, and the Instituto de Salud Publica de Mexico approved all study procedures. A full description of the *HIM Study* and procedures has been previously reported [9].

Population

The study population consisted of men who met the following eligibility criteria: (a) ages 18–70 years; (b) residents of three sites - Sao Paulo, Brazil, or the state of Morelos, Mexico, or central Florida, US; (c) reported no prior diagnosis of penile or anal cancers; (d) had never been diagnosed with genital or anal warts; (e) reported no symptoms of an sexually transmitted infection (STI) or treatment for an STI; (f) not participating in an HPV vaccine study; (g) no history of HIV or AIDS; (h) no history of imprisonment, homelessness, or drug treatment during the past 6 months; and (i) willingness to comply with ten scheduled visits every six months for four years with no plans to relocate in four years.

Men were recruited from different population sources to increase access to a broader age range of men, sexual behaviors, and HPV risk: general population, universities, and organized health care systems (Mexico only). To ensure adequate sample size across the age span, men were recruited in three age strata: 1–30, 31–44, and 45–70 years. In Brazil, men were recruited from the general population at a facility for uro-genital care (Centro de Referencia e Tratamento de Doencas Sexualmente Transmissiveis e AIDS). Men were recruited in Brazil from several different population sources including a public health STI facility. The underlying population was those men attending the clinic who primarily sought information regarding STI testing. Upon initial clinic triage of patients to the facility only men who were asymptomatic and at low risk for STIs were referred to *HIM Study* personnel for potential participation in the *HIM Study*. Of these, only those men who met all study eligibility criteria were offered study participation. In addition, the spouses and partners of

women participating in a large cohort study of the natural history of HPV infection conducted in Sao Paulo were also recruited. Recruitment in Brazil also occurred through general media advertising. At the Cuernavaca, Mexico site, the underlying population was employees and beneficiaries of the Instituto Mexicano de Seguro Social and officials of the Mexican army that are permanently assigned to this geographic area. In the US the underlying population was from the University of South Florida and the greater Tampa metropolitan area. Flyers and posters were distributed throughout the campus and community, and educational presentations were administered on a monthly basis. In addition, men from the broader Tampa Bay, FL community were recruited through the mail and media using brochures and flyers as well as advertisements in local and university papers.All men at each study site were disease free at the time of enrollment.

Study Protocol

The *HIM Study* protocol includes a pre-enrollment run-in visit, a baseline (enrollment) visit, and eight additional visits after enrollment scheduled six months apart. For this analysis, the first 1158 men who completed both the run-in and baseline visits were included.

Risk Factor Questionnaire—An extensive sexual history and health questionnaire given at enrollment assessed socio-demographic characteristics, sexual and contraceptive history, condom use practices, alcohol and tobacco use, and history of abnormal pap smears in female partners. The questionnaire required ~20 minutes to complete and was administered using Computer-Assisted Self-Interviewing (CASI).

HPV Penile and Scrotal Sampling—To maximize sampling and prevent fraying of applicators, three different pre-wetted Dacron applicators were utilized to sample the external genitalia of participants, and later combined to form a single sample for the detection of HPV. This method has been previously shown to maximize HPV detection among men and to result in reproducible genital HPV detection in men [10, 11]. The study clinician at each site first swept 360° around the coronal sulcus and then another 360° around the glans penis and placed this swab into a collection vial containing 450μl of Sample Transport Media (STM, Digene Corp. Gaithersburg, MD). If a man is uncircumcised the foreskin is retracted and the area under the foreskin is also sampled. This swab is placed into the glans penis/coronal sulcus collection vial. A second swab was used to sample the entire skin surface of the shaft of the penis and placed into a vial with 450μl STM. If the man is uncircumcised the outside of the foreskin is sampled and combined with the shaft sample. A third swab was utilized for scrotum sampling and stored in 450μl STM. All HPV samples were stored at −70° C until PCR analyses and genotyping were conducted. Prior to DNA extraction, the three samples obtained from the glans penis/coronal sulcus, the shaft and the scrotum were combined to produce a single clinical specimen representing the genital area. 200μl of this combined specimen was used for DNA extraction.

HPV Analyses—HPV testing of collected material was conducted using polymerase chain reaction (PCR) for amplification of a fragment of the HPV L1 gene [12]. DNA extraction was performed in 200μl of clinical material using the QIAamp DNA Mini Kit (QIAGEN, Valencia, CA) according to the instructions of the manufacturer. DNA was eluted with 100μl of nuclease-free water at 60° C, and stored at 4°C. PCR was performed within 36 hours post-extraction.

Specimens were tested for the presence of HPV by amplifying 50μl of the DNA extracts using the Linear Array HPV Genotyping Test following the instructions of the manufacturer (Roche Diagnostics, Indianapolis, IN). For every PCR plate a negative control (non-template control) and two positive controls (CaSki and C33A Cells DNA) were run to control for

possible contamination and accuracy of HPV and β-globin detection, respectively. In addition to internal controls, kit positive and kit negative controls were run on every PCR plate. Samples were amplified as directed by the linear array protocol and PCR products were analyzed by agarose gel electrophoresis (AGE) using 2% agarose gels to visualize a 450bp band corresponding to HPV amplification prior to genotyping. The purpose of this pre-linear array step is to identify samples that may harbor HPV infections other than the 37 HPV types included in the genotyping assay. Samples that amplified a 450bp band but did not hybridize any of the 37 type specific probes in the linear array were classified as "X-type" or "unclassified".

HPV genotyping was conducted using the Linear Array assay on all samples. This detection method utilizes the PGMY 09/11 consensus PCR products labeled with biotin to detect 37 HPV types. The HPV genotype strip contains 39 probe lines, detecting 37 individual HPV genotypes and two concentrations of the β-globin control probe (Roche Diagnostics, Indianapolis, IN).

β-globin was detected in 99.8% of samples tested (1156/1158). Samples that amplified a 450 bp band corresponding to HPV on AGE but did not hybridize with a specific HPV type on genotype were categorized as unclassified infections (n=170). As it is unclear whether these are HPV infections or co-amplification of other genes [9], we do not include these in risk analyses. The following 13 HPV types were categorized as oncogenic: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 [13]. The other (non-oncogenic) types detected with the Linear Array assay were 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39, and CP6108.

Statistical Analysis

We examined three classifications of HPV infection. A participant was considered positive for 'Any type HPV' if he tested positive for any HPV genotype. The category of "Oncogenic HPV" included those who were positive for only oncogenic genotypes along with those who were positive for both oncogenic and non-oncogenic types. The "Non-oncogenic HPV" category consisted of those participants who only tested positive for non-oncogenic HPV genotypes. Of the 1158 men who provided samples, 50.5% of men were positive for any HPV, 29.8% for oncogenic HPV, 20.7% for non-oncogenic HPV, and 14.7% unclassified infections [9]. Men with unclassified infections were removed from the current analyses resulting in a final sample size for this analysis of 988 men. The control group consisted of those participants who had no detectable HPV (n=403).

Potential risk factors for detection of the three groups of HPV infection were examined using multiple logistic regression models to calculate odds ratios with 95% confidence intervals (95% CI). Those factors with significant associations ($p<0.05$) were then modeled to determine the independent risk factors for HPV detection. Adjusted odds ratios were calculated from multivariable logistic regression models using the backward selection procedure. For the ordered categorical risk factors, a trend test was conducted using the score Chi squared test for linear trend of odds. Participants were given the option of refusing to answer each of the questions on the Web-based survey and these refusals were treated as missing observations.

RESULTS

The mean age of the study population was 32.4 (SD 10.8) with 46.1% reporting white race, 33.6% mixed, and 42.7% Hispanic (Table 1). Approximately 40% of men were circumcised. Median lifetime number of sexual partners was 7, 65.6% reported having one or more female partner in the past 3 months and 52.8% reported some condom use in the past 3

months. Approximately 9% of participants reported sex with a male partner in the past 3 months.

In univariate analyses age was inconsistently associated with HPV detection (Table 2). Risk of any HPV type infection was reduced among those of mixed race (OR 0.74) and Asian/Pacific Islanders (OR 0.18). In addition, significantly reduced risk of oncogenic HPV detection was observed among Asian/Pacific Islanders (OR 0.32) and non-oncogenic detection among those of mixed race (OR 0.64). Increased detection of HPV was observed among men from Brazil for any HPV type (OR 2.12), oncogenic HPV (OR 2.18), and non-oncogenic infections (OR 2.04). Similarly marital status of divorced/separated was consistently associated with increased risk of any HPV type infections (OR 2.63), oncogenic infections (OR 2.27), and non-oncogenic infections (OR 3.23) compared to single and never married men.

Reduced risk of HPV detection was significantly associated with older age at first intercourse (OR 0.38 for any HPV infections among men ages 23–42 compared to ≤13 years), no sex in the past three months (OR 0.30 and 0.44 for oncogenic and any type HPV infections respectively), and having a steady partner (OR 0.55–0.58 for non-oncogenic, any HPV type, and oncogenic HPV) (Table 3) in analyses adjusted for age and country of residence. Significantly higher risk of HPV detection was associated with increasing numbers of lifetime female sexual partners (OR 6.96–9.01 for non-oncogenic, any HPV, and oncogenic HPV infections among men reporting ≥50 partners compared to one partner), number of female partners in the past three months (OR 2.31–3.43 for non-oncogenic, any HPV, oncogenic HPV infections among men reporting 3–30 partners compared to no female partners), number of new female partners in the past three months (OR 2.64–2.85 for non-oncogenic, oncogenic and any HPV type among men with ≥3 new female partners compared to no new partner), and anal sex with either a male or female (OR 1.40–1.45 for any HPV, and oncogenic HPV infections).

In analyses adjusting for age and country of residence men who reported no prior STI history were at significantly reduced risk of HPV detection (OR 0.47–0.55 for oncogenic, any HPV and non-oncogenic HPV infections) (Table 4). Significantly elevated risk was observed for men with current Herpes infection (OR 1.57–1.82 for any type and non-oncogenic HPV infections), and those reporting ever having a partner with genital warts (OR 2.18–2.27 for non-oncogenic, any HPV, and oncogenic HPV infections) or abnormal Pap smears (OR 1.57–2.00 for non-oncogenic, any HPV, and oncogenic HPV infections).

Table 5 presents the final multivariable models of factors independently associated with any HPV type from the analyses above, oncogenic and non-oncogenic HPV infections. In general there was consistency in the factors associated with each of the three categories of HPV infection examined, whereby circumcision, lifetime number of female partners and number of female partners in the past three months were associated with all three categories of HPV infection. Any HPV type infection was significantly and independently associated with Asian/Pacific Islander race (OR 0.19, 95% CI 0.06–0.57), circumcision (OR 0.70, 95% CI 0.52–0.94), increasing number of lifetime female partners (OR 5.81, 95% CI 2.49–13.59 for 50–1000 partners compared to one partner), two female partners in the past 3 months compared to none (OR 2.09, 95% CI 1.25–3.49), and having no sex in the past 3 months (OR 0.42, 95% CI 0.22–0.81). Oncogenic HPV infection was significantly and independently associated with circumcision (OR 0.70, 95% CI 0.50–0.97), increasing number of lifetime female partners (OR 4.86, 95% CI 1.78–13.24 for 50–1000 partners compared to one partner), having any female partners in the past 3 months compared to none (OR 1.54, 95% CI 1.02–2.30), having no sex in the past 3 months (OR 0.19, 95% CI 0.06–0.58), and age (OR 0.50, 95% CI 0.25–0.97 for ages 45–70 compared with 18–24). Non-

oncogenic HPV infection was significantly and independently associated with mixed race (OR 0.58, 95% CI 0.38–0.90 compared to white), circumcision (OR 0.63, 95% CI 0.42–0.93), increasing number of lifetime female partners (OR 5.58, 95% CI 1.98–15.72 for 50–1000 partners compared to one partner), and two female partners in the past 3 months compared to none (OR 1.91, 95% CI 1.03–3.53).

DISCUSSION

This is the first study to examine risk factors for HPV infection in a multi-national sample of men residing in the Americas using a standard protocol for specimen collection, processing, HPV detection, and risk factor assessment. Circumcision was consistently associated with a significantly reduced risk of any, oncogenic, and non-oncogenic HPV infections, and lifetime number of female partners and number of female partners in the past three months were consistently associated with increased risk of the three categories of HPV infection. Country of residence, Brazil, Mexico, and the US, was not independently associated with HPV detection in men. Although in univariate analyses men residing in Brazil appeared to have a higher prevalence of infection, this association failed to reach statistical significance after accounting for sexual behavior. Unlike what has been observed among women we found no evidence for an association between age and HPV detection in men.

We observed strong independent associations between sexual behavior and HPV detection in men, similar to what we and others have previously observed among men [1–4, 14]. Interestingly, in both univariate and multivariable analyses risk estimates did not increase linearly with exposure, but rather appeared to increase, then plateau with higher levels of exposure. For example, the odds ratios for any HPV increased with increasing number of lifetime sexual partners peaking at an odds ratio of 6.65 among men who reported 20–49 partners. Among men who reported 50–1000 partners the odds ratio was 5.81. This pattern of association was observed for any HPV type infection and oncogenic infections and across all three categories of HPV infection when number of female partners in the past three months was also examined. Other studies have observed a similar plateau in risk for HPV infection among men with increasing number of lifetime sexual partners [3], and number of sex-worker partners [2]. This plateau in risk despite increasing exposure may be due to several different factors including reporting bias and influence of immunity. Men may be overestimating the number of partners they have had in their lifetime, which would result in attenuation to the null with the higher categories of sexual partners. Alternatively, the plateau may be biologically driven such that men with higher exposure are more likely to develop an antibody response and perhaps higher titer levels. However, the few published studies reporting HPV antibody status among men suggest that a smaller proportion of men than women are HPV antibody positive, despite a high HPV DNA prevalence among men [15]. In addition, men appear to have lower titer levels than do females [1]. Unfortunately, there are no published data to estimate the extent of sexual (or HPV) exposure needed to stimulate an antibody response in men.

In this study, recent sexual behavior was significantly associated with HPV detection across categories of HPV infection. Despite apparent differences in the magnitude of these associations across HPV categories the overlapping confidence intervals suggest that the relationship between recent sexual activity and HPV detection of all HPV categories of infection were similar. In our previous study among US men the association between recent sexual partners and HPV detection was limited to non-oncogenic infections. However, the risk estimates for any HPV type and oncogenic infections were similar. The lack of statistical significance for these other categories of HPV infection was likely due to the relatively smaller sample size of the US study (n=463) [4]. Similar to the findings in the

current study, Svare and colleagues [3], observed a significant association between number of sexual partners in the past three months and HPV detection.

In the current study men of Asian/Pacific Islander race were significantly less likely to have any HPV DNA detected, and as no cases of non-oncogenic HPV infection were detected in this group the risk for these infections could not be estimated. These findings are consistent with previous reports of low HPV DNA prevalence among male and female university students in Korea [16]. As we accounted for sexual behavior in the current study, differences in sexual behavior by race do not explain these findings. Several reports have demonstrated that variants in innate immune genes are associated with HPV infection and natural history among women [17]. More studies are needed among men and women to better understand the genetic underpinnings of these observations among certain Asian populations.

In this multi-national study where approximately 60% of study participants were un-circumcised we found circumcision to be associated with a significantly reduced risk of any, oncogenic, and non-oncogenic HPV DNA detection (odds ratio of 0.63–0.70). These findings are similar to what we previously reported for a mixed ethnic group of men residing in Tucson, AZ [7], and similar to what others have reported in studies conducted in Spain, Colombia, Brazil, The Philippines and Thailand [8], Mexico [2], and Denmark [3]. Two of the six published studies that evaluated circumcision as a factor in multivariable analyses did not find an association. In the study of Shin and colleagues [16], conducted among university students residing in Korea, a non-significant increased risk of HPV detection (OR1.8) was observed among circumcised men. However, only 12% of study participants were un-circumcised. Our recently published study of US men [4], found no association with HPV infection, however, we used a combined estimate of HPV detected at the anal canal and external genital epithelium including the scrotum, and only included a small proportion of men who were un-circumcised (16%). In further analyses we demonstrated significant reduction in risk of HPV detection specific at the urethral site (OR 0.19) and at the coronal sulcus/glans penis (OR 0.61), and a marginally significant reduction in risk at the shaft (OR 0.55; CI 0.29, 1.03).[18] In a similar study, Hernandez and colleagues [6], found a significant reduction in risk of HPV detection at the coronal sulcus/glans penis. Finally, Castellsague and colleagues [8] demonstrated a profound and significant reduction in invasive cervical cancer risk among women whose male partners were circumcised [8]. Altogether, results from the current study add to the growing body of literature suggesting a protective association between male circumcision and HPV detection. Given that the current study utilized a combined measure of external genital HPV infection, it is possible that the association between circumcision and infection is stronger than reported here.

Few published reports of HPV DNA prevalence among men included men with a broad age range [2, 3, 7, 8, 14, 19, 20], with which to examine age and HPV detection associations. Only two studies, among men residing in Denmark [3] and Mexico [2], observed significant associations, both inverse, between HPV prevalence and age. Similar to the majority of publications reporting HPV prevalence among men we found no evidence of an independent association between HPV DNA detection and age in this multi-national sample of men ages 18–70 years. The significance of these findings for HPV transmission to female sexual partners needs to be addressed in prospective female-male HPV transmission studies.

The cross-sectional nature of the current study allowed us to estimate the association between participant characteristics and sexual behaviors but precludes us from drawing conclusions regarding causality. Only a prospectively designed study can assess the effects of certain characteristics on the incidence and clearance of HPV infections. For example, it is possible that male circumcision influences HPV DNA detection by altering rates of HPV persistence, such as reported by Kjaer and colleagues [21], or duration of HPV infections, as

reported from a US study.[22] Misclassification of reported sexual behaviors may have resulted from participants' discomfort in disclosing accurate information. However, Metzger and colleagues [23], demonstrated that application of sensitive sexual history questionnaires using a computer assisted self-administered approach, such as used in this study, resulted in higher levels of sexual behavior disclosure. We have taken care to reduce misclassification of HPV test results. To this end we have tested and demonstrated high levels of specimen and HPV testing reproducibility [11]. The participants included in the present study were men who were willing and able to comply with all study requirements and procedures, and therefore are a select population that may not represent the underlying population of men from the communities in which they reside. Therefore, caution should be taken in generalizing the results of this study to all men.

In conclusion HPV detection in men in the current study was strongly related to sexual behavior and circumcision status. Interventions such as circumcision may provide a low cost method to reduce HPV infection; however, the cultural acceptability of this procedure may limit the broad utilization of circumcision in certain countries. Prevention of HPV among men through vaccination may also be a viable public health intervention should vaccine efficacy be demonstrated.

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REFERENCES

1. Dunne EF, Nielson CM, Stone KM, Markowitz LE, Giuliano AR. Prevalence of HPV infection among men: A systematic review of the literature. The Journal of infectious diseases. 2006; 194:1044–1057. [PubMed: 16991079]
2. Vaccarella S, Lazcano-Ponce E, Castro-Garduno JA, Cruz-Valdez A, Diaz V, Schiavon R, Hernandez P, Kornegay JR, Hernandez-Avila M, Franceschi S. Prevalence and determinants of human papillomavirus infection in men attending vasectomy clinics in Mexico. International journal of cancer. 2006; 119:1934–1939.
3. Svare EI, Kjaer SK, Worm AM, Osterlind A, Meijer CJ, van den Brule AJ. 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. [PubMed: 12238658]
4. Nielson CM, Harris RB, Dunne EF, Abrahamsen M, Papenfuss MR, Flores R, Markowitz LE, Giuliano AR. Risk factors for anogenital human papillomavirus infection in men. The Journal of infectious diseases. 2007; 196:1137–1145. [PubMed: 17955431]
5. Lajous M, Mueller N, Cruz-Valdez A, Aguilar LV, Franceschi S, Hernandez-Avila M, Lazcano-Ponce E. Determinants of prevalence, acquisition, and persistence of human papillomavirus in healthy Mexican military men. Cancer Epidemiol Biomarkers Prev. 2005; 14:1710–1716. [PubMed: 16030106]

6. Hernandez BY, Wilkens LR, Zhu X, McDuffie K, Thompson P, Shvetsov YB, Ning L, Goodman MT. Circumcision and Human Papillomavirus Infection in Men: A Site-Specific Comparison. The Journal of infectious diseases. 2008
7. Baldwin SB, Wallace DR, Papenfuss MR, Abrahamsen M, Vaught LC, Giuliano AR. Condom use and other factors affecting penile human papillomavirus detection in men attending a sexually transmitted disease clinic. Sex Transm Dis. 2004; 31:601–607. [PubMed: 15388997]
8. Castellsague X, Bosch FX, Munoz N, Meijer CJ, Shah KV, de Sanjose S, Eluf-Neto J, Ngelangel CA, Chichareon S, Smith JS, Herrero R, Moreno V, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med. 2002; 346:1105–1112. [PubMed: 11948269]
9. Giuliano AR, Lazcano-Ponce E, Villa L, Flores R, Salmeron J, Lee J-H, Papenfuss M, Abrahamsen M, Jolles E, Nielson CM, Baggio ML, Silva R, et al. The Human Papillomavirus Infection in Men (HIM) Study: HPV Prevalence and Type-Distribution among Men Residing in Brazil, Mexico, and the U.S. Cancer Epidemiol Biomarkers Prev. 2008 In Press.
10. Giuliano AR, Nielson CM, Flores R, Dunne EF, Abrahamsen M, Papenfuss MR, Markowitz LE, Smith D, Harris RB. The optimal anatomic sites for sampling heterosexual men for human papillomavirus (HPV) detection: the HPV detection in men study. The Journal of infectious diseases. 2007; 196:1146–1152. [PubMed: 17955432]
11. Flores R, Abalos AT, Nielson CM, Abrahamsen M, Harris RB, Giuliano AR. Reliability of sample collection and laboratory testing for HPV Detection in Men. J Virol Methods. 2008; 149:136–143. [PubMed: 18279976]
12. Gravitt PE, Peyton CL, Alessi TQ, Wheeler CM, Coutlee F, Hildesheim A, Schiffman MH, Scott DR, Apple RJ. Improved amplification of genital human papillomaviruses. Journal of Clinical Microbiology. 2000; 38:357–361. [PubMed: 10618116]
13. Cogliano V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F. Cancer WIAfRo. Carcinogenicity of human papillomaviruses. Lancet Oncology. 2005; 6:204. [PubMed: 15830458]
14. Franceschi S, Castellsague X, Dal Maso L, Smith JS, Plummer M, Ngelangel C, Chichareon S, Eluf-Neto J, Shah KV, Snijders PJ, Meijer CJ, Bosch FX, et al. Prevalence and determinants of human papillomavirus genital infection in men. British journal of cancer. 2002; 86:705–711. [PubMed: 11875730]
15. Kreimer AR, Alberg AJ, Viscidi R, Gillison ML. Gender differences in sexual biomarkers and behaviors associated with human papillomavirus-16, -18, and -33 seroprevalence. Sex Transm Dis. 2004; 31:247–256. [PubMed: 15028941]
16. Shin HR, Franceschi S, Vaccarella S, Roh JW, Ju YH, Oh JK, Kong HJ, Rha SH, Jung SI, Kim JI, Jung KY, van Doorn LJ, et al. Prevalence and determinants of genital infection with papillomavirus, in female and male university students in Busan, South Korea. The Journal of infectious diseases. 2004; 190:468–476. [PubMed: 15243918]
17. Vol. 90: Human Papillomaviruses. International Agency for Research on Cancer; 2007. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.
18. Nielson C, Schiaffino M, Dunne EF, Salemi JL, Giuliano AR. Associations between male anogenital HPV infection and circumcision by anatomic site sampled and lifetime number of female partners. The Journal of infectious diseases. 2008 In press.
19. Castellsague X, Ghaffari A, Daniel RW, Bosch FX, Munoz N, Shah KV. Prevalence of penile human papillomavirus DNA in husbands of women with and without cervical neoplasia: a study in Spain and Colombia. The Journal of infectious diseases. 1997; 176:353–361. [PubMed: 9237700]
20. van der Snoek EM, Niesters HG, Mulder PG, van Doornum GJ, Osterhaus AD, van der Meijden WI. Human papillomavirus infection in men who have sex with men participating in a Dutch gay-cohort study. Sex Transm Dis. 2003; 30:639–644. [PubMed: 12897686]
21. Kjaer SK, Munk C, Winther JF, Jorgensen HO, Meijer CJ, van den Brule AJ. Acquisition and persistence of human papillomavirus infection in younger men: a prospective follow-up study among Danish soldiers. Cancer Epidemiol Biomarkers Prev. 2005; 14:1528–1533. [PubMed: 15941967]

22. Lu B, Wu Y, Nielson CM, Flores R, Abrahamsen ME, Papenfuss MR, Harris RB, Giuliano AR. Factors Associated with Acquisition and Clearance of Human Papillomavirus Infection among a Cohort of U.S. Men: A Prospective Study. The Journal of infectious diseases. 2008 In press.

23. Metzger DS, Koblin B, Turner C, Navaline H, Valenti F, Holte S, Gross M, Sheon A, Miller H, Cooley P, Seage GR 3rd. Randomized controlled trial of audio computer-assisted self-interviewing: utility and acceptability in longitudinal studies. HIVNET Vaccine Preparedness Study Protocol Team. Am J Epidemiol. 2000; 152:99–106. [PubMed: 10909945]

Table 1

Socio-demographic characteristics of study participants (N=988)

	N	%
Age		
Mean (SD)		32.4 (10.8)
Median(range)		30 (18–70)
18–24	313	31.7
25–29	163	16.5
30–34	149	15.1
35–39	134	13.6
40–44	128	13.0
45–70	101	10.2
Country of residence		
US	333	33.7
Brazil	343	34.7
Mexico	312	31.6
Race		
White	447	46.1
Black	155	16.0
Asian/Pacific Islander	22	2.3
American Indian/Alaska Native	20	2.1
Mixed	326	33.6
Ethnicity		
Hispanic	415	42.7
Non-Hispanic	557	57.3
Circumcision (clinician-reported)		
No	590	59.7
Yes (includes partial)	398	40.3
Lifetime number of sex partners		
Mean (SD)		18.3 (57.7)
Median (range)		7 (1–2000)
Number of female partners in past 3 months		
None	328	34.4
1	389	40.8
2	129	13.5
3–30	108	11.3
Condom use with vaginal or anal sex in past 3 months		
Never	368	40.8
Sometimes	292	32.4
Always	184	20.4
No vaginal or anal sex in the past 3 months	58	6.4
Had sex in the past 3 months		

	N	%
Yes	882	89.3
No	106	10.7
Number of new female partners in the past 3 months		
None	650	69.6
1	192	20.6
2	49	5.3
3–30	43	4.6
Number of male partners in the past 3 months		
None	817	91.1
1	34	3.8
2	12	1.3
3–4	34	3.8

Table 2

Associations between socio-demographic characteristics and HPV infection with any, oncogenic or non-oncogenic types at baseline.

	Any type HPV+ (n=998)			Oncogenic HPV+ (n=748)			Nononcogenic HPV+ (n=643)		
	%	OR	95% CI	%	OR	95% CI	%	OR	95% CI
Age									
18–24	53.0	1.00		42.1	1.00		28.6	1.00	
25–29	62.0	1.44	0.98–2.12	49.2	1.33	0.89–2.05	39.8	**1.65**	**1.01–2.71**
30–34	67.1	**1.81**	**1.20–2.72**	59.2	**1.99**	**1.28–3.09**	37.2	1.47	0.85–2.55
35–39	59.7	1.31	0.87–1.98	43.2	1.04	0.65–1.68	41.9	**1.80**	**1.08–3.00**
40–44	62.5	1.48	0.97–2.25	44.8	1.12	0.68–1.62	46.1	**2.13**	**1.27–3.56**
45–70	57.4	1.19	0.76–1.88	38.6	0.86	0.50–1.48	41.9	**1.80**	**1.03–3.12**
Race									
White	62.2	1.00		47.7	1.00		42.3	1.00	
Black	61.3	0.96	0.66–1.40	48.7	1.04	0.69–1.59	38.8	0.86	0.54–1.38
Asian/Pacific Islander	22.7	**0.18**	**0.06–0.49**	22.7	**0.32**	**0.12–0.90**	0.0	--	--
American Indian/Alaska Native	85.0	3.44	0.99–16.93	72.7	2.93	0.76–11.23	75.0	**4.09**	**1.08–15.41**
Mixed	54.9	**0.74**	**0.55–0.99**	42.8	0.82	0.59–1.14	31.9	**0.64**	**0.44–0.92**
Country of Residence									
US	51.7	1.00		37.6	1.00		31.8	1.00	
Brazil	69.4	**2.12**	**1.55–2.91**	56.8	**2.18**	**1.53–3.12**	48.8	**2.04**	**1.39–3.01**
Mexico	56.1	1.20	0.88–1.63	44.5	1.33	0.93–1.90	32.2	1.02	0.68–1.52
Marital Status									
Single, never married	55.0	1.00		43.3	1.00		31.3	1.00	
Married	58.7	1.17	0.87–1.55	45.3	1.08	0.78–1.50	37.2	1.30	0.90–1.88
Cohabitating	66.4	**1.62**	**1.06–2.47**	50.6	1.34	0.83–2.17	48.7	**2.08**	**1.25–3.46**
Divorced/Separated	76.3	**2.63**	**1.52–4.55**	63.5	**2.27**	**1.24–4.15**	59.6	**3.23**	**1.72–6.08**

Note-. OR: odds ratio. CI: confidence interval.

Bolded factors represent a significant effect (p<0.05)

Table 3

Association between sexual and health behaviors and HPV infection with any, onocogenic or non-oncogenic types at baseline.

	Any type HPV+ (n=998)			Oncogenic HPV+ (n=748)			Nononcogenic HPV+ (n=643)		
	%	OR*	95% CI*	%	OR*	95% CI*	%	OR*	95% CI*
Current Smoker									
Yes	64.0	1.00		52.6	1.00		40.0	1.00	
No	57.9	0.71	0.55–1.02	44.1	**0.70**	**0.49–0.99**	36.9	0.83	0.56–1.23
Circumcision (clinician-reported)									
No	62.2	1.00		49.2	1.00		40.4	1.00	
Yes	54.8	1.03	0.72–1.47	41.8	1.08	0.75–1.60	33.1	0.87	0.56–1.35
Age at first sexual intercourse									
13 or less	68.9	1.00		54.8	1.00		50.0	1.00	
14–17	64.5	0.91	0.56–1.49	51.8	0.97	0.55–1.69	42.5	0.84	0.47–1.51
18–22	51.8	**0.57**	**0.34–0.97**	39.6	0.62	0.34–1.14	29.6	**0.52**	**0.27–0.98**
23–42	45.0	**0.38**	**0.17–0.84**	31.3	0.41	0.16–1.05	26.7	0.37	0.14–1.00
Never	48.8	**0.45**	**0.24–0.86**	34.4	**0.44**	**0.21–0.92**	30.0	0.49	0.22–1.06
p-trend			***p*<0.001**			***p*<0.001**			***p*=0.004**
Lifetime number of female partners									
1	30.2	1.00		18.5	1.00		17.0	1.00	
2–9	51.1	**2.54**	**1.42–4.54**	37.7	**2.82**	**1.35–5.87**	30.5	**2.23**	**1.03–4.81**
10–19	70.4	**5.58**	**2.90–10.71**	61.9	**7.47**	**3.34–16.45**	43.0	**3.35**	**1.42–7.89**
20–49	78.1	**8.71**	**4.42–17.16**	67.9	**10.64**	**4.65–24.33**	59.3	**6.83**	**2.88–16.23**
>=50	74.6	**8.15**	**3.49–19.04**	60.0	**9.01**	**3.26–24.92**	58.8	**6.96**	**2.46–19.67**
p-trend			***p*<0.001**			***p*<0.001**			***p*<0.001**
Had sex with male or female in the past 3 months									
Yes	61.5	1.00		49.0	1.00		38.7	1.00	
No	40.6	**0.44**	**0.29–0.66**	22.2	**0.30**	**0.17–0.53**	28.4	0.64	0.39–1.06
Number of female partners in the past 3 months									
None	49.4	1.00		33.1	1.00		32.5	1.00	
1	58.4	**1.63**	**1.20–2.22**	46.0	**1.94**	**1.35–2.79**	35.5	1.24	0.85–1.84
2	76.0	**3.40**	**2.13–5.42**	66.3	**3.85**	**2.30–6.46**	54.4	**2.72**	**1.51–4.78**

	Any type HPV+ (n=998)			Oncogenic HPV+ (n=748)			Nononcogenic HPV+ (n=643)		
	%	OR*	95% CI*	%	OR*	95% CI*	%	OR*	95% CI*
3–30	75.0	**3.05**	**1.85–5.02**	64.9	**3.43**	**1.97–5.99**	53.5	**2.31**	**1.27–4.21**
p- trend			***p*<0.001**			***p*<0.001**			***p*<0.001**
New female partners in the past 3 months									
None	56.6	1.00		42.7	1.00		35.9	1.00	
1	60.9	1.27	0.90–1.78	48.6	1.32	0.90–1.93	38.0	1.19	0.77–1.83
2	81.6	**3.39**	**1.59–7.23**	71.0	**3.37**	**1.49–7.65**	66.7	**4.00**	**1.69–9.50**
3–20	79.1	**2.85**	**1.32–6.14**	69.0	**2.76**	**1.20–6.35**	60.9	**2.64**	**1.09–6.39**
p- trend			***p*<0.001**			***p*<0.001**			***p*<0.001**
Had anal sex with male or female									
No	53.5	1.00		40.0	1.00		32.6	1.00	
Yes	64.7	**1.40**	**1.07–1.83**	52.2	**1.45**	**1.07–1.97**	42.6	1.32	0.94–1.86
Male partners only in the past 3 months									
No	59.3	1.00		46.4	1.00		37.1	1.00	
Yes	57.7	0.74	0.41–1.43	40.5	0.63	0.31–1.28	40.5	0.90	0.45–1.84
Number of male partners in the past 3 months									
None	59.7	1.00		46.8	1.00		37.7	1.00	
1	58.8	0.88	0.43–1.80	46.2	0.94	0.42–2.10	36.4	0.75	0.30–1.87
2	66.7	0.94	0.27–3.27	50.0	0.81	0.19–3.46	50.0	1.24	0.29–5.32
3–4	64.7	0.81	0.38–1.71	50.0	0.82	0.35–1.94	45.5	0.83	0.34–2.04
Current steady partner									
Yes	63.4	1.00		50.3	1.00		41.8	1.00	
No	49.3	**0.56**	**0.42–0.75**	36.8	**0.58**	**0.39–0.77**	28.1	**0.55**	**0.38–0.81**
Condom use with vaginal or anal sex in past 3 months									
Never	58.7	1.00		445	1.00		38.2	1.00	
Sometimes	68.8	**1.50**	**1.07–2.11**	59.4	**1.72**	**1.17–2.52**	42.8	1.11	0.77–1.83
Always	57.6	0.87	0.60–1.28	42.2	0.79	0.50–1.23	38.6	0.98	0.61–1.58
No sex in past 3 mos.	32.8	**0.34**	**0.18–0.61**	9.3	**0.12**	**0.04–0.36**	27.8	0.62	0.32–1.21

*OR (odds ratio) with its 95% CIs (confidence interval) were adjusted for age and country of residence.

Table 4

Association between history of STI and HPV infection with any, oncogenic or non–oncogenic types at baseline.

	Any type HPV+ (n=998)			Oncogenic HPV+ (n=748)			Non–oncogenic HPV+ (n=643)		
	%	OR*	95% CI*	%	OR*	95% CI*	%	OR*	95% CI*
Ever diagnosed with any STI (self–reported)									
Yes	73.6	1.00		61.3	1.00		54.4	1.00	
No	56.2	**0.52**	**0.35–0.77**	43.1	**0.47**	**0.30–0.75**	34.5	**0.55**	**0.34–0.88**
Don't Know	69.0	0.75	0.31–1.80	57.1	0.65	0.24–1.71	47.1	0.87	0.30–2.54
Current STI diagnosis**									
Chlamydia	80.0	2.90	0.61–14.12	66.7	2.31	0.41–13.01	66.7	3.36	0.58–19.41
Gonorrhea	100.0	--	--	--	--	--	100.0	--	--
Herpes	68.7	**1.57**	**1.04–2.37**	52.3	1.45	0.89–2.54	2.3	**1.82**	**1.12–2.85**
Syphilis	75.0	1.46	0.39–5.54	62.5	1.23	0.28–5.36	57.1	1.64	0.35–7.72
Genital wart(s)									
No	58.7	1.00		45.4	1.00		7.0	1.00	
Yes	68.5	1.67	0.92–3.04	58.5	1.71	0.87–3.29	43.3	1.53	0.72–3.27
Ever had partner with genital warts									
No	57.9	1.00		44.3	1.00		36.8	1.00	
Yes	78.1	**2.19**	**1.17–4.10**	65.9	**2.27**	**1.14–4.51**	62.2	**2.18**	**1.06–4.09**
Don't know	58.4	0.92	0.69–1.24	46.8	1.05	0.75–1.46	34.5	0.77	0.53–1.13
Ever had partner with abnormal Pap smear									
No	55.6	1.00		40.7	1.00		36.2	1.00	
Yes	69.0	**1.78**	**1.19–2.66**	56.3	**2.00**	**1.27–3.16**	48.3	**1.57**	**0.96–2.55**
Don't know	61.2	1.25	0.93–1.66	50.6	**1.52**	**1.09–2.11**	35.7	0.95	0.66–1.38

*OR (odds ratio) with its 95% CIs (confidence interval) were adjusted for age and country of residence.

**Reference group consists of those participants testing negative for the infection

Table 5

Multivariable analysis of risk factors for any, oncogenic and non–oncogenic HPV infections: *TheHIM Study.*

	Any HPV+ [1]		Oncogenic HPV+ [2]		Non–Oncogenic HPV+ [3]	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age						
18–24	1.00		1.00		1.00	
25–29	1.12	0.70–1.78	1.02	0.60–1.73	1.32	0.73–2.41
30–34	1.01	0.62–1.65	1.11	0.65–1.92	0.77	0.39–1.50
35–39	0.84	0.51–1.37	0.64	0.36–1.15	1.23	0.67–2.27
40–44	0.80	0.48–1.32	0.60	0.33–1.09	1.18	0.63–2.22
45–70	0.63	0.36–1.12	**0.50**	**0.25–0.97**	0.82	0.40–1.66
Race						
White	1.00		1.00		1.00	
Black	0.85	0.55–1.33	0.92	0.57–1.53	0.79	0.47–1.34
Asian/Pacific Islander	**0.19**	**0.06–0.57**	0.36	0.12–1.07	--	--
American Indian	4.24	0.79–17.52	3.27	0.62–17.29	4.26	0.83–21.76
Mixed	0.74	0.37–1.57	0.82	0.38–1.79	**0.58**	**0.38–0.90**
Circumcision (clinician–reported)						
No	1.00		1.00		1.00	
Yes	**0.70**	**0.52–0.94**	**0.70**	**0.50–0.97**	**0.63**	**0.42–0.93**
Lifetime number of female partners						
1	1.00		1.00		1.00	
2–9	**2.11**	**1.17–3.78**	**2.21**	**1.06–4.60**	1.92	0.88–4.20
10–19	**4.58**	**2.35–8.91**	**5.25**	**2.35–11.73**	**2.94**	**1.21–7.15**
20–49	**6.65**	**3.37–13.13**	**6.93**	**3.06–15.70**	**5.42**	**2.26–13.00**
50–1000	**5.81**	**2.49–13.59**	**4.86**	**1.78–13.24**	**5.58**	**1.98–15.72**
Had sex in the past 3 months						
Yes	1.00		1.00		1.00	
No	**0.42**	**0.22–0.81**	**0.19**	**0.06–0.58**	0.76	0.36–1.62
Number of female partners in the past 3 months						
None	1.00		1.00		1.00	

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	Any HPV+ [1]		Oncogenic HPV+ [2]		Non–Oncogenic HPV+ [3]	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
1	1.13	0.79–1.62	**1.54**	**1.02–2.30**	1.14	0.74–1.77
2	**2.09**	**1.25–3.49**	**2.96**	**1.70–5.16**	**1.91**	**1.03–3.53**
3–30	1.49	0.85–3.61	**2.24**	**1.22–4.11**	1.39	0.70–2.74
Country of residence						
US	1.00		1.00		1.00	
Brazil	1.38	0.84–2.27	1.33	0.76–2.33	1.17	0.62–2.21
Mexico	1.12	0.53–2.28	1.22	0.54–2.76	0.92	0.32–2.64

[1]The variables retained in the multivariable logistic model for Any HPV were circumcision, lifetime number of female partners, sex in the past 3 months, and number of female partners in the past 3 months.

[2]The variables retained in the model for oncogenic HPV were circumcision, lifetime number of female partners, and number of female partners in the past 3 months.

[3]The variables retained in the model for only non–oncogenic HPV were race, circumcision, lifetime number of female partners, and number of female partners in the past 3 months.