MALE HUMAN PAPILLOMAVIRUS (HPV) PREVALENCE AND ASSOCIATION WITH CONDOM USE IN MEXICO, BRAZIL AND THE UNITED STATES

By

Kimberly K. Repp

A THESIS

Presented to the Department of Public Health & Preventive Medicine
and the Oregon Health & Science University
School of Medicine
in partial fulfillment of
the requirements for the degree of

Master of Public Health

May 2011

Department of Public Health and Preventive Medicine

School of Medicine

Oregon Health & Science University

CERTIFICATE OF APPROVAL

This is to certify that the Master's thesis of
Kimberly K. Repp
has been approved

Mentor/Advisor

Member

Member

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

I would like to thank my dog Cyrus for the emotional support through another graduate degree. I promise this is the last one…probably.

ABSTRACT

Reported associations of condom use for male human papillomavirus infection have been inconsistent. We investigated the association between self-reported frequency of condom use and detection of genital HPV among men in a multinational cohort. A cross-sectional analysis was conducted in men aged 18-70 from Mexico, Brazil and the US. Men answered questionnaires on sexual history, condom use and sociodemographic characteristics. Among 2,261 men reporting recent vaginal sex, the proportion of men with any HPV, any oncogenic and nononcogenic type only, were calculated by frequency of condom use (5 categories, from “always” to “never”). Prevalence ratios were used to examine the associations between "always" vs not always using condoms and HPV detection. A multivariable model was used to adjust for confounders. Effect modification by country was evaluated. The proportion of men with any HPV was 70.6%, with any oncogenic was 34%, only nononcogenic was 32% and multiple types was 22%. For any HPV type, the proportion of HPV-positive men ranged from the highest of 76.2% for men who used condoms half the time to the lowest of 65.9% for men who always used condoms. The adjusted prevalence ratio for always vs not always using condoms was 0.70 (95% CI, 0.55-0.90). Condom use was consistently associated with lower HPV prevalence in the US. However, there was no association in Mexico and Brazil. Consistent condom use was strongly associated with lower HPV prevalence in men in the US. However, prevalence was high even among those who reported always using condoms.

INTRODUCTION

Human papillomavirus (HPV) is a non-enveloped double-stranded DNA virus in the Papillomaviridae family. Over 100 types of HPV have been identified that can infect skin or mucosa, with approximately 40 types able to infect the genital tract mucosa. HPV causes complex infections associated with a range of diseases, from cervical dysplasia to anal and penile cancers in males [1]. Low-risk anogenital types 6 and 11 are associated with genital warts and mild cervical dysplasia, where high risk types 16, 18, 31 and 45 are associated with high-grade dysplasia and anogenital cancers [2]. HPV-16 and 18 account for 70% of cancers of the cervix, vagina and anus and for approximately 30-40% of cancers of the vulva, penis and oropharynx [3]. HPV-16 is frequently detected in men [4-8], especially in men who have sex with men (MSM) [9]. In men, 80-85% of anal cancers and approximately 50% of penile cancers are associated with HPV infection [10]. Overall, HPV is responsible for 5.2% of all human cancers [11]. The financial burden of HPV is astronomical. Pharmacoeconomic data from the US indicates that HPV infection and HIV carry similar medical costs and HPV infection is more costly then genital herpes and hepatitis B combined in the 15-25 age group [11]. The burden of disease in healthcare, emotional well-being and financially from HPV infection is considerable.

HPV is highly infective and the most commonly sexually transmitted pathogen [12]. This year in the US, 6.2 million new HPV infections are expected [13], with one of every two people acquiring a genital HPV infection in their lifetimes [14]. The infection cycle is initiated when HPV particles reach the basal layer of the epithelium, where they bind and enter into cells through small breaks [3]. HPV is transmitted through genital contact, most often through vaginal and anal sex [14]. However, hand carriage of genital

HPV has been identified in humans with genital warts, suggesting the possibility of transmission via finger-genital contact [15]. In a study of male university students, the 24-month cumulative incidence of new infection of any genital HPV type was 62.4% [7]. Another study found the observed 6-month cumulative incidence of HPV infection following acquisition of a new male partner was 17.0% in women, and the median per-act transmission probability was 40% [12]. Assuming this median probability, this means that within 11 sexual acts, HPV transmission would almost certainly occur. The rapid transmission rate combined with carcinogenicity of HPV for both genders, makes understanding HPV a public health priority.

The majority of HPV infections are symptomless and both genders can function as carriers. The estimated female HPV prevalence is 33% [13]. The probability that a woman is an HPV carrier and her risk of developing cervical cancer are directly related to the presence of HPV DNA in the penis or urethra of her male sexual partner [16]. Male sexual behavior is a major determinant of the incidence of cervical cancer [17]. Recognizing men as carriers of HPV and acknowledging the effect their sexual activity has on HPV transmission to women, has substantial potential to inform policy for vaccination and sexual education.

Prevalence

The reported distribution and prevalence of HPV infection in men has fluctuated widely based on country, number/location of genital sampling sites and study design. Unfortunately, there is no standardized screening procedure for collecting or analyzing HPV samples in men. In an international literature review for studies in which multiple anatomic sites or specimens were evaluated, 56% of studies reported ≥20% prevalence

with the overall reported range of 1.3%-72.9% [18]. In one of the few global HPV prevalence studies, the prevalence of any HPV varied depending on the isolation site (7.9%-21.0%) with the overall prevalence from any site being 21% [19]. Cross-sectional studies have reported differences in prevalence of up to 36% by country using identical sampling methods at each site [20].

The reported male HPV prevalence in Mexico, Brazil and the US has varied considerably. An international study of HPV prevalence of these three countries found the overall prevalence of any HPV was 65.2% [21]. In a study of only Mexico, the prevalence of HPV was 8.7% in a population of men who requested a vasectomy in a public clinic [22] in contrast to a reported HPV prevalence of 44.6% in Mexican soldiers [23]. In Arizona, the prevalence of HPV was 28.2% in men attending an STD clinic, with oncogenic HPV found in 12% of participants and nononcogenic types found in 14.8% of men [24]. Location, sampling methods and study type are clearly important factors to consider when interpreting HPV prevalence. Additionally, understanding HPV burden at a country-level will help inform distribution of the quadrivalent vaccine that has demonstrated effectiveness for preventing HPV infection in men [25].

Risk factors

Understanding risk factors associated with HPV infection in men may allow their reduction and control, thus reducing HPV burden. Factors historically associated with HPV infection in men include: circumcision status, education, lifetime number of sexual partners, age, age at sexual debut, country and patterns of condom use.

Male circumcision has been repeatedly associated with reduced HPV infection and reduced cervical cancer odds in female partners [24, 26-31]. A randomized control

trial demonstrated a reduction in high-risk HPV infection after circumcision [32], possibly explaining why women with circumcised partners are at a lower risk of cervical cancer than other women. Increased clearance of any and oncogenic HPV was also associated with circumcision in a US cohort [33]. Circumcision was protective for two cohorts in Mexico [22, 23]. A recent large 5-continent cohort however, found no protection provided by male circumcision [19]. The role of circumcision in prevention of HPV infection requires clarification.

Various other risk factors have been variably associated with HPV infection: age, age of sexual debut, education and co-infection with other STIs. In Columbia, limited education and presence of antibodies to *Chlamydia trachomatis* in husbands, were risk factors for cervical neoplasia in their wives [34]. A study in China also found higher HPV prevalence in men who received fewer years of education and those who had more sex partners [35]. Presence of *C. trachomatis* or *Neisseria gonorrhea* were significant risk factors for HPV infection in numerous studies [3, 16, 26, 34, 36], but two studies indicated infection with *C. trachomatis* was not a significant risk factor for HPV infection [19, 37]. In our study, we evaluated presence of semen and non-semen-transmitted STIs in addition to HPV to help elucidate the role of co-infection as a risk factor for HPV and a marker for risky sexual behavior and condom use.

Increased number casual sexual partners and no condom use were significant risk factors found in Finnish conscript study [38]. The number of sexual partners before age 20 years was a significant predictor of HPV infection in healthy Mexican military men [23]. The finding of high numbers of sexual partners increasing HPV risk was also supported by an odds ratio of 2.3 for having over 50 lifetime sexual partners in a large

case-control study [20]. The association of a large number of sexual partners as a risk factor for HPV is demonstrated in the majority of studies [5, 19, 39-41]. Previous studies have found an interaction between recent number of sexual partners and the association with condoms [42] and we evaluate this and other potential interactions to determine the effect of these choices on the association of condom use and HPV infection.

Condoms

Latex condoms are impermeable to most viruses but HPV has been isolated from male genital skin areas that are not covered by a condom. Since HPV is not transmitted by semen, condom usage has long been assumed to be less effective than for other STDs such as gonorrhea or HIV [43]. However, multiple studies have demonstrated reduced risk of HPV infection with consistent and proper condom use [4, 24, 26-28, 41, 42]. A meta-analysis determined however, that data are too inconsistent to conclude that condoms prevent HPV infection [44]. Agreeing with this finding, the US National Institutes of Health concluded that there was insufficient evidence for the effectiveness of condoms in preventing HPV transmission in 2000 [43]. Critics argue, however, with the high transmissibility of HPV, any potential protective association of condoms would disappear over multiple intercourse acts [12]. The effect of condom use has not been clearly and consistently demonstrated across previous studies. Our large, international cross-sectional study is needed to give a clear picture of HPV prevalence and association with condom use.

The HPV in Men (HIM) Study cohort used in this analysis was specifically designed to assess HPV infection in a large cohort of men in three countries to determine the persistence of HPV infection in men and assess the factors independently associated

with acquisition and persistence HPV [45]. The association of condom use and associated risk factors of HPV infection requires elucidation in order to reduce risk factors and prevent further infection in the population. The purposes of this study were to determine HPV prevalence in the largest international male cohort to date, quantify the association of condom use on HPV infection, and identify population level risk factors for HPV infection. There is no cure for HPV infection and development of effective preventive measures such as condom use and vaccines is critical to reduce the HPV burden [25].

SUBJECTS, MATERIALS, AND METHODS

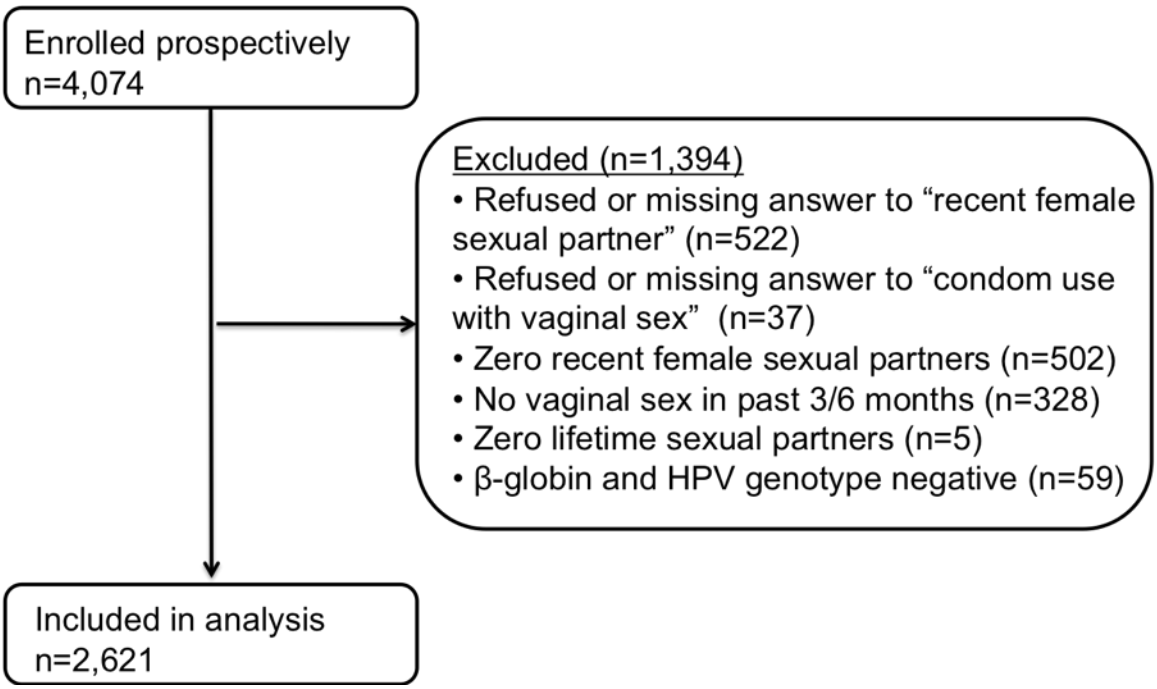
Study design, population, clinical sampling and HPV testing procedures have been described in detail elsewhere [21]. A total of 4,074 men completed an enrollment visit and of these, 2,261 men reported having vaginal sex in the past 3 or 6 months were included in the analysis. A cross sectional study of HPV infection in these 2,621 men from the ongoing HIM study was completed. Participants were recruited from the general population, universities and organized health care systems (Mexico only) in São Paula, Brazil; Cuernavaca, Mexico; Tampa, Florida and surrounding areas [21]. Men were eligible for our cross-sectional analysis if they were (1) ages 18 to 70 years, (2) residents of one of the three sites, (3) had vaginal sexual intercourse with a woman in the past 3 or 6 months, (4) had no previous diagnosis of genital warts or penile or anal cancer, (5) had no current diagnosis of a sexually transmitted disease, (6) were not participating in an HPV vaccine study and (7) no history of imprisonment, homelessness, or drug treatment in during the past 6 months. Written informed consent was obtained from all participants and human subjects committees in the respective three countries reviewed all procedures (Human Subjects Committees of the University of South Florida, the Centro de

Referencia e Tratamento de Doencas Sexualmente Transmissiveis e AIDS, Brazil, and the National Institute of Public Health of Mexico) [21].

Risk Factor Questionnaire

All men completed an extensive risk factor questionnaire that covered detailed sexual history and practices, sociodemographic characteristics, condom use patterns, alcohol and tobacco use, partner sexual history and partner history of abnormal pap tests. Participants were given the option of refusing to answer at each question on the questionnaire. There were two questionnaires used in this study with minor phrasing changes on several questions used in this analysis. Depending on the questionnaire, men were specifically asked their lifetime and recent number of vaginal sex partners in the past 3 months or vaginal sex partners in the past 6 months. After determining the responses were similar, results for recent number of sexual partners in the past 3 months and recent number of sexual partners in the past 6 months were combined into a single variable for this analysis. Men were also asked their frequency of condom use during vaginal sex with any partner in the past 3 or 6 months ("always," "more than half the time," "half the time," "less than half the time," and "never") [42]. Men who did not answer the condom use question, or reported zero lifetime vaginal sex partners, or refused to answer if they had a recent female sexual partner or did not report or refused to answer vaginal sex in the previous 3 or 6 months were excluded from analysis (Figure 1).

Figure 1. Formation of analytic cohort.



HPV penile and scrotal sampling

Sampling techniques have explained in detail elsewhere [21]. Briefly, all participants' external genitalia were swabbed with three prewetted Dacron applicators. The areas swabbed include: coronal sulcus, glans penis, and entire surface of the shaft of the penis and scrotum. Prior to DNA extraction, the three swabs were combined to produce one DNA sample per participant per clinic [21].

HPV DNA detection and genotyping

Detailed protocol for HPV analysis has been published elsewhere [21, 46]. Briefly, HPV testing of swabbed cellular material was conducted using polymerase chain reaction (PCR) for amplification of a fragment of the HPV L1 gene [47]. Specimens were tested for presence of HPV using the Linear Array HPV genotyping test [46] and HPV genotyping was conducted on all samples regardless of HPV PCR result. Samples that were human β-globin negative with no HPV genotype were excluded from analysis. The oncogenic HPV types detected in this assay include: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56,

58, 59 and 66 [48]. The nononcogenic types detected with the line blot methodology are: 6, 11, 26, 40, 42, 53-55, 61, 62, 64, 67-73, 81-84, IS39, and CP6108. All unclassified samples were characterized by direct sequencing of a fragment of the L1 gene [21].

Statistical analysis

A participant was considered positive for "any HPV" if he tested HPV-positive by PCR or genotyping. A positive β-globin test without detection of HPV DNA by PCR or genotyping was defined as "HPV negative." The category of "any oncogenic type" included those were positive for at least one oncogenic type. Single or multiple infections with only nononcogenic HPV types were classified as "nononcogenic type only." Specimens testing HPV positive by PCR but negative for any HPV genotype were categorized as "unclassified." A list of outcomes and covariates used in analysis is presented in Table 1. All independent variables listed in Table 1 were evaluated for inclusion into the multivariable model.

Frequency and mean values were calculated for all variables used in analysis in order to allow qualitative comparison of the full cohort to the analytic cohort. Variables of the analytic cohort were compared across the 5-level condom use using Pearson's χ^2 test for categorical variables. Differences in the distribution of HPV prevalence were explored by country and associations were tested with Pearson's χ^2 test.

The association of HPV detection and condom use was characterized using Poisson regression. Prevalence ratios (PR) were calculated due to the high prevalence of HPV [49-52]. The associations between dichotomous "always" vs "not always" condom use and each HPV outcome (any HPV, any oncogenic and only nononcogenic) were evaluated using Poisson regression with robust estimates for standard error. The

associations between tri-level "always", "sometimes" and "never" condom use and each HPV outcome were also evaluated using Poisson regression. Confounding was controlled by retaining any variable in the multivariable model that altered the unadjusted prevalence ratio (PR) by >10%. Effect modification of condom use by recent number of sexual partners in the past 3 or 6 months [42] and by country was hypothesized. Tests of interaction were considered statistically significant if $p \leq 0.10$. Analyses were conducted using Stata IC 11.1 software for Macintosh (StataCorp).

RESULTS

Cohort

A total of 4,074 men completed an enrollment visit. Of these, 2,261 men reported having vaginal sex in the past 3 or 6 months and were included in the analysis. The distribution of sociodemographic characteristics, alcohol and tobacco use, sexual history and condom use patterns is shown for both cohorts in Table 2. Men included in the analytic cohort were similar to those in the full cohort. However, more men in the analytic cohort had a steady partner and were <18 years of age at sexual debut.

Behavioral and other factors by frequency of condom use for the analytic cohort are presented in Table 3. Men who always used a condom were more likely to be younger, more educated, from Brazil or the US, non-Hispanic, single, without a steady partner and more likely to have 2+ partners in the past 3 or 6 months. Compared to men that used condoms more than half the time, a greater proportion of men who reported using condoms half the time or less tested positive for herpes simplex virus, syphilis, gonorrhea and/or chlamydia at the clinical visit (Table 3).

Prevalence

The HPV prevalence by country for any type, oncogenic, nononcogenic, unclassified and multiple infections is presented in Table 4. Overall prevalence for any HPV in the study population was 70.6%. Thirty-four percent of infections were any oncogenic type, 22% were only nononcogenic types and 32% were infected with multiple HPV types. The prevalence of any HPV infection was highest in Brazil (75.9%) and lowest in Mexico (66.7%, $p<0.001$). Nononcogenic type only infection was also highest in Brazil (25.3%) but lowest in the US (19.2%, $p=0.006$), with any oncogenic type demonstrating a similar country prevalence pattern ($p=0.009$). Unclassified infections were highest in the US (17.4%) with lower prevalence in Brazil (12.7%) and Mexico (12.3%). Across the study population, 8.4% of men were infected with vaccine-type 16 and 2.3% were infected with vaccine-type 18. Significant differences in prevalence were observed for HPV 16 across countries ($p=0.002$) with the Brazil having the highest prevalence of HPV 16 (9.8%). Brazil also had the highest prevalence of infection with one or more vaccine-type (types 6, 11, 16 or 18) at 39.7% with no significant difference observed across countries (data not shown). The age-specific prevalence of any HPV type by country was similar to our past studies [21].

Condom use

The proportion of HPV detected by frequency of condom use is displayed in Table 5. There was a general trend of increased HPV positive test results as condom use declined. However, there was also a trend of "never" condom use demonstrating a similar proportion of HPV positive results as "always" condom use for most of the HPV types. For any type HPV, the proportion of HPV-positive samples ranged from highest of

76.2% for men who used condoms half the time to the lowest of 65.9% for men who always used condoms (p=0.001).

Association with condom use by country

The crude association between HPV type and always using condoms differed by country (Table 6). The prevalence of any HPV type in Brazil was 75.9%, 66.7% in Mexico and 68.4% in the US. "Always" condom use was significantly associated with reduced detection for any HPV in the US crude model (crude PR, 0.79, 95% confidence interval [CI], 0.70-0.89). Also in the US crude model, condom use was associated with lower prevalence for any oncogenic HPV (crude PR, 0.66, 95% CI, 0.51-0.84) and only nononcogenic HPV (crude PR, 0.62, 95% CI, 0.44-0.89).

After adjustment for smoking pack-years, monthly alcohol intake and recent number of sexual partners, the association between any HPV type and always condom use differed by country (P = 0.025). Only the US demonstrated the positive association of condom use with detection of any HPV type (adjusted PR, 0.70, 95% CI, 0.55-0.90). There was borderline statistical significance for detection of any HPV type in Brazil in the adjusted model (adjusted PR, 0.84, 95% CI, 0.71-1.01). There was no significant association of condom use and HPV detection in the adjusted models for Mexico and Brazil. The interaction terms for condom use and country were not significant for any oncogenic (p=0.78) or only nononcogenic types (p=0.91). When multivariable models were fit without the interaction term and adjusted for country and other independent variables, the main association of condom use was still not significant. There was no interaction detected for recent number of sexual partners for any of the three HPV outcomes.

In the tri-level condom analysis (Table 7), the US continued to demonstrate a protective association of condom use for detection of any HPV type (adjusted PR, 0.72, 95% CI, 0.56-0.93). The point prevalence ratios for "sometimes" condom uses were higher than "always" condom users in the US and Brazil, but not Mexico. The interaction terms for condom use and country were significant in the multivariable adjusted model by the Wald test for any HPV type (p=0.08) using 0.10 as the significance level. The interaction terms for condom use and recent number of sexual partners were significant in the multivariable adjusted model for any oncogenic HPV (p=0.07). There was no significant interaction of condom use with country or recent sexual partners found for nononcogenic HPV in the tri-level condom analysis.

DISCUSSION

Our results demonstrate a high prevalence of HPV in men that is consistent with our other studies [2, 21, 42] and others [7, 23, 36]. Always using condoms was associated with the lowest proportion of HPV detection for any HPV, oncogenic types and only nononcogenic types (Table 5). For example, for any type of HPV, the proportion of positive samples among those who "always" used condoms was 65.9% versus 76.2 for "half the time" and 68.2% for "never" using condoms. There was a U-shaped trend for HPV detection with "always" condom use having similar HPV detection to "never" use, with the condom use levels in between usually having the highest detection of HPV.

Country had a strong association with condom use and the detection of HPV. Consistent with our previous studies, statistically significant differences were observed in the distribution of all study characteristics evaluated by country [21]. The US demonstrated the strongest association of "always" condom use. In adjusted models for

the US, “always” condom use was significantly associated with lower odds of detection for any HPV type. In the adjusted Brazilian model, “always” condom use was borderline protective for any HPV type, but not any oncogenic or only non-oncogenic. Interestingly, in Mexico there was no protective association of “always” condom use for any model of any HPV type. The significant differences in prevalence of any HPV, any oncogenic, nononcogenic only, unclassified, multiple types and types 16, 11 by country are striking. These results suggest Brazil and the US would most immediately benefit from the quadrivalent vaccine which protects from infection against HPV-6, 11, 16 and 18 in men [25].

There are many factors involved with condoms preventing STD transmission: user experience, STD infectivity, cumulative risk, user failure, method failure and STD mode of transmission [53]. Possible reasons for our study failing to find a significant relationship between condom use and HPV detection could be due to one or more of these factors. Condom breakage, slippage, use of inappropriate lubricants and application errors are disturbingly common [54-59]. Experience seems to determine successful condom usage; repeated use is a predictor of lowered failure rate in both male and female condoms [55, 60].

A randomized crossover trial comparing male condom failure rates in the US and Brazil found that there was a significant difference in “any problem” reported, with Brazil reporting significantly less condom problems than the US [61]. Both countries reported similar male condom breakage and slippage in withdrawal, but the Brazilian participants reported significantly lower partial slippage, total slippage and semen leakage than the US [61]. However, the Prostrate-specific antigen (PSA) detected from

postcoital samples of vaginal fluid indicated the PSA detection rate was similar between the US and Brazil. Thus the two countries experiences were similar but self-reporting behavior was different with Brazil systematically underreporting condom use problems. In our study, Brazil reported the highest HPV prevalence, had the highest proportion of STI positive participants, the largest numbers for recent number of sexual partners and the highest proportion of participants reporting ≥21 lifetime partners. Combining this with the possibility of systematic underreporting of condom problems by the Brazilian participants could explain the lack of protectiveness of condoms seen in this population. In terms of the US showing a protective association of condoms, condom use errors are common among subjects reporting consistent condom use [59] and perhaps the US participants in this study experienced less condom errors. We report that the majority (77.2%) of sexually active males does not always use a condom and the global burden of HPV is 70.6%.

To our knowledge, this study is the largest male cohort reporting condom use, risk factors for HPV infection and HPV prevalence in the US, Mexico and Brazil. The limitations of our study include the cross-sectional nature of the study, self-report of sensitive health information, combined HPV samples that include sites not covered by a condom, and no assessment of correct condom usage. Inaccurate reporting of condom use can reduce the possibility of detecting a true 2-fold reduction of infection risk from using condoms by 25-30% [62]. A strong protective association of condom usage was observed in the US.

SUMMARY AND CONCLUSIONS

At the most basic level, we need to understand what factors make a person choose use to always use condoms. Knowledge of HPV was positively correlated with condom use, but not significantly associated with other risk behaviors in a cross sectional study [63]. Sexual communication and the sexual enjoyment value of condoms were consistent correlates of condom use across gender and sexual orientation [64]. Condom use and excellent self-rated health were significantly correlated with awareness of HPV [65]. It seems that open partner communication, investment in person health and general education about sexually transmitted infections are helpful factors for increasing condom use and reduction of disease transmission.

After adjustment for alcohol intake, smoking and recent female sexual partners, we found a significant protective association of condoms on detection of any HPV type in the US. This association was not observed in Brazil or Mexico, nor was it observed for any oncogenic or only nononcogenic HPV types. Evaluation of all independent variables used in the analysis revealed that they were significantly different by country and most were significantly independently associated with condom use and HPV detection. The interaction terms involving country depended on categorization of the condom variable and establishment of the Type 1 error threshold. Research suggests that the power afforded by artificially inflating your Type 1 error for interaction terms is often more than offset by the increase of "false positives" [66]. We chose to set our interaction term at a higher threshold (0.10 vs. 0.05) due to the clinical relevance of the interaction and the precedent of these interactions in the male HPV literature, even though our sample size afforded high power. Models that did not have significant interaction were still built with "country" as a covariate. Although we adjusted for the association of country, population

differences in the form of residual confounders could be driving the reduced association of condoms on HPV detection. Our estimates of association are based on prevalence ratios, which, given the high prevalence of HPV, are less biased estimates of risk than are odds ratios, which have been reported in previous studies [21, 44]. This is likely to explain some of the difference in reported strength of association from other studies. For example, our adjusted prevalence ratio of 0.70 in the US corresponds to an adjusted odds ratio of 0.51 for the same model. Therefore, our findings are likely similar to previous reports that used OR [23, 40, 42] instead of the more conservative PR used here.

The most important variable that could be masking the protective association of condoms is proper condom use. We do not have information on the participant's ability to effectively use condoms, if (or how often) they experienced slippage or breakage, which could lead to differential misclassification of exposure. This means even for those who reported "always" condom use might have condom errors that reduce or eliminate the protective association of condoms, which would bias our result to the null.

Of the of people who reported "never" condom use, 23% reported being single, only 21% had 2+ female partners in the past 3 or 6 months and 90% considered themselves to have a steady partner. This is contrast to "always" condom users whom 63% reported being single, 44% reported 2 or more female sexual partners in the past 3 or 6 month and 63% reported having a steady partner. These data suggest that the "never" condom users are in a lower risk group for HPV and the "always" users are at a higher risk for HPV with more sexual partners. Thus it is possible the "always" condom users are actually using condoms more frequently with more partners and any association from improper use would be diluting the effect of their condom use. In contrast, those who

aren't using condoms are not having exposure to new HPV infection so the association of "never" using condoms is biased towards the null.

In our study, Brazil reported the lowest proportion of "always" condom use and the US reported the highest proportion of "always" condom users. Perhaps the US observed more of a protective association of condoms because condoms are used more in the US population, leading to reduced condom use errors. Additionally, perhaps those who "never" use condoms are mostly made up of older monogamous couples in long-term relationships that have little or no exposure to HPV. In combination, these factors could explain the lack of a protective association of condoms seen for most HPV outcomes and countries.

Another potential reason for condoms not demonstrating a protective association on HPV infection is the route of transmission. HPV is present on many skin surfaces not covered by a male condom. It is quite likely when applying a condom, the male touches the outside of the condom after touching the shaft of the penis or other genital areas that are HPV infected, thus placing the virus on the outside of the condom allowing transmission to his partner. To my knowledge, there are no epidemiological studies evaluating *how* males put on condoms. The few studies evaluating population HPV education have found abysmally low understanding of transmission and disease characteristics. If people are not aware of HPV, how HPV is transmitted and how to best protect yourself if you chose to be sexually active then this HPV epidemic with its associated cancers will continue.

One of the strengths of this study is its large size - this is the largest male cohort known to evaluate HPV prevalence. Men were self-selected for participation in the study

by advertisement in local papers and at university. There is potential for self-selection bias because men who choose to participate in an HPV study may be representative of those who participate in more risky behaviors. Indeed, we found that regardless of condom use, the international burden of male HPV was 70.6% which is slightly higher than some studies. In addition to confirming other studies that have found similar prevalence, this information clearly demonstrates the immediate need for massive prevention efforts to control transmission. With 10.7% of the male population infected with HPV types known to cause cancer in women and men the need for an effective vaccine for males is immediate. The distribution of oncogenic HPV determined in the study can help guide the distribution of the quadrivalent vaccine recently show to prevent HPV in men [25].

REFERENCES

1. Giuliano AR, Salmon D. The case for a gender-neutral (universal) human papillomavirus vaccination policy in the United States. Cancer Epidemiology Biomarkers & Prevention **2008**; 17:805-808.

2. Dunne EF, Nielson C, Stone KM, Markowitz LE, Giuliano A. Prevalence of HPV infection among men: A systematic review of the literature. The Journal of Infectious Diseases **2006**; 194:1044-1057.

3. Munoz N, Castellsague X, Degonzalez A, Gissmann L. Chapter 1: HPV in the etiology of human cancer. Vaccine **2006**; 24:S1-S10.

4. Partridge JM, Koutsky LA. Genital human papillomavirus infection in men. Lancet Infect Dis **2006**; 6:21-31.

5. Thompson DL, Douglas JM, Jr., Foster M, et al. Seroepidemiology of infection with human papillomavirus 16, in men and women attending sexually transmitted disease clinics in the United States. J Infect Dis **2004**; 190:1563-74.

6. Newall AT, Brotherton JM, Quinn HE, et al. Population seroprevalence of human papillomavirus types 6, 11, 16, and 18 in men, women, and children in Australia. Clin Infect Dis **2008**; 46:1647-55.

7. Partridge JM, Hughes JP, Feng Q, et al. Genital human papillomavirus infection in men: incidence and risk factors in a cohort of university students. J Infect Dis **2007**; 196:1128-36.

8. Burchell A, Winer R, Desanjose S, Franco E. Chapter 6: Epidemiology and transmission dynamics of genital HPV infection. Vaccine **2006**; 24:S52-S61.

9. Heiligenberg M, Michael KM, Kramer MA, et al. Seroprevalence and determinants of eight high-risk human papillomavirus types in homosexual men, heterosexual men, and women: a population-based study in Amsterdam. Sex Transm Dis **2010**; 37:672-80.

10. Giuliano AR, Tortolero-Luna G, Ferrer E, et al. Epidemiology of human papillomavirus infection in men, cancers other than cervical and benign conditions. Vaccine **2008**; 26 Suppl 10:K17-28.

11. Steben M, Duartefranco E. Human papillomavirus infection: Epidemiology and pathophysiology. Gynecologic Oncology **2007**; 107:S2-S5.

12. Burchell AN, Richardson H, Mahmud SM, et al. Modeling the sexual transmissibility of human papillomavirus infection using stochastic computer simulation and empirical data from a cohort study of young women in Montreal, Canada. American Journal of Epidemiology **2006**; 163:534-543.

13. Weinstock H, Berman S, Cates Jr. W. Sexually transmitted diseases among American youth: Incidence and prevalence estimates, 2000. Perspectives on Sexual and Reproductive Health **2004**; 36:6-10.

14. Centers for Disease Control and Prevention. Fact sheet: Genital HPV. Available at: http://www.cdc.gov/std/hpv/hpv-fact-sheet.pdf. Accessed 2/26/2011.

15. Sonnex D, Struss S, Gray JJ. Detection of human papillomavirus DNA on the fingers of patients with genital warts. Sexually Transmitted Infections **1999**; 75:317-319.

16. Bosch FX, de Sanjose S. The epidemiology of human papillomavirus infection and cervical cancer. Disease Markers **2007**; 23:213-227.

17. Bosch FX, Castellsague X, Munoz N, et al. Male sexual behavior and human papillomavirus DNA: key risk factors for cervical cancer in Spain. J Natl Cancer Inst **1996**; 88:1060-1075.

18. Dunne EF, Nielson CM, Stone Katherine M, Markowitz LE, Giuliano A. Prevalence of HPV infection among men: a systematic review of the literature. The Journal of Infectious Diseases **2006**; 194:1044-1057.

19. Vardas E, Giuliano AR, Goldstone S, et al. External genital human papillomavirus prevalence and associated factors among heterosexual men on 5 continents. J Infect Dis **2011**; 203:58-65.

20. Franceschi S, Castellsague X, Dal Maso L, et al. Prevalence and determinants of human papillomavirus genital infection in men. British Journal of Cancer **2002**; 86:705-711.

21. Giuliano AR, Lazcano-Ponce E, Villa LL, et al. The human papillomavirus infection in men study: human papillomavirus prevalence and type distribution among men residing in Brazil, Mexico, and the United States. Cancer Epidemiology Biomarkers & Prevention **2008**; 17:2036-2043.

22. Vaccarella S, Lazcano-Ponce E, Castro-Garduno JA, et al. Prevalence and determinants of human papillomavirus infection in men attending vasectomy clinics in Mexico. Int J Cancer **2006**; 119:1934-9.

23. Lajous M, Mueller N, Cruz-Valdez A, et al. Determinants of prevalence, acquisition, and persistence of human papillomavirus in healthy Mexican military men. Cancer Epidemiol Biomarkers Prev **2005**; 14:1710-6.

24. 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. Sexually Transmitted Diseases **2004**:601-607.

25. Giuliano A, Palefsky J, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. The New England Journal of Medicine **2011**; 364:401-411.

26. Shew ML, Fortenberry JD, Wanzhu T, et al. Association of condom use, sexual behaviors, and sexually transmitted infections with duration of genital human papillomavirus infection among adolescent women, 2006. Archives of Pediatrics and Adolescent Medicine **2006**; 160:151-156.

27. Winer R, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. The New England Journal of Medicine **2006**; 354:2645-2654.

28. Bleeker MCG, Hogewoning CJA, Voorhorst FJ, et al. Condom use promotes regression of human papillomavirus-associated penile lesions in male sexual partners of women with cervical intraepithelial neoplasia. International Journal of Cancer **2003**; 107:804-810.

29. Castellsague X, Bosch FX, Munoz N, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. The New England Journal of Medicine **2002**; 346:1105-1112.

30. Nielson Carrie M, Schiaffino Melody K, Dunne Eileen F, Salemi Jason L, Giuliano Anna R. Associations between male anogenital human papillomavirus infection and

circumcision by anatomic site sampled and lifetime number of female sex partners. The Journal of Infectious Diseases **2009**; 199:7-13.

31. Hernandez BY, Wilkens LR, Zhu X, et al. Circumcision and human papillomavirus infection in men: a site-specific comparison. J Infect Dis **2008**; 197:787-94.

32. Auvert B, Sobngwi-Tambekou J, Cutler E, et al. Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: results of a randomized controlled trial conducted in Orange Farm, South Africa. J Infect Dis **2009**; 199:14-9.

33. Lu B, Wu Y, Nielson CM, et al. Factors associated with acquisition and clearance of human papillomavirus infection in a cohort of US men: a prospective study. J Infect Dis **2009**; 199:362-71.

34. Munoz N, Castellsague X, Bosch FX, et al. Difficulty in elucidating the male role in cervical cancer in Colombia, a high-risk area for the disease. J Natl Cancer Inst **1996**; 88:1068-1075.

35. Tang X, Xu AE, Dong XP, Sun XK, Shen H, Liu JF. Epidemiological investigation of human papillomavirus infection in men attending a sexually transmitted disease clinic in Hangzhou area. Biomed Environ Sci **2006**; 19:153-7.

36. Smith JS, Backes DM, Hudgens MG, et al. Prevalence and risk factors of human papillomavirus infection by penile site in uncircumcised Kenyan men. Int J Cancer **2010**; 126:572-7.

37. 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**; 14:1528-33.

38. Hippelainen M, Syrjanen S, Hippelainen M, et al. Prevalence and risk factors of genital human papillomavirus (HPV) infections in health males: a study on Finnish conscripts. Sexually Transmitted Diseases **1993**; 20:321-328.

39. Nyitray A, Nielson CM, Harris RB, et al. Prevalence of and risk factors for anal human papillomavirus infection in heterosexual men. J Infect Dis **2008**; 197:1676-84.

40. Giuliano AR, Lazcano E, Villa LL, et al. Circumcision and sexual behavior: factors independently associated with human papillomavirus detection among men in the HIM study. Int J Cancer **2009**; 124:1251-7.

41. Smith JS, Moses S, Hudgens MG, et al. Human papillomavirus detection by penile site in young men from Kenya. Sex Transm Dis **2007**; 34:928-34.

42. Nielson CM, Harris RB, Nyitray AG, Dunne EF, Stone KM, Giuliano AR. Consistent condom use is associated with lower prevalence of human papillomavirus infection in men. J Infect Dis **2010**; 202:445-51.

43. Holmes KK, Levine R, Weaver M. Effectiveness of condoms in preventing sexually transmitted infections. Bull World Health Organ **2004**; 82:454-461.

44. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? Sexually Transmitted Diseases **2002**; 29:725-735.

45. Giuliano A. Natural history of HPV infection in men: the Health in Men (HIM) Study. Available at: http://epi.grants.cancer.gov/ResPort/HPVmen.html. Accessed September 24, 2010 2010.

46. Gravitt P, Peyton CL, Apple RJ, Wheeler CM. Genotyping of 27 human papillomavirus types by using L1 consensus PCR products by a single-hybridization, reverse line blot detection method. J Clin Microbiol **1998**; 36:3020-3027.

47. Gravitt P, Peyton CL, Alessi TQ, et al. Improved amplification of genital human papillomaviruses. J Clin Microbiol **200**; 38:357-361.

48. Cogliano V, Baan R, Straif K, Grosse Y, Secretan B, Ghissassi F. Carcinogenicity of human papillomaviruses. Lancet Oncol **2005**; 6:204.

49. Spiegelman D. Easy SAS calculations for risk or prevalence ratios and differences. American Journal of Epidemiology **2005**; 162:199-200.

50. Zocchetti C, Consonni D, Bertazzi PA. Relationship between prevalence rate ratios and odds ratios in cross-sectional studies. International Journal of Epidemiology **1997**; 26:220-223.

51. Pearce N. Effect measures in prevalence studies. Environmental Health Perspectives **2004**; 112:1047-1050.

52. Thompson ML, Meyers JE, Kriebel D. Prevalence odds ratio or prevalence ratio in the analysis of cross sectional data: what is to be done? Occupational and Environmental Medicine **1998**; 55:272-277.

53. Fitch JT, Stine C, Hager D, Mann J, Adam MB, McIlhaney J. Condom effectiveness: factors that influence risk reduction. Sexually Transmitted Diseases **2002**; 29:811-817.

54. Crosby R, DiClemente RJ, Yarber WL, Snow G, Troutman A. An event-specific analysis of condom breakage among African American men at risk of HIV acquisition. Sexually Transmitted Diseases **2008**; 35:174-177.

55. Valappil T, Kelaghan J, Macaluso M, et al. Female condom and male condom failure among women at high risk of sexually transmitted diseases. Sexually Transmitted Diseases **2005**; 32:35-43.

56. Duerr A, Gallo MF, Warner L, Jamieson DJ, Kulczycki A, Macaluso M. Assessing male condom failure and incorrect use. Sexually Transmitted Diseases **2011**; 38:1-7.

57. Crosby R, Milhausen R, Sanders SA, Graham CA, Yarber WL. Two heads are better than one: the association between condom decision-making and condom use errors and problems. Sexually Transmitted Infections **2008**; 84:198-201.

58. Crosby RA, Yarber WL, Sanders SA, et al. Men with broken condoms: who and why? Sexually Transmitted Infections **2006**; 83:71-75.

59. Shlay JC, McClung MW, Patnaik JL, Douglas JM. Comparison of sexually transmitted disease prevalence by reported condom use: errors among consistent condom users seen at an urban sexually transmitted disease clinic. Sexually Transmitted Diseases **2004**; 31:526-532.

60. Crosby R. Condom-use errors and problems: a neglected aspect of studies assessing condom effectiveness. American Journal of Preventive Medicine **2003**; 24:367-370.

61. Chen MP, Macaluso M, Blackwell R, et al. Self-reported mechanical problems during condom use and semen exposure: comparison of two randomized trials in the United States of America and Brazil. Sexually Transmitted Diseases **2007**; 24:557-562.

62. Devine OJ, Aral SO. The impact of inaccurate reporting of condom use and imperfect diagnosis of sexually transmitted disease infection in studies of condom effectiveness. Sexually Transmitted Diseases **2004**; 31:588-595.

63. Holcomb B, Bailey JM, Crawford K, Ruffin IV MT. Adults' knowledge and behaviors related to HPV infection. Journal of the American Board of Family Medicine **2004**; 17:26-31.

64. Catania JA, Coates T, J., Kegeles S, et al. Condom use in multi-ethnic neighborhoods of San Francisco: The population-based AMEN (AIDS in Multi-Ethnic Neighborhoods) study. American Journal of Public Health **1992**; 82:284-287.

65. Nielsen A, Munk C, Liaw KL, Kjaer SK. Awareness of human papillomavirus in 23 000 Danish men from the general male population. Eur J Cancer Prev **2009**; 18:236-9.

66. Marshall SW. Power for tests of interaction: effect of raiging the Type I error rate. Epidemiologic Perspectives & Innovations **2007**; 4:1-7.

Table 1. Variables used in regression analysis

Outcome variables	Primary independent variable	Covariates
Any HPV	Condom use	Age
Any oncogenic HPV		Ethnicity
Only nononcogenic HPV		Race
		Marital status
		Has a steady partner
		Amount of education
		Current cigarette smoker
		Smoking pack-years
		Monthly alcohol intake
		Circumcised
		Age at first sexual intercourse
		Lifetime number of partners
		No. of female partners in the past 3 or 6 months (combined)
		History of any sexually transmitted disease
		Partner history of sexually transmitted disease
		Partner with abnormal Pap smear in the past 6 months
		Country at enrollment
		Positive for herpes simplex virus, syphilis, gonorrhea and/or chlamydia
		Frequency of sexual intercourse

Table 2. Full Cohort versus analytic cohort

Variable	Full Cohort N=4,074 *n* (%)	Analytic cohort N=2,621 *n* (%)
Age		
18-19 years	412 (10.1)	254 (9.7)
20-24 years	820 (20.1)	584 (22.3)
25-29 years	625 (15.3)	419 (16.0)
30-34 years	613 (15.1)	397 (15.2)
35-40 years	663 (16.3)	417 (15.9)
41-45 years	461 (11.3)	283 (10.8)
46-50 years	184 (4.5)	103 (3.9)
51+ years	296 (7.3)	164 (6.3)
Ethnicity		
Hispanic	1,836 (45.1)	1,116 (42.6)
Non-Hispanic	2,203 (54.1)	1,484 (56.6)
Refused	35 (0.9)	21 (0.8)
Race		
White	1,825 (44.8)	1250 (47.7)
Black	636 (15.6)	418 (16.0)
Asian	109 (2.7)	73 (2.8)
Pacific Islander	3 (0.1)	2 (0.1)
American Indian	80 (2.0)	47 (1.8)
Mixed	1,235 (30.3)	711 (27.1)
Unknown/Refused	186 (4.6)	120 (4.6)
Marital status		
Single	1,838 (45.1)	1,186 (45.3)
Married	1,384 (34.0)	854 (32.6)
Cohabiting	484 (11.9)	339 (12.9)
Divorced/Separated	357 (8.8)	235 (9.0)
Refused	11 (0.3)	7 (0.3)
Has a steady partner		
No	1,175 (28.8)	506 (19.3)
Yes	2,883 (70.8)	2,108 (80.4)
Refused	16 (0.4)	7 (0.3)

Amount of education		
<12 years	900 (22.1)	502 (19.2)
Completed 12 years	1,089 (26.7)	687 (26.2)
13-15 years	1,038 (25.5)	728 (27.8)
Completed 16 years	785 (19.3)	530 (20.2)
≥ 17 years	248 (6.1)	168 (6.4)
Refused	14 (0.3)	6 (0.2)
Current cigarette smoker		
No	3,104 (76.2)	1,999 (76.3)
Yes	963 (23.6)	619 (23.6)
Refused	7 (0.2)	3 (0.1)
Smoking pack-years (quartiles)		
0.1-0.70 pack-years	408 (24.6)	277 (25.9)
0.71-2.50 pack-years	415 (25.0)	273 (25.5)
2.51-8.10 pack-years	407 (24.5)	253 (23.6)
8.2+ pack-years	429 (25.9)	267 (25.0)
Monthly alcohol intake		
0 drinks	1,106 (25.7)	562 (21.9)
1-30 drinks	1,848 (46.7)	1,187 (46.3)
31-60 drinks	444 (11.2)	327 (12.8)
≥61 drinks	649 (16.4)	486 (19.0)
Circumcised		
No	2,583 (63.4)	1,602 (61.1)
Yes	1,407 (34.5)	977 (37.3)
Partial	84 (2.1)	42 (1.6)
Age at first sexual intercourse		
<18 years	2,312 (56.8)	1,721 (65.7)
≥18 years	1,762 (43.3)	900 (34.3)
Lifetime number of partners		
1-5 partners	1,395 (34.2)	849 (32.4)
6-10 partners	810 (19.9)	628 (24.0)
11-20 partners	620 (15.2)	494 (18.9)
21+ partners	630 (15.5)	529 (20.2)
Refused	223 (5.5)	121 (4.6)
No. of female partners in the past 3 or 6 months (combined)		

0 partners	847 (22.0)	
1 partner	1,654 (45.0)	1,159 (60.7)
2 partners	519 (14.1)	509 (19.4)
3 partners	262 (7.1)	255 (9.7)
4+ partners	270 (7.3)	267 (10.2)
History of any sexually transmitted disease		
No	3,288 (80.9)	2,128 (81.3)
Yes	658 (16.2)	416 (15.9)
Don't know	120 (3.0)	73 (2.8)
Partner history of sexually transmitted disease		
No	1,977 (48.6)	1,180 (45.1)
Yes	654 (16.1)	450 (17.2)
Don't know	1,435 (35.3)	986 (37.7)
Partner with abnormal Pap smear in the past 6 months		
No	2,081 (51.1)	1,170 (44.6)
Yes	580 (14.2)	431 (16.4)
Don't know	1,398 (34.3)	1,015 (38.7)
Refused	15 (0.4)	5 (0.2)
Country at enrollment		
United States	1,343 (33.0)	923 (35.2)
Brazil	1,401 (34.9)	936 (35.7)
Mexico	1,330 (32.7)	762 (29.1)
Positive for Herpes Simplex virus, syphilis, gonorrhea and/or chlamydia		
Positive ≥1 STD	912 (22.5)	569 (21.8)
Negative for all STDs	3,151 (77.6)	2,046 (78.2)
Condom use		
Always	723 (22.0)	599 (22.9)
Not Always	2,560 (78.0)	2,022 (77.2)

Table 3. Characteristics of Men in the Human Papillomavirus (HPV) Study by Condom Use

	No. (%) of participants, by frequency of condom use (N=2,621)					
Variable	Always (n=599)	Greater than half the time (n=431)	Half the time (n=214)	Less than half the time (n=423)	Never (n=954)	*P*
Age						<0.001
18-19 years	105 (17.5)	58 (13.5)	20 (9.4)	42 (9.9)	29 (3.0)	
20-24 years	144 (24.0)	131 (30.4)	59 (27.6)	124 (29.3)	126 (13.2)	
25-29 years	82 (13.7)	83 (19.3)	45 (21.0)	70 (16.6)	139 (14.6)	
30-34 years	85 (14.2)	56 (13.0)	29 (13.6)	66 (15.6)	161 (16.9)	
35-40 years	80 (13.4)	54 (12.5)	38 (17.8)	66 (15.6)	179 (18.8)	
41-45 years	58 (9.7)	29 (6.7)	13 (6.1)	34 (8.0)	149 (15.6)	
46-50 years	21 (3.5)	9 (2.1)	5 (2.3)	12 (2.8)	56 (5.9)	
51+ years	24 (4.0)	11 (2.6)	5 (2.3)	9 (2.1)	115 (12.1)	
Ethnicity						0.001
Hispanic	208 (34.7)	181 (42.0)	90 (42.0)	188 (44.4)	449 (47.1)	
Non-Hispanic	388 (64.8)	247 (57.3)	121 (56.5)	231 (54.6)	497 (52.1)	
Refused	3 (0.5)	3 (0.7)	3 (1.4)	4 (1.0)	8 (0.8)	
Race						<0.001
White	291 (48.6)	209 (48.5)	107 (50.0)	199 (47.0)	444 (46.5)	
Black	109 (18.2)	78 (18.1)	33 (15.4)	67 (15.8)	131 (13.7)	
Asian	36 (6.0)	11 (2.5)	3 (1.4)	13 (3.1)	10 (1.1)	
Pacific Islander	1 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.1)	

American Indian	11 (1.8)	10 (2.3)	5 (2.3)	6 (1.4)	15 (1.6)	
Mixed	115 (19.2)	99 (23.0)	59 (27.6)	120 (28.4)	318 (33.3)	
Unknown/Refused	36 (6.0)	24 (5.6)	7 (3.3)	18 (4.3)	35 (3.7)	
Marital status						<0.001
Single	380 (63.4)	254 (58.9)	120 (56.1)	207 (48.9)	225 (23.6)	
Married	114 (19.0)	98 (22.7)	49 (22.9)	115 (27.2)	478 (50.1)	
Cohabiting	50 (8.3)	44 (10.0)	26 (12.2)	70 (16.6)	149 (15.6)	
Divorced/Separated	51 (8.5)	33 (7.7)	18 (8.4)	31 (7.3)	102 (10.7)	
Refused	4 (0.7)	2 (0.5)	1 (0.5)	0 (0)	0 (0)	
Has a steady partner						<0.001
No	215 (35.9)	87 (20.2)	51 (22.8)	59 (14.0)	94 (9.9)	
Yes	380 (63.4)	342 (79.4)	163 (76.2)	364 (86.1)	859 (90.0)	
Refused	4 (0.7)	2 (0.5)	0 (0)	0 (0)	1 (0.1)	
Amount of education						<0.001
<12 years	97 (16.2)	56 (13.0)	47 (22.0)	71 (16.8)	231 (24.2)	
Completed 12 years	168 (28.1)	113 (26.2)	52 (24.3)	117 (27.7)	237 (24.8)	
13-15 years	200 (33.4)	142 (33.0)	55 (25.7)	119 (28.1)	212 (22.2)	
Completed 16 years	103 (17.2)	87 (20.2)	42 (19.6)	94 (22.2)	204 (21.4)	
≥ 17 years	30 (5.0)	32 (7.4)	15 (17.0)	22 (5.2)	69 (7.2)	
Refused	1 (0.2)	1 (0.2)	3 (1.4)	0 (0)	1 (0.1)	
Current cigarette smoker						0.172
No	473 (79.0)	342 (79.4)	165 (77.1)	313 (74.0)	706 (74.0)	
Yes	125 (20.9)	88 (20.4)	49 (22.9)	109 (25.8)	248 (26.0)	
Refused	1 (0.2)	1 (0.2)	0 (0)	1 (0.2)	0 (0)	

Smoking pack-years (quartiles)						<0.001
0.1-0.70 pack-years	51 (24.5)	48 (33.8)	26 (32.1)	56 (32.0)	96 (20.7)	
0.71-2.50 pack-years	52 (25.0)	46 (32.4)	23 (28.4)	41 (23.4)	111 (23.9)	
2.51-8.10 pack-years	56 (26.9)	30 (21.1)	19 (23.5)	49 (28.0)	99 (21.3)	
8.2+ pack-years	49 (23.6)	18 (12.7)	13 (16.1)	29 (16.6)	158 (34.1)	
Monthly alcohol intake						<0.001
0 drinks	126 (21.8)	68 (16.2)	50 (23.8)	84 (20.2)	234 (25.0)	
1-30 drinks	271 (46.9)	196 (46.6)	94 (44.8)	170 (40.9)	456 (48.7)	
31-60 drinks	80 (13.8)	56 (13.3)	25 (11.9)	68 (16.4)	98 (10.5)	
≥61 drinks	101 (17.5)	101 (24.0)	41 (19.5)	94 (22.6)	149 (15.9)	
Circumcised						0.205
No	350 (58.4)	259 (60.1)	135 (63.1)	202 (66.7)	576 (60.4)	
Yes	241 (40.2)	163 (37.8)	77 (36.0)	137 (32.4)	359 (37.6)	
Partial	8 (1.3)	9 (2.1)	2 (0.9)	4 (1.0)	19 (2.0)	
Age at first sexual intercourse						0.062
<18 years	389 (64.9)	293 (68.0)	152 (71.0)	289 (68.3)	598 (62.7)	
≥18 years	210 (35.1)	138 (32.0)	62 (29.0)	134 (31.7)	356 (37.3)	
Lifetime number of partners						0.611
1-5 partners	210 (35.1)	125 (29.0)	69 (32.2)	132 (31.2)	313 (32.8)	
6-10 partners	136 (22.7)	108 (25.1)	48 (22.4)	102 (24.1)	234 (24.5)	
11-20 partners	97 (16.2)	86 (20.0)	39 (18.2)	87 (20.6)	185 (19.4)	
21+ partners	120 (20.0)	95 (22.0)	50 (23.4)	85 (20.1)	179 (18.8)	

Refused	36 (6.0)	17 (3.9)	8 (3.7)	17 (4.0)	43 (4.5)	
No. of female partners in the past 3 or 6 months (combined)						<0.001
1 partner	337 (56.3)	192 (44.6)	97 (45.3)	211 (49.9)	753 (78.9)	
2 partners	126 (21.0)	95 (22.0)	61 (28.5)	106 (25.1)	121 (12.7)	
3 partners	65 (10.9)	61 (14.2)	27 (12.6)	60 (14.2)	42 (4.4)	
4+ partners	71 (11.9)	83 (19.3)	29 (13.6)	46 (10.9)	38 (4.0)	
History of any sexually transmitted disease						0.337
No	484 (81.2)	361 (83.8)	172 (80.4)	355 (83.9)	756 (79.3)	
Yes	99 (16.6)	58 (13.5)	38 (17.8)	56 (13.2)	165 (17.3)	
Don't know	13 (2.2)	12 (2.8)	4 (1.9)	12 (2.8)	32 (3.4)	
Partner history of sexually transmitted disease						0.160
No	284 (47.7)	185 (42.2)	88 (41.1)	169 (40.1)	454 (47.6)	
Yes	96 (16.1)	84 (19.5)	39 (18.2)	76 (18.0)	155 (16.3)	
Don't know	216 (36.2)	162 (37.6)	87 (40.7)	177 (41.9)	344 (36.1)	
Partner with abnormal Pap smear in the past 3 or 6 months						0.058
No	293 (48.9)	185 (42.9)	83 (38.8)	181 (42.8)	428 (44.9)	
Yes	72 (12.0)	68 (15.8)	41 (19.2)	71 (16.8)	179 (18.8)	
Don't know	232 (38.7)	177 (41.1)	90 (42.1)	170 (40.2)	346 (36.3)	
Refused	2 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.1)	

Country at enrollment						<0.001
United States	248 (41.1)	162 (37.6)	74 (34.6)	128 (30.3)	311 (32.6)	
Brazil	231 (38.6)	166 (38.5)	76 (35.5)	171 (40.4)	292 (30.6)	
Mexico	120 (20.0)	103 (23.9)	64 (29.9)	124 (29.3)	351 (36.8)	
Positive for Herpes Simplex virus, syphilis, gonorrhea and/or chlamydia						0.432
Positive ≥1 STD	117 (19.6)	87 (20.2)	48 (22.4)	100 (23.7)	217 (22.8)	
Negative for all STDs	480 (80.4)	343 (77.6)	166 (77.6)	322 (76.3)	735 (77.2)	

Table 4. Summary results for grouped HPV type distribution by country at enrollment

	Brazil (n=936)	Mexico (n=762)	United States (n=923)	Total (n=2,621)	P for χ^{2*}
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Any HPV type	710 (75.9)	508 (66.7)	631 (68.4)	1849 (70.6)	<0.001
Any oncogenic type	354 (37.8)	245 (32.2)	293 (31.7)	892 (34.0)	0.009
Oncogenic types					
16	90 (9.8)	41 (5.4)	90 (9.6)	221 (8.4)	0.002
18	23 (2.4)	10 (1.3)	27 (2.9)	60 (2.3)	0.081
Nononcogenic type(s) only	237 (25.3)	169 (22.2)	177 (19.2)	583 (22.4)	0.006
Nononcogenic types					
6	68 (7.3)	55 (7.2)	54 (5.9)	177 (6.8)	0.398
11	12 (1.3)	19 (2.5)	4 (0.4)	35 (1.3)	0.001
Unclassified type(s) only	119 (12.7)	94 (12.3)	161 (17.4)	374 (14.3)	0.003
Multiple types	368 (39.3)	227 (29.8)	242 (26.2)	837 (31.9)	<0.001

*comparing proportions HPV-positive across country

Table 5. HPV detection by frequency of condom use

	No. (%) of participants, by frequency of condom use (N=2,621)					
HPV detected	Always (n=599)	Greater than half the time (n=431)	Half the time (n=214)	Less than half the time (n=423)	Never (n=954)	*P*
Any HPV type	395 (65.9)	325 (75.4)	163 (76.2)	315 (74.5)	651 (68.2)	0.001
Any oncogenic type	177 (29.6)	166 (38.5)	81 (37.9)	182 (43.0)	286 (30.0)	<0.001
Oncogenic types						
16	37 (6.2)	44 (10.2)	16 (7.5)	52 (12.3)	72 (7.6)	0.005
18	7 (1.2)	18 (4.2)	3 (1.4)	14 (3.3)	18 (1.9)	0.009
Nononcogenic type(s) only	123 (20.5)	102 (23.7)	56 (26.2)	87 (20.6)	215 (22.5)	0.385
Nononcogenic types						
6	35 (5.8)	40 (9.3)	15 (7.0)	34 (8.0)	53 (5.6)	0.076
11	9 (1.5)	7 (1.6)	3 (1.4)	6 (1.4)	10 (1.1)	0.906
Unclassified type(s) only	95 (15.9)	57 (13.2)	26 (12.2)	46 (10.9)	150 (15.7)	0.090
Multiple types	170 (28.4)	152 (35.3)	77 (36.0)	173 (40.9)	265 (27.8)	<0.001

Table 6. Prevalence Ratios (PR) with 95% Confidence Intervals (CI) for crude and adjusted models of the associations between Human Papillomavirus (HPV) and frequency of condom use

Any HPV by frequency of condom use	Crude model PR[a,c]	Adjusted Model PR[b,c]
Interaction of country x condom use, p=0.025		
United States		
Always	0.79 (0.70-0.89)	0.70 (0.55-0.90)
Not always	ref	ref
Brazil		
Always	0.96 (0.88-1.05)	0.84 (0.71-1.01)
Not always	ref	ref
Mexico		
Always	1.04 (0.92-1.19)	1.05 (0.89-1.25)
Not always	ref	ref
Monthly alcohol intake		
0 drinks		ref
1-30 drinks		1.03 (0.92-1.16)
31-60 drinks		1.02 (0.88-1.18)
≥61 drinks		1.09 (0.96-1.23)
No. of female partners in the past 3 or 6 months (combined)		
1 partner		ref
2 partners		1.10 (1.00-1.22)
3 partners		1.12 (0.99-1.27)
4+ partners		1.12 (1.00-1.26)

[a] Unadjusted Poisson model (HPV and condom use with vaginal sex only)
[b] Multivariable models are adjusted for monthly alcohol intake, log pack-years of smoking, interaction

of country and condom use and number of female sexual partners in the past 3 or 6 months.
[c]Prevalence ratios and CIs determined by Poisson regression with robust standard errors

Any oncogenic HPV by frequency of condom use	Crude model PR[a,c]	Adjusted Model PR[b,c]
Interaction of country x condom use, p=0.78		
United States		
Always	0.66 (0.51-0.84)	0.72 (0.47-1.10)
Not always	ref	ref
Brazil		
Always	0.91 (0.74-1.10)	0.82 (0.59-1.16)
Not always	ref	ref
Mexico		
Always	1.01 (0.76-1.34)	0.88 (0.60-1.29)
Not always	ref	ref
Monthly alcohol intake		
0 drinks		ref
1-30 drinks		0.96 (0.76-1.22)
31-60 drinks		1.07 (0.81-1.42)
≥61 drinks		1.07 (0.84-1.38)
No. of female partners in the past 3 or 6 months (combined)		
1 partner		ref
2 partners		1.38 (1.13-1.69)
3 partners		1.26 (0.97-1.65)
4+ partners		1.71 (1.37-2.13)

Only nononcogenic HPV by frequency of condom use	Crude model PR[a,c]	Adjusted Model PR[b,c]
Interaction of country x condom use, p=0.91		
United States		
Always	0.62 (0.44-0.89)	0.88 (0.51-1.50)
Not always	ref	ref
Brazil		
Always	1.13 (0.88-1.44)	1.00 (0.63-1.62)
Not always	ref	ref
Mexico		
Always	0.97 (0.67-1.41)	0.89 (0.52-1.53)
Not always	ref	ref
Monthly alcohol intake		
0 drinks		ref
1-30 drinks		1.16 (0.84-1.60)
31-60 drinks		1.00 (0.66-1.53)
≥61 drinks		0.98 (0.68-1.42)
No. of female partners in the past 3 or 6 months (combined)		
1 partner		ref
2 partners		1.28 (0.53-1.70)
3 partners		1.19 (0.82-1.73)
4+ partners		0.95 (0.38-1.46)

Table 7. Prevalence Ratios (PR) with 95% CI for crude and adjusted models of the associations between HPV and frequency of condom use

Any HPV by frequency of condom use	Crude model PR[a,c]	Adjusted Model PR[b,c]
Interaction of country x condom use, p=0.08		
United States		
Always	0.81 (0.71-0.93)	0.72 (0.56-0.93)
Sometimes	1.05 (0.96-1.16)	1.03 (0.88-1.21)
Never	ref	ref
Brazil		
Always	1.03 (0.93-1.15)	0.92 (0.75-1.12)
Sometimes	1.13 (1.03-1.23)	1.14 (0.99-1.32)
Never	ref	ref
Mexico		
Always	1.08 (0.94-1.25)	1.08 (0.90-1.30)
Sometimes	1.08 (0.97-1.21)	1.05 (0.91-1.22)
Never	ref	ref
Monthly alcohol intake		
0 drinks		ref
1-30 drinks		1.03 (0.92-1.16)
31-60 drinks		1.01 (0.87-1.17)
≥61 drinks		1.07 (0.95-1.22)
No. of female partners in the past 3 or 6 months (combined)		
1 partner		ref
2 partners		1.09 (0.98-1.20)
3 partners		1.09 (0.97-1.25)

4+ partners	1.08 (0.95-1.23)
Log smoking pack-year	1.02 (0.99-1.05)

[a] Unadjusted Poisson model (HPV and condom use with vaginal sex only)
[b] Multivariable models are adjusted for monthly alcohol intake, log pack-years of smoking,