Factors associated with human papillomavirus (HPV) infection in men in Brazil, Mexico, and the United States

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CERTIFICATE OF APPROVAL

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ABSTRACT

Background: Human papillomavirus infection (HPV) is the most common sexually transmitted infection and is strongly associated with cervical and other anogenital cancers. Little is known about the epidemiology of HPV in men, and risk factor studies of HPV infection in men are just beginning to enter the literature. The objective of this study was to determine characteristics associated with HPV infection in men across multiple countries.

Methods: A cross-sectional analysis was conducted among men without signs of HPV living in Brazil, Mexico, and the U.S., who enrolled in the HPV in Men (HIM) study from 2005–2006. 3,593 men reported ever having sex with a male or female partner and were included in the analysis. Participants were surveyed about sexual behaviors; tested for HPV with genital swab PCR and genotyping; and tested for chlamydia, syphilis, herpes simplex virus (HSV), and gonorrhea. Multivariable regression was used to estimate HPV prevalence ratios (PR) and identify factors independently associated with any HPV type and oncogenic HPV within the entire cohort and individual countries. For factors associated with HPV in any country, interaction terms by country were tested.

Results: Overall HPV prevalence was 68%. Prevalence was highest in Brazil (74% positive for any HPV type, 36% positive for at least one oncogenic type), followed by the U.S. (67% positive for any type, 31% positive for oncogenic), and Mexico (63% positive for any type, 29% positive for oncogenic). Factors independently associated with any type of HPV within the entire cohort included increasing lifetime number of sexual partners, increasing recent number of sexual partners, younger age at sexual debut, co-infection with HSV, having a recent partner with genital warts or a recent abnormal Pap smear, and recent anal sex with another man. Factors independently associated with oncogenic HPV included increasing lifetime number of sexual partners, increasing recent number of sexual partners, younger age at sexual debut, co-infection with chlamydia, having a partner with genital warts or a recent abnormal Pap smear, identifying as a man who has sex with other men, being married, and high monthly alcohol intake. No interactions by country were statistically significant (all $p > 0.8$).

Conclusions: In this large, multi-national cohort, HPV was highly prevalent among asymptomatic men (~70%). Risk factors for HPV did not vary by country, suggesting that characteristics associated with HPV infection in men are largely similar across different geographies. Factors associated with any type of HPV infection were similar to those for oncogenic HPV. Lifetime and recent number of sexual partners have emerged as two risk factors that have been consistently associated with all types of HPV infection both in our study and across the literature.

SECTION 1. EXTENDED BACKGROUND AND LITERATURE REVIEW

Background on HPV infection

HPV is the most common sexually transmitted infection[1,2], responsible for significant morbidity and mortality around the world. According to the CDC, an estimated 20 million Americans are currently infected with HPV, with an estimated 6 million people becoming newly infected each year[3,4]. Roughly 50%-80% of U.S. adults will become infected with HPV at some point in their lives, with many infections occurring only transiently[5].

Persistent infection with HPV is etiologically related to a number of known cancers, including anal, oropharyngeal, vulvar, and vaginal cancers in women and anal, oropharyngeal, and penile cancers in men[6]. In men, 80-85% of anal cancers and close to 50% of penile cancers are associated with HPV infection. In women, HPV DNA is prevalent in virtually all cases of cervical cancer, as well as in 36-40% of vulvar cancer cases and close to 90% of vaginal cancers[7]. Lastly, HPV is also associated with the development of benign condylomata acuminata (genital warts) in both men and women.

HPV has gained most of its notoriety by being the necessary infectious cause of cervical cancer, the most common cancer caused by HPV. Rates of cervical cancer within the U.S. have steadily declined over the past several decades[8], mainly through the availability of effective techniques for detection, such as the Papanicolaou (Pap) test and with the recent advent of the quadrivalent HPV vaccine. Despite these improvements, however, cervical cancer remains the second most common cancer in women worldwide[9], despite it being considered a largely preventable disease.

There are over 100 known strains of the human papillomavirus, including about 40 strains which are specific to infecting the genital tract. These 40 are further subdivided into non-oncogenic subtypes (so called “low-risk”), such as types 6 and 11 which cause genital warts and other benign cutaneous lesions, and oncogenic subtypes (so called “high-risk”), such as types 16 and 18 which in some women can lead to cervical cancer.

Transmission of HPV occurs between sexual partners, most often through vaginal or anal sex, but all manner of sexual contact can lead to acquisition. However, most HPV infections are clinically unapparent to those who harbor the infection. The fact that HPV is typically asymptomatic allows it to be passed between sexual partners unknowingly. The result is that one individual can conceal multiple HPV strains at any given time, a finding which has been substantiated by evidence showing that co-infection with multiple HPV subtypes is common[10,11]. Typically, women discover they have HPV by the Pap test, which looks for cervical changes associated with infection. If these changes are noted under the microscope, PCR testing is done on the sample to determine whether there is high-risk vs. low-risk HPV DNA present. Men, on the other hand, have no clinically available test to determine if they are currently infected; only investigational studies researching HPV infection in men possess the ability to test men for HPV. That said, there is no universally accepted test, analogous to the Pap test for women, that is employed for men. Instead, research studies use different and overlapping techniques to detect

HPV positivity in men, including sampling urine, semen, serum, and a number of different anatomical sites that can be collected and processed by a variety of methods.

When an individual becomes infected with HPV, the natural history is that the virus tends to linger within the host, sometimes for only a few years (several studies have showed a 90% clearance within two years[12,13]), but in many individuals for up to decades[14,15]. The ability for these infections to be so long-lasting has to do with the immunoevasive nature of the virus; over generations, HPV has evolved to reach an equilibrium such that infection does not typically overtake the host, meanwhile the virus is not particularly limited in its reproductive capacity by the host's immune response. Over time, however, most infections are cleared, as is evidenced by the perpetually declining age-specific prevalence of HPV infections that spans until menopause[16-20]. A key area of interest currently is uncovering the determinants for transient vs. persistent infection within individuals, uncovering the factors which encourage certain individuals to develop HPV-related disease and others to remain disease-free.

HPV infection in men

Most research has focused on HPV in women because of its association with cervical cancer and its recent popularity in the press in connection with the HPV vaccine (approved in 2006 for girls, and in 2009 for boys). Male infection with HPV is an important area of study, however, insomuch as it is highly prevalent in sexually active men and contributes to significant morbidity and mortality in both that individual, as well in his male and/or female sexual partners. Improving our understanding of male HPV infection is a serious clinical issue that can help reduce transmission of HPV to women as well as improve the health of men worldwide.

In the developing world, rates of cervical cancer vastly outweigh rates of HPV-related disease in men. In the developed world, however, where surveillance for cervical changes in women is high-quality and widespread, the number of HPV-related cancers in men – such as penile, oral, and anal cancer – roughly equals the cervical cancer rate in women[21]. Additionally, several studies have established the influence of male HPV infection on the rates of HPV infection and related disease in women[22-25]. In particular, one international study demonstrated that the husbands of women with cervical cancer have a higher prevalence of HPV than husbands of control women[26], highlighting the direct relationship between male HPV infection and HPV-related disease in women.

While much is known about cervical HPV, much less is known about the epidemiology of HPV infection in men. Exactly how ubiquitous HPV infection is remains a subject of great debate. A recent systematic review of the literature assessing the prevalence of HPV in men showed a wide range of purported infection, ranging from 1.3%-72.9%[27]. (Comparatively, a systematic review of HPV prevalence in women ranged from 14-90%[28].) This wide range is likely attributable to several factors, including the fact that the disease is largely asymptomatic, that there is no gold standard test, and that it is not a reportable illness (meaning that most men who possess the virus go unnoticed by the medical profession). But even for men involved in clinical research studies where testing for HPV is possible, there is no standardized method of sample collection in men, as mentioned previously. As such, it is difficult to

draw a clear conclusion regarding the true prevalence of HPV in men worldwide, though it stands to reason that rates are sufficiently high to warrant further investigation.

Prevalence of HPV worldwide

As stated above, a review of the literature has revealed a wide range of HPV prevalence among men, much of which appears to vary according to geography. In a previously published research paper using the current study's dataset (the HPV in Men Study), investigators sampled multiple anatomic sites of 1,160 men from Brazil, Mexico, and the U.S., and found an overall HPV prevalence of 65.2% (with multiple infections detected in 25.7% of men enrolled)[11]. HPV prevalence varied significantly by country and was highest in Brazil at 72.3%, followed by Mexico at 61.9% and the United States at 61.3%. Additionally, HPV type distribution varied across countries. For example, in Brazil and in the U.S., HPV-16 was the most common oncogenic infection detected, whereas in Mexico, HPV-59 was the most common oncogenic HPV type. Similarly for the non-oncogenic strains, HPV-62 was the most commonly detected type in Brazil, whereas HPV-84 was the most common in Mexico and the U.S. This study highlights the fact that, not only does overall HPV prevalence differ between countries, but that there are proportional differences between types of HPV strains that differ according to country, as well.

Outside of the current study, however, there have been several other studies conducted in the U.S. to estimate HPV prevalence. A brief list includes:

- A National Health and Nutrition Examination Survey in 2003-2004 of 4,303 people aged 14-59 years tested for the 4 strains available in the current vaccine (HPV-6, 11, 16, and 18)[29]. For any HPV vaccine type, the seroprevalence was 32.5% among females and 12.2% among males.
- In men attending an STD clinic in the U.S., 443 men were tested for HPV, resulting in an overall prevalence of 28.2%[30].
- A prospective study of 290 U.S. men ages 18-44 showed that more than 50% of study participants developed HPV over the course of the study period of about 15.5 months, with about half of these infections being oncogenic forms of the virus[31]. The most common type of infection was with the oncogenic strain HPV-16. (Also interestingly, the median time to clearance of any HPV infection was 5.9 months, with similar clearance times for oncogenic and non-oncogenic strains.)

There are many international studies, as well, which reiterate this wide range of prevalences. For example:

- In a pooled analysis of five case-control studies that enrolled men from Spain, Colombia, Brazil, Thailand, and the Philippines, a total of 1921 husbands were enrolled, roughly half of whom had wives with diagnosed invasive cervical cancer[26]. Among the husbands of women with cervical cancer, 17.5% had penile HPV infection; among the husbands of the control women, penile HPV infection was detected in 13%. HPV-16 was the most common type in both groups. Interestingly, however, HPV prevalence varied drastically between countries, with the highest prevalence found in Brazil (36% and 39% among the husbands of case and control

women, respectively), followed by Colombia (32% and 29%, respectively), Spain (12% and 3%, respectively), and the Philippines (6% and 5%, respectively).

- In Amsterdam, a study conducted among 85 heterosexual men attending an STD clinic found that 28% of men were found positive for HPV DNA (compared to 23% for women)[32]. (Interestingly, this study also found a difference in viral persistence between men and women, with 20% of infections in women lasting long-term, compared to only 6% of infections in men.)
- In Denmark, several studies have occurred. In one prospective study of 374 young Danish soldiers, HPV prevalences at two sequential examinations 6-8 months apart were 33.8% and 31.9%[33]. In another study examining STD clinic attendees, HPV DNA was detected in 45% of the 216 men studied[34].
- In Germany, a study of 96 males attending an infertility clinic found that 13.5% were positive for HPV[35].
- In Mexico, several studies have also been done. In a study of 1,030 healthy military men, overall HPV prevalence was 44.6%, roughly half of which were multiply infected[36]. In another study of 120 healthy, sexually-active men living in Cuernavaca, HPV positivity was 42.7%[37]. Lastly, in a third study of 779 men attending a vasectomy clinic, prevalence of any type of HPV was 8.7%[38].
- In São Paulo, Brazil, a study of 50 male partners of HPV-infected women revealed an HPV DNA positivity of 76%[39].
- In Busan, South Korea, a study of in 381 sexually-active male university students demonstrated an HPV prevalence of 10.6% (compared to 38.8% in females)[40].
- In Kisumu, Kenya, a study of 98 HIV-negative, uncircumcised men aged 18-24 years participated in an HPV detection study and found that prevalence was approximately 50%[41]. HPV-16 was the most common type identified.

Taken together, there are substantial discrepancies between the reported ranges of HPV prevalence across the world. Several factors may be contributing to this finding, including variation in study technique influencing HPV detection rates, differences in viral persistence based on genotype or host factors, as well as differences in individual and population-based risk factors that may vary within countries and contribute to a true prevalence difference by geography. Future studies are needed to help explain this range in prevalence, specifically examining the unique risk factors within each country that may be underlying this phenomenon.

Risk factors for HPV acquisition

Numerous studies over the years have evaluated the various risk factors that contribute to the acquisition of oncogenic and non-oncogenic HPV in women. Variables that appear to consistently predict genital HPV infection include young age, proximity to first intercourse, and number of male sexual partners (both recently and lifetime)[16,42-45].

In men, however, risk factors for HPV infection are just beginning to enter the literature. Not surprisingly, the most common risk factors are similar to those found in women, with young age being one of the main risk factors for harboring any type of HPV in men[34]. Other important risk factors relate

to patterns of sexual behavior. There have been five cross-sectional studies which showed that young age at first sexual intercourse; high number of recent, regular, and lifetime sexual partners; female sex partners' lifetime number of sex partners; and a high frequency of sexual intercourse are all associated with greater rates of HPV detection[22,23,26,34,46]. In addition, longitudinal studies have also found that men who have anal intercourse with men[36] as well as those who have ≥ 3 sex partners[33] were both independently associated with HPV acquisition.

Another risk factor shown to be associated with HPV is condom use. One cross-sectional study that controlled for confounding showed a significant reduction in the risk of HPV infection in men who used condoms consistently[23]. They found that regular condom use was associated with reduced risk for both oncogenic and overall HPV (which includes both oncogenic and non-oncogenic strains, as well as several unclassified strains). In addition, another study demonstrated that condom use, in the setting of circumcised men only, significantly reduced the risk of HPV[22]. A third longitudinal study found that any pattern of condom use, either consistent or occasional use, was independently associated with a reduced risk of acquiring HPV[33]. This study pointed out, however, that although rates of HPV acquisition were reduced among men who reported use of condoms at every intercourse, many of these "perfect users" still acquired HPV. Taken together, it appears that any type of condom use, preferably consistent but even if used on occasion, is associated with decreased rates of HPV in men, although it does not prevent infection altogether.

The role of circumcision in HPV infection turns out to be quite controversial in the literature, with much data to support the argument on both sides. On the one hand, several cross-sectional studies have evaluated the role of circumcision and found that, when they controlled for confounding, the risk of HPV infection was significantly lower in those men who were circumcised[23,34,36,38,47-50]. The implication from these studies is that circumcised men are less likely to pass on HPV to their partners, resulting in lower rates of HPV-associated disease for not only the circumcised men themselves but also for their partners. One such study actually showed that this impact is not simply theoretical by actually demonstrating lower rates of cervical cancer in the female partners of circumcised men[22]. Newer studies have also pointed out that, in addition to HPV acquisition, HPV clearance and persistence of the virus may be affected by circumcision. Two recent studies out of Uganda that randomized participants to either an intervention arm (immediate circumcision) or a control arm (delayed circumcision) found that circumcision decreased the incidence of having multiple HPV subtype infections as well as increased clearance of the virus[51].

On the opposing side of the circumcision argument are several studies that failed to show a difference in HPV acquisition based on circumcision status[52-54]. A meta-analysis of the literature performed in 2007 confirmed this fact, stating that there was no significant association between circumcision status and HPV infection based on the current available literature[55]. A follow-up article published in 2009 by the same author maintains this claim, in spite of several randomized trials that showed otherwise (and were published after their 2007 meta-analysis)[56]. Their argument is that circumcision status has no impact on HPV infection rates, and states that this conclusion has been erroneously drawn in previous studies on the basis of a sampling bias. That is, the penile location from which HPV can be isolated differs by

circumcision status. HPV is found primarily on the penile shaft in circumcised men and on the glans in uncircumcised men[47,49,57,58]. The fact that the sampling method is not consistent between studies and may have an impact on study findings creates this sampling bias. Overall, the dispute about circumcision's role as a risk factor in HPV status underscores the difficulty in drawing conclusions based on studies that use different techniques for detecting HPV in men, and highlights the need for a common sampling method practiced by all future studies.

Lastly on the topic of circumcision, it is important to point out for the purposes of the current study that the question of circumcision's association with HPV infection has been examined using the present study's dataset[59]. Researchers concluded that circumcision was indeed associated with a reduced risk of HPV detection across all categories of HPV evaluated (oncogenic, non-oncogenic, unclassified, and multiple types). They purport that circumcision may, therefore, be a low-cost practice that could reduce HPV infection in men, and subsequently in their partners.

Numerous other risk factors have been associated with prevalent HPV, including smoking, a history of other sexually transmitted infection, race and ethnicity, education level, and socioeconomic status[26,34,36,38,40,60].

Rationale for the current study

As it stands, no study exists that compares the risk factors for HPV among men from such a large cohort of men from distinct geographical regions. The aim of the current study, therefore, is to establish the unique risk factors for HPV that may be driving the disease within each country. The HPV Study in Men dataset is uniquely suited to examine this research question. As a cross-sectional study of roughly four thousand men from three countries, it allows us to examine the natural history of and risk factors associated with this infection. Gaining a better understanding of the factors associated with HPV infection in men across different geographies can lead to better prevention techniques used by the patient as well as education by the provider, which could improve the health of both men and women across the globe.

Preliminary studies

Several studies have been previously published using members of the HPV in Men (HIM) Study population. As was previously mentioned, a study published in 2008 using a total of 1,160 men found that overall HPV prevalence was 65.2% (with 12.0% oncogenic types only, 20.7% non-oncogenic types only, 17.8% both oncogenic and non-oncogenic, and 14.7% unclassified infections)[11]. HPV prevalence was significantly different between the three countries, being highest in Brazil at 72.3%, followed the United States at 61.3% and Mexico 61.9%. A subsequent study, published in 2009 and using a smaller subset of the developing cohort (a total of 988 men), examined factors that were independently associated with HPV detection in all three countries[59]. They found that "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 3 months. "Oncogenic HPV" detection was independently associated with lifetime and recent number of sexual partners, and having sex in the past 3 months. "Non-oncogenic HPV" infection was independently associated with lifetime number of sexual partners.

Lastly, they found that circumcision was associated with reduced risk of HPV detection across all categories of HPV evaluated. Thus, they concluded that HPV detection in men is strongly related to sexual behavior and circumcision status.

SECTION 2. JOURNAL ARTICLE

BACKGROUND

HPV is the most common sexually transmitted infection[1,2], responsible for significant morbidity and mortality around the world. While much is known about HPV infection in women, much less is known about the epidemiology of HPV infection in men. Male infection with HPV is an important area of study, as it is highly prevalent in sexually active men and contributes to significant morbidity and mortality in both that individual and his male and/or female sexual partners[22-25]. In men, HPV infection can result in anal, penile, and oropharyngeal cancers, as well as benign genital warts.

Risk factor analyses for HPV in men are just beginning to enter the literature. The emerging risk factors include young age[34], as well as a number of sexual behavior characteristics, including young age at first sexual intercourse; high number of recent, regular, and lifetime sexual partners; female sex partners' lifetime number of sex partners; a high frequency of sexual intercourse; and having anal intercourse with other men[22,23,26,33,34,36,46]. In addition, several studies have demonstrated that condom use is associated with decreased rates of HPV in men[22,23,33]. Lastly, multiple studies have examined the role of circumcision in HPV infection with conflicting results. Several cross-sectional studies found that the risk of HPV infection is lower in men who are circumcised[23,34,36,38,47-49,59], whereas several studies showed no association[50,52-56]. Numerous other risk factors have been associated with prevalent HPV, including smoking, a history of other sexually transmitted infection, race and ethnicity, education level, and socioeconomic status[26,34,36,38,40,60].

None of these studies, however, have compared these risk factors within a large cohort of men from multiple countries. Gaining a better understanding of the factors associated with HPV infection in men across different geographies can help lead to better prevention strategies, thereby reducing the burden of HPV infection and its related disease in men and women worldwide.

METHODS

Study enrollment and protocol. Subjects from this study were gathered from participants of the HPV in Men (HIM) study, which was a cross-sectional study developed to assess the epidemiology of HPV infection in men. Details of study enrollment and protocol are detailed elsewhere[11]. In brief, men were recruited from 2005 – 2006 from São Paulo, Brazil; Cuernavaca, Mexico; and Tampa, Florida in the United States, all from a wide range of enrollment sources. 3,593 men reported ever having sex with a male or female partner and were included in the current analysis. Figure 1 provides a flowchart for individuals who were excluded from our analysis, including 103 men who lacked an HPV result (were β-globin and PCR negative) and 378 men who reported no history of any lifetime sexual activity. Participants were surveyed about their sexual behaviors; tested for HPV with genital and anal swabs; and tested for chlamydia, syphilis, herpes simplex virus (HSV), and gonorrhea. This method of HPV collection has been detailed elsewhere[11], and has been shown to maximize HPV detection in a manner that is reproducible[61,62]. PCR was used to amplify HPV DNA, followed by genotyping for 37 strains on all samples regardless of PCR findings. Based on these results, positive samples were grouped into one of three categories: 1) infection with an oncogenic strain, 2) infection with a non-oncogenic strain, and 3)

infection with an unclassified strain, resulting from a sample that yielded a positive PCR result but did not hybridize with a specific genotype.

Statistical analysis. Two outcomes were examined in this analysis: positive for "any HPV type" and positive for "any oncogenic HPV type." The former was defined as testing positive for HPV by either PCR or genotyping; the latter was defined as testing positive by either method for any of the oncogenic strains (thus, subjects in this category could be positive for oncogenic strains only or both oncogenic and non-oncogenic strains simultaneously). For a more thorough listing of the variables included in this analysis, please see Appendix 1.

Participant characteristics were summarized using descriptive statistics (Table 1). The distribution of HPV type by country was examined using Pearson's χ^2 test (Table 2), and a Poisson regression model was used to assess the trend of prevalence of any HPV type over increasing age for each country (Table 3). Associations between each outcome variable and potential risk factor were explored using bivariate Poisson regression, and variables were considered as candidate variables for the multivariate regression model if they achieved a bivariate level of significance of 0.25 or less. A separate regression model was created for each outcome variable, both for the entire cohort as a whole as well as separately for each of the three countries. Variables included in the final model were significant at a p-value of 0.05 or less. Interaction terms were tested between country and each of the variables in the final model. Missing responses for each predictor variable were grouped into a "Refused or Missing" category and all observations were used in the analysis.

RESULTS

Descriptive characteristics of study sample. Selected demographic and sexual behavior characteristics of study participants are presented in Table 1. Median age within the entire cohort was 31 years; median age was 34 years in Brazil and 33 years in Mexico, however U.S. participants were notably younger with a median age of 23. The greatest proportion of men in Brazil and the U.S. identified as single (39% and 69%, respectively), whereas in Mexico most participants were married (57%). In all three countries, most men were never-smokers. Of those who smoked, higher rates of heavy smoking (>8.9 pack-years) were noted in Brazil (15%) and the U.S. (13%), compared to Mexico (5%). The majority of men reported between 1-30 alcoholic drinks per month, with the proportion of heavy drinking (≥61 alcoholic drinks per month) being the highest in the U.S. (23%), followed by Brazil (15%) and Mexico (11%). About 80% of men in the U.S. were circumcised, whereas the proportions were only 14% and 12%, respectively, in Brazil and Mexico. The main sources of enrollment varied between countries; in Brazil it was a flyer/poster (38%) or TV (27%), in Mexico it was word of mouth (47%) or corporation/business participation (31%), and in the U.S. it was word of mouth (40%) or a flyer/poster (19%).

In regards to sexual behavior characteristics, the majority of men in all three countries reported having a current steady partner (77% overall). Most also reported having between 2-9 lifetime sexual partners, with the median number being highest in Brazil (10), followed by the U.S. (7) and Mexico (5). It was most common for men to report having either zero or one recent sexual partner (defined as being in the

past 3 or 6 months in two versions of the questionnaire, and combined in this analysis), with only a small percentage reporting more than 4 recent sexual partners (8% overall). Condom use among recently sexually active men (also recorded as in the past 3 or 6 months, but combined in this analysis) was such that the highest percentages of men reported either never using condoms (20%) or always using condoms (36%).

All participants were tested for a concurrent sexually transmitted infection (HSV, chlamydia, syphilis, and gonorrhea), however most were not concurrently infected. Among those who were infected, HSV represented the most common co-infection, with 39% infected in Brazil, 9% in Mexico, and 13% in the U.S. Men were also asked about their recent sexual partners, and most responded that their partners did not have an STD, warts, or a recent abnormal Pap smear. In regards to sexual orientation, 16% of men in Brazil reported that they have sex with other men, compared to 9% in the U.S. and 5% in Mexico. Accordingly, higher rates of anal sex with another man in the past 6 months were reported in Brazil (10%), compared to the U.S. (4%) or Mexico (1%).

HPV prevalence. A total of 2,445 men (68%) in the cohort were positive for any HPV type, with 1,137 men (32%) positive for at least one oncogenic type. HPV prevalence varied significantly by country ($p<0.0001$) (Table 2). Brazil had the highest rates of HPV infection (74% positive for any type, 36% positive for oncogenic), followed by the U.S. (67% positive for any type, 31% positive for oncogenic), and Mexico (63% positive for any HPV type, 29% positive for oncogenic).

Stratifying HPV prevalence by age (Table 3), HPV positivity did not increase by age within the entire cohort (p for trend = 0.132). Within individual countries, however, HPV positivity increased with age in the U.S. ($p = 0.006$) and decrease with age in Brazil ($p = 0.011$). In Mexico, no significant trend was noted between HPV prevalence and age ($p = 0.236$). Adjusting for recent number of partners did not change any of these associations (data not shown).

Factors associated with any HPV type. In the bivariate analysis, multiple demographic and sexual behavior characteristics were associated with any HPV type (Table 4). The results from multivariate logistic regression modeling revealed that several of these factors were independently associated with HPV infection within the entire cohort (Table 5). Importantly, interactions between country and each of the variables significant in the final model were not significant, therefore country-specific prevalence ratios for HPV infection are not shown.

In the entire cohort, an increasing number of lifetime sexual partners was significantly associated with any HPV type (PR 1.004, 95% CI: 1.003-1.006). Increasing number of recent partners was also associated with any HPV type and, compared to no recent partners, having 3 recent partners was associated with an increase of HPV prevalence of 23% (PR 1.23, 95% CI: 1.12-1.34). Younger age at sexual debut was significantly associated with decreased prevalence of HPV, where every one-year increase in age at sexual debut was associated with a 1% decrease in HPV prevalence (PR 0.99, 95% CI: 0.98-0.99). Persons who were co-infected with HSV had an increased prevalence of HPV infection of 6% (PR 1.06, 95% CI: 1.01-1.12). Various partner characteristics were also significant, including having had a recent partner

with warts (an 11% increase in HPV prevalence; PR 1.11, 95% CI: 1.03-1.20) or a recent abnormal Pap smear (an 9% increase; PR 1.09, 95% CI: 1.03-1.16). Lastly, having had anal sex with another man in the past 6 months was associated with an increased prevalence of any HPV type of 13% (PR 1.13, 95% CI: 1.02-1.25).

Factors associated with oncogenic HPV. Multiple demographic and sexual behavior characteristics were associated with oncogenic HPV infection in the bivariate analysis (Table 6). Multivariate logistic regression modeling revealed that many of the same factors that were significantly associated with any HPV type were also associated with oncogenic HPV (Table 5). Again, interaction terms between country and each of the variables were not significant. Factors that were associated with both oncogenic HPV and any HPV type included: increasing lifetime number of partners (PR 1.01, 95% CI: 1.01-1.01 for each additional partner), increasing number of recent partners (e.g. compared to no recent partners, having 3 recent partners was associated with an increased HPV prevalence of 54%; PR 1.53, 95% CI: 1.25-1.86), younger age at sexual debut (PR 0.98, 95% CI: 0.97-0.99 for each year increase in age), and having had a recent sexual partner that has warts (PR 1.24, 95% CI: 1.03-1.49) or a recent abnormal recent Pap smear (PR 1.31, 95% CI: 1.14-1.50). Similarly, co-infection with another STD, in this case chlamydia, was positively associated with oncogenic HPV (PR 1.40, 95% CI: 1.08-1.82). As well, having sex with other men, compared to having sex with women only, was associated with an increased prevalence of oncogenic HPV of 63% (PR 1.63, 95% CI: 1.04-2.56). Factors that were uniquely associated with oncogenic HPV included being married (PR 0.83, 95% CI: 0.73-0.94) and a monthly alcohol intake of ≥61 drinks (PR 1.30, 95% CI: 1.12-1.52).

Summary of findings. Overall, multiple sexual behavior characteristics were independently associated with HPV infection in men. Factors significantly associated with any type of HPV infection vs. oncogenic HPV infection were largely similar and included an increasing number of lifetime sexual partners, increasing number of recent partners, younger age at sexual debut, co-infection with another STD (such as HSV or chlamydia), having had a recent sexual partner with increased markers of HPV infection (such as warts or a recent abnormal Pap smear), and having sex with other men. Each of these factors may indicate increased levels of sexual activity, suggesting that sexual behavior is strongly associated with HPV infection in men.

DISCUSSION

In this large, multi-national cohort, we have identified multiple sexual behavior characteristics that are independently associated with HPV infection in men. Importantly, these risk factors did not vary across country, suggesting that characteristics associated with HPV infection in men are largely similar across different geographies. In addition, we confirm previous studies' findings that thorough testing at multiple anatomic sites reveals a very high prevalence of HPV among asymptomatic men[11,31,63].

Several factors that were significantly associated with HPV in our analysis have also been significant in previous studies. In particular, both lifetime and recent number of sexual partners have been repeatedly associated with HPV infection across multiple studies [23,26,34,38,63], though the association was weak in our study. Having sex with other men has been associated with HPV infection in one other

study [36], and was one of the strongest risk factors in our study. This is particularly important in an investigation as large as ours, given that smaller studies may not have previously had the power to detect this valuable association.

Our analysis identified several novel risk factors for HPV infection in men. To our knowledge, no other study has identified younger age at sexual debut, co-infection with another STD (HSV or chlamydia), partner characteristics (the presence of genital warts or a recent abnormal Pap smear), being married, and high levels of alcohol use as significant risk factors for HPV infection in men. It appears that previous studies may not have addressed these variables, nonetheless they remain important risk factors given that they may indicate higher levels of sexual activity and are significantly associated with an increased prevalence of HPV.

Interestingly, several factors that were not significant in our study have been identified as risk factors in other studies. In a publication using a smaller subset of the HIM cohort, circumcision was negatively associated with all categories of HPV infection [59]. Within the greater literature, publications have reported conflicted findings in regards to circumcision. Multiple studies have demonstrated a significant association between circumcision and decreased rates of HPV [22,23,34,36,38,47-51], whereas others have not [52-54,56,63]. One possible explanation for the null association seen in our study may relate to the fact that in the U.S., most men were circumcised, whereas in Brazil and Mexico most were uncircumcised. Because the rates of circumcision were so divergent between countries in our study, it may be difficult to make comparisons across country. Taken together, we conclude that the value of circumcision in preventing HPV transmission remains a possibility but is unclear.

In addition, regular condom use has been identified as a protective factor in several other studies[22,23,33,38,64], but not in ours. Because HPV is most often found on the penile shaft, it is reasonable that condom use would reduce the risk of transmission of HPV. However, HPV has also been shown to be highly prevalent among other anatomical sites not protected by condoms [65], suggesting that it may provide only partial protection against transmission.

Young age, not significantly associated with HPV infection in our study, has traditionally been thought of as a risk factor for HPV in women. It has been shown that most women clear this infection within a few years[16,42,45]. Our study confirms previous studies' findings, however, that prevalence of HPV in men appears to be constant across age groups[11,31,63]. It is not clear why this phenomenon of decreasing age-specific prevalence exists for women and not for men, particularly given that viral persistence studies in men demonstrate that clearance of the virus, as in women, occurs rapidly, most within the first 6-12 months after infection[31,66]. [66,67]

Most of the same risk factors emerged for our two outcomes (any HPV type vs. oncogenic), suggesting that sexual behavior patterns that promote HPV acquisition are highly similar between different strains of HPV infection. It should be noted, however, that the magnitude of the association (prevalence ratios) was generally higher for variables associated with oncogenic HPV than with any HPV. In addition, two additional variables were uniquely associated with oncogenic HPV, being married and high monthly

alcohol intake. While these appear to be novel risk factors, they also may be reflective of higher levels of sexual activity.

This study serves as the largest multi-national study of its kind examining factors associated with HPV infection in men. Viral sampling employed highly rigorous methods[61] and assessed for a large number of HPV genotypes. Anatomic sampling was thorough, and a highly exhaustive 800-item questionnaire was administered. Clinical testing for co-infection with other STDs allowed for a more complete depiction of each man's unique sexual risk profile. While many of the variables in this analysis relied on self-report, a separate study demonstrated high test-retest reliability for men using this type of self-interview[68]. The cross-sectional nature of this study allowed us to assess various exposures and outcomes simultaneously, but does not allow us to make conclusions about causality or issues relating to infection duration. For these questions, a longitudinal cohort study that addresses HPV acquisition and duration is needed.

Misclassification bias is possible given that much of the data regarding risk factors was obtained from self-report. The highly detailed nature of the questionnaire allowed us to examine the internal consistency of responses, however, limiting this type of bias. Similarly, recall bias may have occurred, however most of the questions asked participants to recall their sexual behaviors only for the past 3-6 months, which would limit this type of bias compared to if a more distant time period were asked about.

The voluntary participation of subjects may have affected the generalizability of our findings, but is a limitation of any volunteer-based study. In addition, while our study recruited men from three different countries, it mainly drew from only one metropolitan area within each country, which may also reduce generalizability to the national level. Efforts were made, however, to draw from a variety of sources within these communities to increase the diversity of the cohort.

In sum, this study confirms that sexual behavior characteristics, and not sociodemographic characteristics, are associated with HPV infection in men. Factors associated with HPV infection in men often reflect higher levels of sexual activity confirming that, much like in women, sexual behavior patterns are most strongly associated HPV infection in men. Importantly, lifetime and recent number of partners are two risk factors that have been consistently associated with all types of HPV infection both in our study and across the literature. Given that screening and treatment options are not available for men, efforts aimed at reducing exposure to risk factors and preventing HPV infection are the most valuable public health tools to reduce the burden of HPV-related disease in both men and women.

SECTION 3. EXTENDED DISCUSSION AND CONCLUSIONS

In this large, multi-national cohort, we have identified multiple sexual behavior characteristics that are independently associated with HPV infection in men. Importantly, these risk factors did not vary across country, suggesting that characteristics associated with HPV infection in men are largely similar across different geographies. In addition, we confirm previous studies' findings that thorough testing at multiple anatomic sites reveals a very high prevalence of HPV among asymptomatic men[11,31,63].

Several factors we identified as significant predictors of HPV infection were also significant in previous studies. In particular, both lifetime and recent number of sexual partners have been repeatedly associated with HPV infection across multiple studies[23,26,34,38,63]. While these variables were only weakly associated with HPV infection in our study, they have arisen as two factors which have been the most consistently associated with HPV in men across the literature. Additionally, having sex with other men has been associated with HPV infection in one other study[36], and was one of the strongest risk factors in our study. This is particularly important in a study as large as ours, given that smaller studies may not have previously had the power to detect this valuable association. Lastly, partner characteristics, including the presence of genital warts or a recent abnormal Pap smear, were significant predictors of any type of HPV and oncogenic HPV in our study. One study did identify having a partner with warts as a risk factor for oncogenic HPV in bivariate analysis[63], however most other studies did not appear to include this variable in their analysis. Nevertheless, having a recent partner with signs of HPV infection remains a plausible explanation for increased risk of HPV acquisition.

Our analysis also identified several novel risk factors for HPV infection in men. To our knowledge, no other study has identified younger age at sexual debut, co-infection with another STD (HSV or chlamydia), being married, and high levels of alcohol use as significant risk factors for HPV infection in men. One potential explanation is that many other studies did not address these variables in their study. It is reasonable, however, that these factors would be associated with higher rates of HPV given that they may be indicative of higher levels of sexual activity.

Interestingly, several factors that were not significant in our study were previously identified as risk factors in other studies. In a publication using a smaller subset of the HIM cohort, Asian/Pacific Islander race was positively associated with any HPV infection, and circumcision was negatively associated with all categories of HPV infection, neither of which we found in the current study[59]. In regards to circumcision, the verdict appears split within the literature, as multiple studies have demonstrated an association between circumcision and decreased rates of HPV[22,23,34,36,38,47-51], whereas others have not[52-54,56,63]. One possible explanation for the null association seen in our study may relate to the sizeable discrepancy between rates of circumcision in our sample. In the U.S., the vast majority of men were circumcised, whereas in Brazil and Mexico it was just the opposite. Thus, because the rates of circumcision were so divergent between countries in our study, it may be difficult to make comparisons across country. Taken together, however, we conclude that the value of circumcision in preventing HPV transmission is a possibility but remains unclear.

In addition, regular condom use was identified as a protective factor in several other studies[22,23,33,38,64], but not in ours. Because HPV is most often found on the penile shaft, it makes sense that condom use would reduce the risk of transmission of HPV. However, HPV has also been shown to be highly prevalent among other anatomical sites not protected by condom use[65], suggesting that it may provide only partial protection against transmission.

Young age, not significantly associated with HPV infection in our study, has traditionally been thought of as a risk factor for HPV in women. It has been shown that most women clear this infection within a few years[16,42,45]. Our study confirms previous studies' findings, however, that prevalence of HPV in men appears to be constant across age groups[11,31,63]. It is not clear why this phenomenon of decreasing age-specific prevalence exists for women and not for men, particularly given that viral persistence studies in men demonstrate that clearance of the virus, as in women, occurs rapidly, most within the first 6-12 months after infection[31,66]. [66,67]

Comparing our two outcomes, any HPV type vs. oncogenic HPV, most of the same risk factors emerged, although oncogenic had a few more risk factors that were significant. Overall, this suggests that the patterns of sexual behavior that promote HPV acquisition may be highly similar between different strains of HPV infection. It should be noted, however, that the magnitude of the association (prevalence ratios) was generally higher for variables associated with oncogenic HPV than with any HPV. This implies that a stronger association is seen between the risk factors we have identified and acquiring an HPV type that is associated with cancer.

There are several public health implications of the findings in this study. Several modifiable sexual behavior characteristics have been identified that, if prevented, could decrease rates of HPV acquisition, such as high alcohol intake. Reducing exposure to these modifiable risk factors could lessen the transmission of HPV and reduce disease burden. However, many of the risk factors we identified may be difficult to modify, including lifetime and recent number of sexual partners. This would advocate for other risk reduction strategies, in particular the HPV vaccine.

Given the very high prevalence of HPV infection in research studies such as ours, one might postulate that screening men would be a useful public health tool. As it stands, however, no FDA-approved test is clinically available. This is likely because no therapy has been identified for men who are infected, making screening of little benefit to that individual. Thus, prevention of infection remains the most valuable method for reducing HPV-related disease in men, given that HPV testing is not publicly accessible.

There are several important strengths of this study. First, this study serves as the largest multi-national study of its kind examining factors associated with HPV infection in men. In addition, the methods employed in this study were quite comprehensive. Viral testing was completed using the most rigorous and reproducible methods available[61]. Multiple anatomic sites were assessed, 37 genotypes of HPV were tested for, and a highly exhaustive questionnaire with over 800 questions was administered. In

addition, clinical testing for co-infection with other STDs allowed for a thorough depiction of each man's unique sexual risk profile.

While many of the variables in this analysis relied on self-report, a separate study was conducted to address this potential concern that self-reported information on sexual behavior may not be valid[68]. The authors conducted a test-retest reliability study of 1,069 men from all three countries, with all of the men completing the same computer-assisted self-interview. Reliability coefficients for each study site and the combined population were high for almost all questions. As such, the authors concluded that high test-retest reliability exists for men using this type of self-interview on sexual behavior.

As with any study, there are limitations that may influence the interpretation of results. The cross-sectional nature of this study allowed us to assess various exposures and outcomes simultaneously, but does not allow us to make conclusions about causality or issues relating to infection duration. For these questions, a longitudinal cohort study that addresses HPV infection acquisition and duration is needed.

There are two potential sources of bias that could have affected our results. Misclassification bias is possible given that much of the data regarding risk factors was obtained from self-report. Participants may have inaccurately portrayed or remembered their risk profile. The exhaustive nature of the questionnaire limited this type of bias by allowing us to examine the internal consistency of responses. Similarly, recall bias may have occurred due to the self-report nature of this study, however most of the questions asked participants to recall their sexual behaviors only for the past 3-6 months, which would have limited this type of bias compared to if a more distant time period was asked about.

Lastly, the men who volunteered to be in the study may be different from the men who chose not to enroll, reducing the generalizability of our findings. This is a weak point of any study where participants voluntarily participate. In addition, while our study recruited men from three different countries, it mainly drew from only one metropolitan area within each country, which may also reduce generalizability to the national level. Efforts were made, however, to draw from a variety of sources within these communities to increase the diversity of the cohort. As well, study eligibility criteria were designed to exclude men with active sexually transmitted infections, so as not to overestimate the prevalence of HPV infections.

In sum, this study, building on the past literature, adds to our growing understanding of the factors associated with HPV infection in men. This study confirms that sexual behavior characteristics, and not sociodemographic characteristics, are associated with HPV infection in men. Factors associated with HPV infection in men often reflected higher levels of sexual activity confirming that, much like in women, sexual behavior patterns are the strongest predictors of HPV infection in men. Importantly, lifetime and recent number of partners are two risk factors that have been consistently positively associated with all types of HPV infection, both in this study and in multiple prior studies. Efforts aimed at reducing preventing HPV acquisition, either through vaccination or the reduction of modifiable risk factors, are the most valuable public health tools and can reduce the burden of HPV-related disease in men and women worldwide.

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APPENDIX 1. LIST OF VARIABLES INCLUDED IN ANALYSIS

Description of factors tested in our analysis

Variable	Type	Description
Age (years)	Continuous	Range 18-70
Race	Categorical	White Black Asian/Pacific Islander American Indian Mixed
Ethnicity	Categorical	Hispanic Non-Hispanic
Marital status	Categorical	Single, never married Married Cohabiting Divorced/Separated/Widowed
Education	Categorical	<12 years Completed 12 years 13-15 years Completed 16 years $\geq$ 17 years
Cigarette smoker	Categorical	Never Past Current
Smoking pack-years (quartiles)	Categorical	Never smoked 0.1-0.75 >0.75-2.79 >2.79-8.89 >8.9
Monthly alcohol intake (drinks)	Categorical	0 1-30 31-60 $\geq$ 61
Circumcised	Categorical	No Yes Partial
Recruitment source	Categorical	Newspaper/Magazine Class presentation Radio TV Internet/Email Flyer/Poster Mail Word of mouth Enrolled in other study School/University Health Dept/Hospital/Health Fair

		Military zone Corporation/Business Other
Current steady partner	Categorical	Yes/No
Number of lifetime sexual partners	Continuous	Range 0-50+
Age at first sexual intercourse (years)	Continuous	Range 1-40
Number of recent sexual partners[1]	Categorical	None recent 1 2 3 4+
Recent condom use[1]	Categorical	Not always Always No vaginal sex in past 3-6 months
Current infection with another STD	Categorical	HSV Chlamydia Syphilis Gonorrhea
Sex partner with an STD in past 6 months	Categorical	Yes/No
Sex partner with warts in past 6 months	Categorical	Yes/No
Sex partner with a recent abnormal Pap in past 6 months	Categorical	Yes/No
Sexual orientation	Categorical	Sex with women only Sex with men only Sex with women and men
Anal sex with another man in past 6 months	Categorical	Yes/No

[1] In past 3 and 6 months combined.

Description of outcomes assessed in our analysis

Variable	Description
Positive for "any HPV"	Sample tested positive during either PCR or genotyping analysis
Negative for "any HPV"	Sampled tested negative for both PCR and genotyping analysis (but was beta-globin positive)
"Any oncogenic type" present	Sample genotyping was positive for any oncogenic strain, or was positive for both oncogenic and non-oncogenic strains

APPENDIX 2. FIGURES

Figure 1. Analytic cohort of men included in the present study.

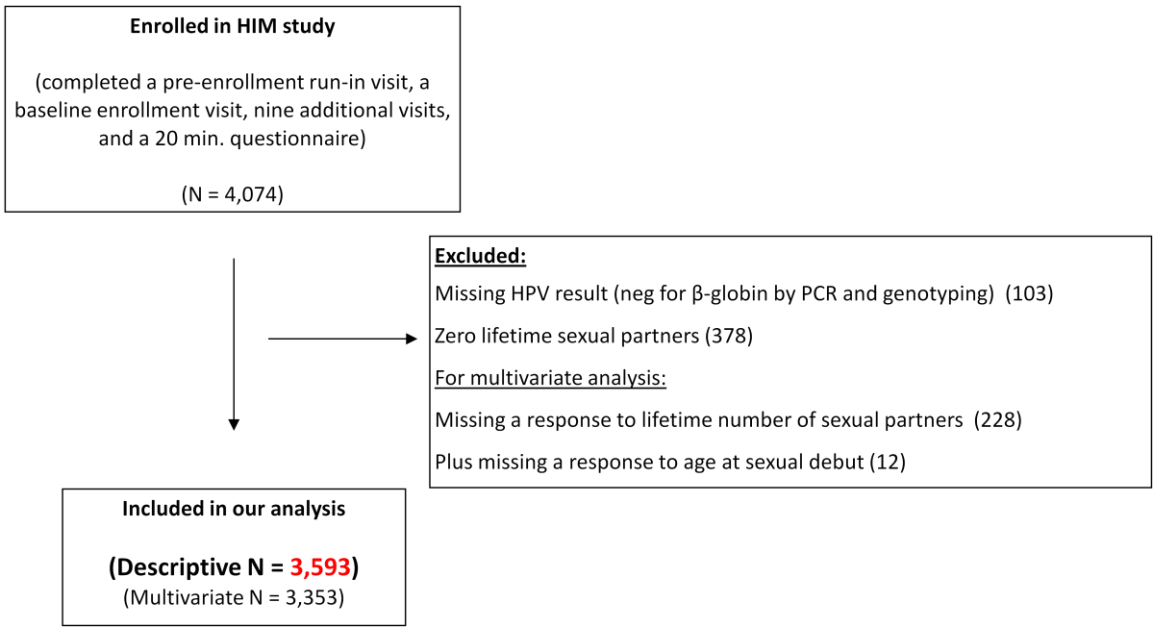

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Table 1. Characteristics of participants in the Human Papillomavirus in Men (HIM) study by country

	Brazil (n=1,249)	Mexico (n=1,215)	United States (n=1,129)	Total (n=3,593)
	n (%)	*n* (%)	*n* (%)	*n* (%)
Demographic characteristics				
Age (years)				
18-19	27 (2.2)	37 (3.1)	246 (21.8)	310 (8.6)
20-24	187 (15.0)	165 (13.6)	371 (32.9)	723 (20.1)
25-29	217 (17.4)	235 (19.3)	108 (9.6)	560 (15.6)
30-34	234 (18.7)	244 (20.1)	78 (6.9)	556 (15.5)
35-39	191 (15.3)	204 (16.8)	99 (8.8)	494 (13.8)
40-44	228 (18.3)	173 (14.2)	83 (7.4)	484 (13.5)
45-70	165 (13.2)	157 (13.0)	144 (12.8)	466 (13.0)
Median	34	33	23	31
Race				
White	770 (61.7)	67 (5.5)	767 (67.9)	1,604 (44.6)
Black	352 (28.2)	2 (0.2)	184 (16.3)	538 (15.0)
Asian/Pacific Islander	21 (1.7)	0	74 (6.6)	95 (2.6)
American Indian	68 (5.4)	0	2 (0.2)	70 (2.0)
Mixed	0	1,093 (90.0)	33 (2.9)	1,126 (31.3)
Unknown/Refused	38 (3.0)	53 (4.4)	69 (6.1)	160 (4.5)
Ethnicity				
Hispanic	274 (21.9)	1,211 (99.7)	174 (15.4)	1,659 (46.2)
Non-Hispanic	957 (76.6)	1 (0.1)	947 (83.9)	1,905 (53.0)
Refused	18 (1.4)	3 (0.3)	8 (0.7)	29 (0.8)
Marital status				
Single, never married	484 (38.8)	266 (21.9)	776 (68.7)	1.526 (42.5)
Married	414 (33.2)	697 (57.4)	166 (14.7)	1,277 (35.5)
Cohabiting	211 (16.9)	189 (15.6)	54 (4.8)	454 (12.6)
Divorced/Separated/Widow	137 (11.0)	60 (4.9)	129 (11.4)	326 (9.1)
Refused	3 (0.2)	3 (0.3)	4 (0.4)	10 (0.3)
Education				
<12 years	265 (21.2)	484 (39.8)	34 (3.0)	783 (21.8)
Completed 12 years	468 (37.5)	293 (24.1)	202 (17.9)	963 (26.8)
13-15 years	175 (14.0)	116 (9.6)	614 (54.4)	905 (25.2)
Completed 16 years	268 (21.5)	242 (19.9)	198 (17.5)	708 (19.7)
≥ 17 years	71 (5.7)	73 (6.0)	80 (7.1)	224 (6.2)
Refused	2 (0.2)	7 (0.6)	1 (0.1)	10 (0.3)
Cigarette smoker				
Never	770 (61.7)	541 (44.5)	711 (63.0)	2,022 (56.3)
Past	241 (19.3)	273 (22.5)	186 (16.5)	700 (19.5)
Current	236 (18.9)	399 (32.8)	230 (20.4)	865 (24.1)
Refused/Missing	2 (0.2)	2 (0.2)	2 (0.2)	6 (0.2)
Smoking pack-years (quartiles)				
Never smoked	770 (61.7)	541 (44.5)	711 (63.0)	2,022 (56.3)
0.1-0.75 pack-years	59 (4.7)	216 (17.8)	81 (7.2)	356 (9.9)
>0.75-2.79 pack-years	82 (6.6)	209 (17.2)	65 (5.8)	356 (9.9)

>2.79-8.89 pack-years	128 (10.3)	152 (12.5)	90 (8.0)	370 (10.3)
>8.9 pack-years	181 (14.5)	57 (4.7)	141 (12.5)	379 (10.6)
Refused/Missing	29 (2.3)	40 (3.3)	41 (3.6)	110 (3.1)
Monthly alcohol intake				
0 drinks	349 (28.0)	303 (24.9)	216 (19.1)	868 (24.2)
1-30 drinks	530 (42.3)	644 (53.0)	462 (40.9)	1,636 (45.5)
31-60 drinks	129 (10.3)	107 (8.8)	174 (15.4)	410 (11.4)
≥61 drinks	191 (15.3)	133 (11.0)	262 (23.2)	586 (16.3)
Refused/Missing	50 (4.0)	28 (2.3)	15 (1.3)	93 (2.6)
Circumcised				
No	1,069 (85.6)	1,030 (84.8)	201 (17.8)	2,300 (64.0)
Yes	177 (14.2)	141 (11.6)	898 (79.5)	1,216 (33.8)
Partial	3 (0.2)	44 (3.6)	30 (2.7)	77 (2.1)
Recruitment source				
Newspaper/Magazine	0	4 (0.3)	166 (14.7)	170 (4.7)
Class Presentation	0	0	54 (4.8)	54 (1.5)
Radio	0	0	21 (1.9)	21 (0.6)
TV	335 (26.8)	1 (0.1)	5 (0.4)	341 (9.5)
Internet/Email	17 (1.4)	0	28 (2.5)	45 (1.3)
Flyer/Poster	477 (38.2)	184 (15.1)	210 (18.6)	871 (24.2)
Mail	0	16 (1.3)	144 (12.8)	160 (4.5)
Word of Mouth	146 (11.7)	567 (46.7)	448 (39.7)	1,161 (32.3)
Enrolled in Other Study	2 (0.2)	0	10 (0.9)	12 (0.3)
School/University	124 (9.9)	0	0	124 (3.5)
Health Dept/Hospital/Health Fair	5 (0.4)	0	43 (3.8)	48 (1.3)
Military Zone	0	46 (3.8)	0	46 (1.3)
Corporation/Business	92 (7.4)	379 (31.2)	0	471 (13.1)
Other	51 (4.1)	18 (1.5)	0	69 (1.9)
Sexual behavior characteristics				
Current steady partner				
Yes	988 (79.1)	1,080 (88.9)	692 (61.3)	2,760 (76.8)
No	254 (20.3)	130 (10.7)	435 (38.5)	819 (22.8)
Refused	7 (0.6)	5 (0.4)	2 (0.2)	14 (0.4)
No. of lifetime sexual partners				
1	75 (6.0)	113 (9.3)	122 (10.8)	310 (8.6)
2-9	402 (32.2)	699 (57.5)	499 (44.2)	1,600 (44.5)
10-19	260 (20.8)	202 (16.6)	187 (16.6)	649 (18.1)
20-49	285 (22.8)	109 (9.0)	190 (16.8)	584 (16.3)
50+	117 (9.4)	16 (1.3)	89 (7.9)	222 (6.2)
Refused/Missing	110 (8.8)	76 (6.3)	42 (3.7)	228 (6.4)
Median (IQR)	10 (5 - 25)	5 (3 - 10)	7 (3 - 20)	8 (3 - 17)
Age at first sexual intercourse				
<18 years	899 (72.0)	627 (51.6)	728 (64.5)	2,254 (62.7)
≥18 years	336 (26.9)	570 (46.9)	386 (34.2)	1,292 (36.0)
Refused/Missing	14 (1.1)	18 (1.5)	15 (1.3)	47 (1.3)
Mean (sd)	16 (3.3)	17 (3.4)	17 (2.9)	17 (3.3)

No. of female partners in the past 3 or 6 months (combined[1])				
None recent	270 (21.6)	358 (29.5)	187 (16.6)	815 (22.7)
1 partner	468 (37.5)	508 (41.8)	631 (55.9)	1,607 (44.7)
2 partners	211 (16.9)	173 (14.2)	127 (11.3)	511 (14.2)
3 partners	104 (8.3)	67 (5.5)	86 (7.6)	257 (7.2)
4+ partners	155 (12.4)	30 (2.5)	83 (7.4)	268 (7.5)
Refused/Missing	41 (3.3)	79 (6.5)	15 (1.3)	135 (3.8)
Recent condom use[1]				
Not always	735 (58.9)	537 (44.2)	649 (57.5)	1,921 (53.5)
Always	386 (30.1)	579 (47.7)	327 (29.0)	1,292 (36.0)
No recent sexual activity	118 (9.5)	65 (5.4)	142 (12.5)	325 (9.1)
Refused/Missing	10 (0.8)	34 (2.8)	11 (1.0)	55 (1.5)
Current infection with another sexually transmitted disease				
HSV	484 (38.8)	104 (8.6)	144 (12.8)	732 (20.4)
Chlamydia	30 (2.4)	15 (1.2)	14 (1.2)	59 (1.6)
Syphilis	25 (2.0)	9 (0.7)	0	34 (1.0)
Gonorrhea	9 (0.7)	1 (0.1)	2 (0.2)	12 (0.3)
Sex partner with an STD in the past 6 months				
Yes	278 (22.3)	120 (9.9)	192 (17.0)	590 (16.4)
No	491 (39.3)	631 (51.9)	554 (49.1)	1,676 (46.7)
Don't know	479 (38.4)	458 (37.7)	382 (33.8)	1,319 (36.7)
Refused/Missing	1 (0.1)	6 (0.5)	1 (0.1)	8 (0.2)
Sex partner with warts in the past 6 months				
Yes	117 (9.4)	42 (3.5)	39 (3.5)	198 (5.5)
No	685 (54.8)	782 (64.4)	809 (71.7)	2,276 (63.4)
Don't know	447 (35.8)	385 (31.7)	281 (24.9)	1,113 (31.0)
Refused/Missing	0	6 (0.5)	0	6 (0.2)
Partner with abnormal Pap smear in the past 6 months				
Yes	162 (13.0)	227 (18.7)	166 (14.7)	555 (15.5)
No	589 (47.2)	646 (53.2)	491 (43.5)	1,726 (48.0)
Don't know	495 (39.6)	331 (27.2)	472 (41.8)	1,298 (36.1)
Refused/Missing	3 (0.2)	11 (0.9)	0	14 (0.4)
Sexual orientation				
Sex with women only	1,046 (83.8)	1,153 (94.9)	1,081 (95.8)	3,280 (91.3)
Sex with men only	31 (2.5)	4 (0.3)	10 (0.9)	45 (1.3)
Sex with women and men	172 (13.8)	57 (4.7)	38 (3.4)	267 (7.4)
Refused	0	1 (0.1)	0	1 (0.03)
Anal sex w/man in past 6 months				
No	1,130 (90.5)	1,200 (98.8)	1,105 (97.9)	3,435 (95.6)
Yes	119 (9.5)	15 (1.2)	24 (2.1)	158 (4.4)

[1] In past 3 and 6 months combined.

Table 2. HPV type distribution by country

	Brazil (n=1,249)	Mexico (n=1,215)	United States (n=1,129)	p-value[1]	Total (n=3,593)
	n (%)	*n* (%)	*n* (%)		*n* (%)
Any HPV type	929 (74.4)	762 (62.7)	754 (66.8)	**<0.0001**	2,445 (68.1)
Any oncogenic type	443 (35.5)	348 (28.6)	346 (30.7)	**0.001**	1,137 (31.6)
Oncogenic type(s) only	140 (11.2)	133 (11.0)	162 (14.4)	**0.020**	435 (12.1)
Any nononcogenic type	624 (50.0)	477 (39.3)	387 (34.3)	**<0.0001**	1,488 (41.4)
Nononcogenic type(s) only	321 (25.7)	262 (21.6)	203 (18.0)	**<0.0001**	786 (21.9)
Oncogenic and nononcogenic	303 (24.3)	215 (17.7)	184 (16.3)	**<0.0001**	702 (19.5)
Unclassified type(s) only[2]	165 (13.2)	152 (12.5)	205 (18.2)	**<0.0001**	522 (14.5)
Multiple types	461 (36.9)	325 (26.8)	277 (24.5)	**<0.0001**	1,063 (29.6)
Vaccine types (6, 11, 16, or 18)	227 (18.2)	169 (13.9)	188 (16.7)	**0.015**	584 (16.3)

[1] Pearson's chi-squared

[2] PCR +/genotype -

Table 3. Age-specific prevalence of any HPV type by country

	Brazil (n=1,249)	Mexico (n=1,215)	United States (n=1,129)	Total (n=3,593)
Age (years)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
18-19	20 (74.1)	21 (56.8)	142 (57.7)	183 (59.0)
20-24	154 (82.4)	95 (57.6)	248 (66.9)	497 (68.7)
25-29	158 (72.8)	156 (66.4)	77 (71.3)	391 (69.8)
30-34	177 (75.6)	151 (61.9)	57 (73.1)	385 (69.2)
35-39	143 (74.9)	123 (60.3)	70 (70.7)	336 (68.0)
40-44	165 (72.4)	112 (64.7)	56 (67.5)	333 (68.8)
45-70	112 (67.9)	104 (66.2)	104 (72.2)	320 (68.7)
p for trend	**0.011**	0.236	**0.006**	0.132

Table 4. Bivariate assocations between factors and any HPV type by country

	Brazil (n=1,249)		Mexico (n=1,215)		United States (n=1,129)		Total (n=3,593)	
	PR (95% CI)	*p-value*	*PR (95% CI)*	*p-value*	*PR (95% CI)*	*p-value*	*PR (95% CI)*	*p-value*
Demographic characteristics								
Age (years)	1.00 (0.99 - 1.00)	0.058	1.00 (0.99 - 1.01)	0.133	1.00 (1.00 - 1.01)	0.037	1.00 (0.99 - 1.00)	0.127
Race		0.528				0.072		
White	1.0 (Referent)				1.0 (Referent)			
Black	0.90 (0.77 - 1.04)	0.149			0.95 (0.78 - 1.16)	0.640		
Asian/Pacific Islander	0.93 (0.56 - 1.55)	0.783			0.58 (0.40 - 0.84)	0.004		
American Indian	1.02 (0.77 - 1.34)	0.915			N/A[1]			
Mixed	N/A[1]				0.96 (0.63 - 1.47)	0.849		
Unknown/Refused	0.96 (0.66 - 1.40)				0.94 (0.69 - 1.27)			
Ethnicity								
Hispanic	1.0 (Referent)				1.0 (Referent)			
Non-Hispanic	0.97 (0.83 - 1.13)	0.717			1.09 (0.89 - 1.33)	0.422		
Refused	1.10 (0.65 - 1.85)				1.41 (0.66 - 3.03)			
Marital status		0.707		0.150		0.653		<0.001
Single, never married	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Married	0.93 (0.79 - 1.08)	0.334	0.94 (0.78 - 1.12)	0.469	0.99 (0.81 - 1.22)	0.939	0.93 (0.88 - 0.98)	0.007
Cohabiting	1.02 (0.85 - 1.23)	0.843	1.12 (0.89 - 1.41)	0.318	1.04 (0.75 - 1.46)	0.798	1.08 (1.01 - 1.15)	0.028
Divorced/Separated/Widow	1.01 (0.81 - 1.26)	0.923	1.21 (0.88 - 1.68)	0.244	1.15 (0.92 - 1.42)	0.218	1.11 (1.04 - 1.19)	0.003
Refused	N/A[1]		N/A[1]		N/A[1]		1.17 (0.86 - 1.60)	
Education		0.423		0.469		0.252		0.446
<12 years	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Completed 12 years	1.01 (0.85 - 1.20)	0.819	1.02 (0.85 - 1.22)	0.774	0.87 (0.57 - 1.31)	0.149	1.06 (0.94 - 1.18)	0.102
13-15 years	1.00 (0.80 - 1.24)	0.955	1.14 (0.89 - 1.45)	0.079	0.82 (0.56 - 1.22)	0.036	1.02 (0.91 - 1.15)	0.564
Completed 16 years	0.98 (0.80 - 1.19)	0.675	1.06 (0.87 - 1.29)	0.323	0.82 (0.54 - 1.24)	0.051	1.03 (0.91 - 1.16)	0.493
≥ 17 years	0.84 (0.61 - 1.17)	0.080	1.01 (0.74 - 1.39)	0.882	0.88 (0.56 - 1.40)	0.268	0.98 (0.82 - 1.18)	0.734
Refused	N/A[1]		1.41 (0.63 - 3.17)		N/A[1]		1.36 (0.70 - 2.62)	
Cigarette smoker		0.619		0.489		0.391		0.063
Never	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Past	0.98 (0.83 - 1.16)	0.820	1.09 (0.91 - 1.31)	0.345	1.07 (0.88 - 1.30)	0.509	1.03 (0.97 - 1.09)	0.348
Current	1.08 (0.91 - 1.27)	0.385	1.09 (0.93 - 1.29)	0.294	1.13 (0.94 - 1.35)	0.185	1.06 (1.01 - 1.12)	0.019
Refused/Missing	N/A[1]		N/A[1]		N/A[1]		0.75 (0.34 - 1.67)	
Smoking pack-years (quartiles)		0.463		0.026		0.130		0.004
Never smoked	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
0.1-0.75 pack-years	0.92 (0.67 - 1.27)	0.371	1.17 (0.97 - 1.42)	0.006	0.98 (0.73 - 1.31)	0.799	1.02 (0.94 - 1.10)	0.623
>0.75-2.79 pack-years	1.03 (0.79 - 1.33)	0.690	0.99 (0.80 - 1.21)	0.832	1.07 (0.79 - 1.46)	0.409	0.97 (0.89 - 1.05)	0.458

>2.79-8.89 pack-years	0.98 (0.78 - 1.21)	0.683	1.12 (0.90 - 1.40)	0.081	1.10 (0.85 - 1.43)	0.174	1.05 (0.97 - 1.13)	0.233
>8.9 pack-years	1.07 (0.89 - 1.28)	0.155	1.15 (0.82 - 1.60)	0.159	1.15 (0.93 - 1.42)	0.018	1.13 (1.06 - 1.20)	<0.001
Refused/Missing	1.22 (0.82 - 1.80)		1.00 (0.66 - 1.52)		1.21 (0.85 - 1.73)		1.12 (1.00 - 1.25)	
Monthly alcohol intake		0.011		0.239		0.387		0.002
0 drinks	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
1-30 drinks	1.03 (0.95 - 1.12)	0.488	1.06 (0.95 - 1.18)	0.291	0.98 (0.87 - 1.10)	0.745	1.02 (0.96 - 1.08)	0.601
31-60 drinks	0.97 (0.85 - 1.11)	0.694	1.04 (0.87 - 1.24)	0.675	1.02 (0.88 - 1.17)	0.829	1.01 (0.93 - 1.10)	0.840
≥61 drinks	1.15 (1.05 - 1.26)	0.004	1.16 (1.01 - 1.35)	0.042	1.07 (0.95 - 1.21)	0.265	1.12 (1.05 - 1.20)	0.001
Refused/Missing	1.14 (0.99 - 1.32)		1.08 (0.81 - 1.45)		0.81 (0.50 - 1.31)		1.09 (0.95 - 1.25)	
Circumcised		0.682		0.784		0.285		0.452
No	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Yes	0.93 (0.77 - 1.13)	0.478	1.05 (0.85 - 1.31)	0.630	1.17 (0.96 - 1.43)	0.117	1.01 (0.96 - 1.06)	0.722
Partial	N/A[1]		0.91 (0.61 - 1.36)	0.639	1.08 (0.66 - 1.75)	0.759	0.90 (0.75 - 1.07)	0.241
Sexual behavior characteristics								
Current steady partner		0.290		0.531		0.694		0.426
Yes	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
No	0.92 (0.78 - 1.08)	0.290	1.07 (0.86 - 1.34)	0.531	0.97 (0.84 - 1.12)	0.694	0.98 (0.93 - 1.03)	0.426
Refused	0.94 (0.39 - 2.27)		0.64 (0.16 - 2.57)		N/A[1]		0.94 (0.64 - 1.39)	
No. of lifetime sexual partners[2]	1.00 (1.00 - 1.00)	0.024	1.01 (1.01 - 1.01)	<0.001	1.01 (1.00 - 1.01)	<0.001	1.01 (1.00 - 1.01)	<0.001
Age at first sexual intercourse[3]	0.99 (0.98 - 1.00)	0.142	0.98 (0.97 - 0.99)	0.004	0.97 (0.96 - 0.99)	<0.001	0.98 (0.97 - 0.99)	<0.001
No. of female partners in the past 3 or 6 months (combined[4])		0.001		0.023		0.001		<0.001
None recent	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
1 partner	1.04 (0.87 - 1.25)	0.397	1.16 (0.97 - 1.38)	0.113	1.11 (0.90 - 1.37)	0.109	1.11 (1.04 - 1.18)	0.002
2 partners	1.17 (0.95 - 1.44)	0.003	1.30 (1.04 - 1.63)	0.023	1.13 (0.85 - 1.50)	0.167	1.23 (1.14 - 1.32)	<0.001
3 partners	1.20 (0.93 - 1.55)	0.004	1.46 (1.08 - 1.98)	0.015	1.29 (0.95 - 1.75)	0.002	1.32 (1.22 - 1.44)	<0.001
4+ partners	1.18 (0.94 - 1.49)	0.003	1.60 (1.06 - 2.40)	0.025	1.34 (0.99 - 1.82)	<0.001	1.35 (1.24 - 1.46)	<0.001
Refused/Missing	1.18 (0.82 - 1.71)		1.14 (0.84 - 1.57)		1.01 (0.51 - 1.99)		1.12 (0.99 - 1.28)	
Recent condom use[4]		0.544		0.094		0.099		0.001
Not always	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Always	0.92 (0.80 - 1.06)	0.248	0.90 (0.83 - 0.99)	0.027	1.06 (0.97 - 1.16)	0.206	0.93 (0.89 - 0.98)	0.006
No recent sexual activity	0.88 (0.69 - 1.11)	0.273	0.90 (0.73 - 1.11)	0.332	0.90 (0.78 - 1.04)	0.143	0.89 (0.81 - 0.97)	0.009
Refused/Missing	0.91 (0.43 - 1.91)	0.795	0.80 (0.58 - 1.10)	0.166	0.68 (0.36 - 1.30)	0.247	0.77 (0.61 - 0.98)	0.036
Current infection with another sexually transmitted disease								
HSV	1.04 (0.97 - 1.11)	0.281	1.15 (1.01 - 1.31)	0.037	1.11 (0.99 - 1.23)	0.069	1.13 (1.07 - 1.18)	<0.001

Chlamydia	1.12 (0.76 - 1.67)	0.565	1.17 (0.65 - 2.13)	0.602	1.40 (0.81 - 2.42)	0.232	1.22 (1.09 - 1.38)	0.001
Syphilis and/or gonorrhea	1.06 (0.72 - 1.57)	0.766	1.12 (0.53 - 2.35)	0.770	1.50 (0.37 - 6.00)	0.568	1.15 (0.98 - 1.34)	0.093
Sex partner with an STD in the past 6 months								
No	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Yes	1.06 (0.90 - 1.26)	0.475	1.28 (1.02 - 1.60)	0.036	1.19 (0.98 - 1.44)	0.086	1.18 (1.11 - 1.25)	<0.001
Don't know	1.02 (0.88 - 1.18)		1.05 (0.90 - 1.22)		1.10 (0.93 - 1.29)		1.06 (1.01 - 1.12)	
Refused/Missing	N/A[1]		0.83 (0.27 - 2.59)		N/A[1]		0.77 (0.39 - 1.55)	
Sex partner with warts in the past 6 months								
No	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Yes	1.13 (1.03 - 1.24)	0.007	1.32 (0.13 - 1.54)	0.001	1.15 (0.95 - 1.40)	0.146	1.23 (1.14 - 1.32)	<0.001
Don't know	0.98 (0.92 - 1.06)		1.03 (0.94 - 1.13)		1.12 (1.02 - 1.22)		1.05 (1.00 - 1.10)	
Refused/Missing	N/A[1]		0.81 (0.36 - 1.81)		N/A[1]		0.75 (0.34 - 1.68)	
Partner with abnormal Pap smear in the past 6 months								
No	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Yes	1.12 (0.93 - 1.37)	0.237	1.08 (0.90 - 1.30)	0.411	1.30 (1.06 - 1.59)	0.012	1.15 (1.08 - 1.22)	<0.001
Don't know	1.00 (0.87 - 1.16)		1.10 (0.93 - 1.30)		1.09 (0.93 - 1.28)		1.07 (1.01 - 1.12)	
Refused/Missing	N/A[1]		0.91 (0.40 - 2.03)		N/A[1]		0.99 (0.67 - 1.46)	
Sexual orientation		0.817		0.882		0.963		0.519
Sex with women only	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Sex with men only	1.13 (0.77 - 1.68)	0.530	1.20 (0.39 - 3.73)	0.752	0.90 (0.40 - 2.00)	0.791	1.15 (0.82 - 1.61)	0.410
Sex with women and men	1.01 (0.84 - 1.22)	0.887	1.06 (0.77 - 1.48)	0.694	0.98 (0.66 - 1.47)	0.935	1.06 (0.92 - 1.23)	0.410
Refused	N/A[1]		N/A[1]		N/A[1]		N/A[1]	
Anal sex w/man in past 6 months								
No	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Yes	1.02 (0.91 - 1.13)	0.737	1.06 (0.74 - 1.53)	0.737	1.13 (0.89 - 1.42)	0.322	1.10 (1.00 - 1.21)	0.041

[1] Fewer than 5 observations.

[2] N=3,365 because 228 men declined to answer.

[3] N=3,546 because 47 men declined to answer.

[4] In past 3 and 6 months combined.

Table 5. Factors independently associated with HPV infection in men in the HIM study (adjusted by country)

Any HPV	*PR (95% CI)*	*p-value*
Lifetime number of partners	1.004 (1.003 - 1.006)	<0.001
Number of recent partners		<0.001
None recent	1.0 (Referent)	
1 partner	1.10 (1.03 - 1.18)	0.006
2 partners	1.17 (1.08 - 1.26)	<0.001
3 partners	1.23 (1.12 - 1.34)	<0.001
4+ partners	1.15 (1.05 - 1.26)	0.003
Age at sexual debut	0.99 (0.98 - 0.999)	0.031
Co-infection with another STD		
HSV	1.06 (1.01 - 1.12)	0.046
Recent partner charactertistics		
Partner with warts	1.11 (1.03 - 1.20)	0.010
Partner with abnormal Pap	1.09 (1.03 - 1.16)	0.005
Recent anal sex with a man	1.13 (1.02 - 1.25)	0.019
Country		0.119
United States	1.0 (Referent)	
Brazil	1.05 (0.99 - 1.11)	0.103
Mexico	0.99 (0.93 - 1.05)	0.749

Oncogenic HPV	*PR (95% CI)*	*p-value*
Lifetime number of partners	1.01 (1.01 - 1.01)	<0.001
Number of recent partners		<0.001
None recent	1.0 (Referent)	
1 partner	1.19 (1.02 - 1.39)	0.024
2 partners	1.43 (1.20 - 1.71)	<0.001
3 partners	1.53 (1.25 - 1.86)	<0.001
4+ partners	1.46 (1.19 - 1.79)	<0.001
Age at sexual debut	0.98 (0.97 - 0.998)	0.035
Co-infection with another STD		
Chlamydia	1.40 (1.08 - 1.82)	0.010
Recent partner charactertistics		
Partner with warts	1.24 (1.03 - 1.49)	0.022
Partner with an abnormal Pap	1.31 (1.14 - 1.50)	<0.001
Sexual orientation		<0.001
Sex with women only	1.0 (Referent)	
Sex with men only	1.63 (1.04 - 2.56)	0.032
Sex with women and men	1.04 (0.86 - 1.25)	0.697
Marital status		0.003
Single, never married	1.0 (Referent)	
Married	0.83 (0.73 - 0.94)	0.005
Cohabiting	0.92 (0.79 - 1.09)	0.338
Divorced/Separated/Widowed	1.15 (0.98 - 1.34)	0.083
Monthly alcohol intake		0.004
0 drinks	1.0 (Referent)	
1-30 drinks	1.08 (0.95 - 1.24)	0.238
31-60 drinks	1.09 (0.91 - 1.30)	0.372
≥ 61 drinks	1.30 (1.12 - 1.52)	0.001
Country		0.074
United States	1.0 (Referent)	
Brazil	1.10 (0.97 - 1.25)	0.148
Mexico	1.18 (1.02 - 1.36)	0.024

NOTE. N= 3,353 because 228 observations were missing for lifetime number of partners, and 12 were missing for age at sexual debut.

PR = Prevalence ratio, CI = Confidence interval

Table 6. Bivariate assocations between factors and oncogenic HPV by country

	Brazil (n=1,249)		Mexico (n=1,215)		United States (n=1,129)		Total (n=3,593)	
	PR (95% CI)	*p-value*	*PR (95% CI)*	*p-value*	*PR (95% CI)*	*p-value*	*PR (95% CI)*	*p-value*
Demographic characteristics								
Age (years)	0.98 (0.97 - 0.99)	<0.001	1.00 (0.99 - 1.01)	0.647	1.01 (1.00 - 1.01)	0.042	1.00 (0.99 - 1.00)	0.221
Race		0.582				0.073		
White	1.0 (Referent)				1.0 (Referent)			
Black	0.95 (0.76 - 1.17)	0.623			1.10 (0.84 - 1.46)	0.487		
Asian/Pacific Islander	1.46 (0.80 - 2.67)	0.222			0.39 (0.20 - 0.76)	0.006		
American Indian	0.94 (0.61 - 1.44)	0.776			N/A[1]			
Mixed	N/A[1]				1.07 (0.59 - 1.97)	0.816		
Unknown/Refused	0.88 (0.49 - 1.56)				1.17 (0.77 - 1.76)			
Ethnicity								
Hispanic	1.0 (Referent)				1.0 (Referent)			
Non-Hispanic	1.04 (0.86 - 1.25)	0.745			1.13 (0.87 - 1.46)	0.435		
Refused	1.30 (0.75 - 2.23)				1.36 (0.54 - 3.43)			
Marital status		0.024		0.001		0.184		<0.001
Single, never married	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Married	0.71 (0.56 - 0.89)	0.003	0.76 (0.59 - 0.99)	0.040	0.92 (0.67 - 1.27)	0.619	0.78 (0.70 - 0.88)	<0.001
Cohabiting	0.94 (0.73 - 1.23)	0.665	0.89 (0.63 - 1.25)	0.498	0.86 (0.50 - 1.48)	0.594	0.97 (0.84 - 1.13)	0.707
Divorced/Separated/Widow	0.98 (0.72 - 1.32)	0.871	1.58 (1.05 - 2.38)	0.029	1.34 (0.99 - 1.81)	0.055	1.24 (1.07 - 1.44)	0.004
Refused	N/A[1]		N/A[1]		N/A[1]		1.49 (0.80 - 2.78)	
Education		0.585		0.083		0.356		0.130
<12 years	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Completed 12 years	1.19 (0.92 - 1.55)	0.102	1.06 (0.80 - 1.40)	0.621	0.75 (0.41 - 1.37)	0.242	1.15 (1.00 - 1.33)	0.052
13-15 years	1.10 (0.79 - 1.53)	0.489	1.03 (0.69 - 1.52)	0.879	0.79 (0.45 - 1.38)	0.293	1.07 (0.93 - 1.25)	0.340
Completed 16 years	1.12 (0.83 - 1.50)	0.360	1.37 (1.04 - 1.80)	0.007	0.77 (0.42 - 1.40)	0.276	1.19 (1.02 - 1.38)	0.028
≥ 17 years	1.07 (0.68 - 1.68)	0.734	1.21 (0.78 - 1.89)	0.312	1.01 (0.53 - 1.94)	0.959	1.22 (0.99 - 1.51)	0.062
Refused	N/A[1]		0.55 (0.08 - 3.93)		N/A[1]		1.40 (0.65 - 3.02)	
Cigarette smoker		0.014		0.477		0.161		0.002
Never	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Past	1.00 (0.78 - 1.29)	0.985	1.10 (0.84 - 1.45)	0.490	1.11 (0.83 - 1.48)	0.477	1.05 (0.92 - 1.20)	0.450
Current	1.38 (1.10 - 1.73)	0.005	1.16 (0.91 - 1.47)	0.232	1.28 (0.99 - 1.65)	0.058	1.22 (1.10 - 1.37)	<0.001
Refused/Missing	N/A[1]		N/A[1]		N/A[1]		0.56 (0.09 - 3.35)	
Smoking pack-years (quartiles)		0.119		0.033		0.291		0.059
Never smoked	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
0.1-0.75 pack-years	0.97 (0.61 - 1.55)	0.886	1.37 (1.04 - 1.81)	0.006	1.17 (0.78 - 1.74)	0.357	1.18 (1.01 - 1.38)	0.039
>0.75-2.79 pack-years	1.40 (1.00 - 1.97)	0.009	0.93 (0.68 - 1.28)	0.629	1.08 (0.68 - 1.71)	0.702	1.04 (0.88 - 1.23)	0.667

>2.79-8.89 pack-years	1.13 (0.83 - 1.54)	0.320	1.21 (0.88 - 1.67)	0.164	1.24 (0.93 - 1.72)	0.154	1.17 (1.00 - 1.37)	0.045
>8.9 pack-years	1.08 (0.83 - 1.42)	0.468	1.05 (0.63 - 1.77)	0.812	1.27 (0.93 - 1.72)	0.062	1.17 (1.00 - 1.36)	0.045
Refused/Missing	1.87 (1.16 - 3.02)		0.75 (0.37 - 1.53)		1.11 (0.63 - 1.95)		1.19 (0.92 - 1.55)	
Monthly alcohol intake		0.001		0.005		0.055		<0.001
0 drinks	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
1-30 drinks	1.25 (1.02 - 1.53)	0.029	1.00 (0.80 - 1.26)	0.999	1.15 (0.88 - 1.50)	0.295	1.12 (0.98 - 1.28)	0.092
31-60 drinks	1.06 (0.77 - 1.44)	0.734	1.27 (0.92 - 1.77)	0.145	1.15 (0.84 - 1.59)	0.385	1.14 (0.95 - 1.37)	0.158
≥61 drinks	1.57 (1.25 - 1.97)	<0.001	1.51 (1.14 - 2.00)	0.004	1.43 (1.08 - 1.88)	0.011	1.48 (1.28 - 1.72)	<0.001
Refused/Missing	1.95 (1.45 - 2.63)		1.22 (0.69 - 2.15)		0.77 (0.27 - 2.17)		1.58 (1.22 - 2.05)	
Circumcised		0.732		0.577		0.262		0.924
No	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Yes	0.89 (0.68 - 1.18)	0.431	1.17 (0.85 - 1.59)	0.331	1.28 (0.95 - 1.73)	0.102	1.02 (0.92 - 1.13)	0.699
Partial	N/A[1]		1.14 (0.67 - 1.94)	0.637	1.21 (0.59 - 2.45)	0.605	0.99 (0.71 - 1.39)	0.961
Sexual behavior characteristics								
Current steady partner								
Yes	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
No	0.97 (0.77 - 1.23)	0.815	1.40 (1.04 - 1.89)	0.028	0.90 (0.73 - 1.13)	0.367	1.02 (0.91 - 1.14)	0.734
Refused	1.20 (0.39 - 3.75)		0.73 (0.10 - 5.18)		1.57 (0.22 - 11.21)		1.13 (0.56 - 2.29)	
No. of lifetime sexual partners[2]	1.01 (1.01 - 1.02)	<0.001	1.02 (1.01 - 1.02)	<0.001	1.02 (1.01 - 1.02)	<0.001	1.01 (1.01 - 1.02)	<0.001
Age at first sexual intercourse[3]	0.95 (0.93 - 0.98)	<0.001	0.97 (0.95 - 1.00)	0.020	0.96 (0.93 - 0.99)	0.012	0.96 (0.95 - 0.97)	<0.001
No. of female partners in the past 3 or 6 months (combined[4])		<0.001		<0.001		<0.001		<0.001
None recent	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
1 partner	1.24 (0.93 - 1.66)	0.091	1.22 (0.92 - 1.61)	0.163	1.15 (0.83 - 1.59)	0.318	1.22 (1.05 - 1.41)	0.009
2 partners	1.74 (1.27 - 2.40)	<0.001	1.86 (1.34 - 2.56)	<0.001	1.25 (0.81 - 1.91)	0.230	1.67 (1.42 - 1.97)	<0.001
3 partners	2.12 (1.48 - 3.04)	<0.001	1.64 (1.04 - 2.60)	0.033	1.84 (1.20 - 2.82)	<0.001	1.95 (1.63 - 2.34)	<0.001
4+ partners	1.85 (1.32 - 2.59)	<0.001	2.91 (1.76 - 4.80)	<0.001	1.86 (1.21 - 2.86)	<0.001	2.03 (1.70 - 2.42)	<0.001
Refused/Missing	2.10 (1.28 - 3.42)		1.28 (0.80 - 2.05)		1.36 (0.54 - 3.41)		1.53 (1.18 - 1.98)	
Recent condom use[4]		0.009		<0.001		0.146		<0.001
Not always	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Always	0.76 (0.61 - 0.94)	0.011	0.71 (0.59 - 0.85)	<0.001	1.02 (0.84 - 1.24)	0.831	0.79 (0.71 - 0.88)	<0.001
No recent sexual activity	0.59 (0.40 - 0.87)	0.008	0.57 (0.35 - 0.95)	0.030	0.71 (0.51 - 0.98)	0.039	0.63 (0.51 - 0.78)	<0.001
Refused/Missing	1.00 (0.37 - 2.68)	1.000	0.42 (0.19 - 0.96)	0.039	0.57 (0.16 - 2.02)	0.386	0.56 (0.33 - 0.95)	0.032
Current infection with another sexually transmitted disease								
HSV	0.86 (0.73 - 1.01)	0.060	1.23 (0.93 - 1.63)	0.144	1.18 (0.93 - 1.50)	0.172	1.06 (0.95 - 1.19)	0.308
Chlamydia	1.33 (0.78 - 2.26)	0.299	1.88 (0.93 - 3.79)	0.077	2.13 (1.10 - 4.12)	0.025	1.68 (1.31 - 2.15)	<0.001

Syphilis and/or gonorrhea	1.11 (0.64 - 1.93)	0.701	0.35 (0.05 - 2.47)	0.291	N/A[1]		0.98 (0.63 - 1.52)	0.938
Sex partner with an STD in the past 6 months								
No	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Yes	1.38 (1.08 - 1.75)	0.009	1.30 (0.92 - 1.83)	0.134	1.56 (1.17 - 2.07)	0.002	1.45 (1.28 - 1.65)	<0.001
Don't know	1.20 (0.96 - 1.49)		1.15 (0.92 - 1.45)		1.48 (1.17 - 1.88)		1.27 (1.14 - 1.42)	
Refused/Missing	N/A[1]		1.27 (0.31 - 5.11)		N/A[1]		1.39 (0.57 - 3.42)	
Sex partner with warts in the past 6 months								
No	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Yes	1.53 (1.24 - 1.89)	<0.001	1.61 (1.13 - 2.28)	0.008	1.41 (0.94 - 2.14)	0.100	1.60 (1.36 - 1.88)	<0.001
Don't know	1.13 (0.96 - 1.32)		0.99 (0.81 - 1.20)		1.45 (1.21 - 1.75)		1.18 (1.06 - 1.31)	
Refused/Missing	N/A[1]		1.18 (0.38 - 3.69)		N/A[1]		1.15 (0.37 - 3.56)	
Partner with abnormal Pap smear in the past 6 months								
No	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Yes	1.37 (1.04 - 1.79)	0.025	1.21 (0.91 - 1.59)	0.184	2.17 (1.62 - 2.91)	<0.001	1.47 (1.30 - 1.68)	<0.001
Don't know	1.15 (0.93 - 1.40)		1.18 (0.93 - 1.51)		1.62 (1.27 - 2.08)		1.29 (1.16 - 1.43)	
Refused/Missing	N/A[1]		1.04 (0.33 - 3.25)		N/A[1]		1.06 (0.46 - 2.44)	
Sexual orientation		0.918		0.668		0.770		0.482
Sex with women only	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Sex with men only	1.01 (0.55 - 1.84)	0.978	1.76 (0.44 - 7.06)	0.427	0.65 (0.16 - 2.62)	0.548	1.06 (0.64 - 1.77)	0.810
Sex with women and men	1.06 (0.81 - 1.38)	0.679	1.11 (0.69 - 1.78)	0.666	1.12 (0.64 - 1.94)	0.695	1.14 (0.92 - 1.40)	0.233
Refused	N/A[1]		N/A[1]		N/A[1]		N/A[1]	
Anal sex w/man in past 6 months								
No	1.0 (Referent)		1.0 (Referent)		1.0 (Referent)		1.0 (Referent)	
Yes	0.97 (0.75 - 1.26)	0.809	1.40 (0.75 - 2.63)	0.289	1.37 (0.85 - 2.22)	0.200	1.15 (0.93 - 1.42)	0.206

[1] Fewer than 5 observations.

[2] N=3,365 because 228 men declined to answer.

[3] N=3,546 because 47 men declined to answer.

[4] In past 3 and 6 months combined.