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# A prospective analysis of smoking and human papillomavirus (HPV) infection among men in *The HPV in Men* (HIM) Study

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## Abstract

At present it is unknown whether the higher prevalence of human papillomavirus (HPV) infection among smokers in men is attributed to a higher probability of acquiring an infection or because of longer infection persistence. Thus, we investigated the role of smoking on the (acquisition) and clearance (persistence) of genital HPV infections among 4,026 men in *The HPV in Men (HIM) Study*, a multinational prospective study of the natural history of genital HPV infection in men. Genital HPV infections were grouped any-, oncogenic-, and non-oncogenic HPV infections and smoking status was categorized as current-, former, and never smokers. The incidence of any-, oncogenic-, and non-oncogenic HPV infections was significantly higher among current smokers compared to former- and never smokers ($P < 0.01$). In multivariable analyses adjusting for sexual behavior and potential confounders, when compared to never smokers, current smokers exhibited significantly higher probability of acquiring any- (Hazard Ratio [HR] = 1.23; 95% confidence interval [CI] 1.02 – 1.50) and non-oncogenic (HR = 1.21; 95% CI 1.00 – 1.45) infections and a borderline significant probability for oncogenic infections (HR = 1.18; 95% CI 0.98 – 1.41). Although the median duration of HPV infection was generally longer among current smokers, we found no statistically significant associations in the multivariable analyses. Overall, these results demonstrated that current smoking exhibited the highest incidence and highest probability of acquiring genital HPV infections.

### Keywords

HPV; epidemiology; incidence; smoking

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## Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted infections, with more than 14 million new infections occurring annually in the United States.[1] More than 120 different HPV types have been identified of which more than 30 are transmitted through sexual activity. Of the approximately 5 to 15% of cancer cases that are attributed to infections nearly half are attributable to HPV.[2] HPV is associated with multiple cancers in both men and women, the virus is readily transmitted from person to person, and thus can affect disease risk in both genders.[3-5] However, most HPV infections are transient and subclinical, are usually self-cleared, and do not result in clinical disease. Studies on the health consequences of HPV infections in men have been lagging and to date there are limited published data documenting the factors associated with HPV acquisition, persistence, and duration, the latter of which is the obligate step in the progression to malignancy.

The prevalence of HPV infection among men has been estimated to be as high as 73%[6] and numerous factors have been shown to modify HPV prevalence including age,[7] race,[8] sexual orientation,[7] and circumcision,[9] to name a few. Revealing factors that may have an influence on HPV incidence (acquisition) and clearance (persistence) may reveal new underpinnings of this infection and lead to strategies to reduce HPV-related disease burden. At present little is known about the relationship between smoking and HPV natural history among men. Since smoking[10] and HPV are both important and prevalent risk factors among men, it is important to determine the potential influence of smoking on the natural history of HPV infection in men. Among women, cigarette smoking is associated with higher HPV prevalence,[11-13] incidence,[14,15] and persistence,[16,17] and in a previous report among men[18] we found current smoking was associated with an increased detection of any prevalent HPV infection (odds ratio [OR]=1.19; 95% confidence interval [CI]: 1.01–1.41) and prevalent oncogenic HPV infection (OR=1.24; 95% CI: 1.05–1.47). Presently it is unclear whether the higher prevalence of HPV infection among smokers in men is attributed to higher probability of acquisition of an infection or a longer duration of an infection. Thus, the purpose of this analysis is to assess the role of smoking on the incidence and clearance of HPV infections among men in *The HPV in Men (HIM) Study*

## Materials and Methods

### Study population

The *HIM Study* is a multinational prospective study of the natural history of genital HPV infection in men ages 18 to 70 years residing in Brazil, Mexico, and the USA. Men were eligible for participation if they were residents of southern Florida, USA, São Paulo, Brazil, or Cuernavaca, Mexico; reported no previous diagnosis of penile or anal cancers; reported no previous diagnosis of genital or anal warts; had not participated in an HPV vaccine study; reported no previous diagnosis of HIV; reported no current penile discharge or burning during urination; were not being treated for sexually transmitted infections; had not been imprisoned or homeless during the past 6 months; had not received drug treatment during the past 6 months; had no plans to relocate in the next 4 years; and were willing to comply with ten scheduled visits every 6 months for 4 years. All study subjects in this analysis completed at least two visits. The median number of clinic visits completed was four visits and the median interval between visits 6.23 months.

Men were recruited according to three age groups (18 to 30 years, 31 to 44 years, and 45 to 70 years) from the general population, universities, and organized health-care systems. Specifically, in Brazil, men were recruited from a large clinic in São Paulo that was providing genitourinary services, including tests for HIV and sexually transmitted

infections, and the general population through television, radio, and newspaper advertisements. In Mexico, men were recruited in Cuernavaca and Morelos, through a large health plan, from factories and the military. In the USA, men were mainly recruited from the University of South Florida and the general community in Tampa, FL. A full description of cohort procedures, HPV prevalence, and factors associated with prevalent infections has already been reported elsewhere.[16] Human-subjects' committees of the University of South Florida, FL, USA, the Ludwig Institute for Cancer Research, São Paulo, Brazil, the Centro de Referencia e Tratamento de Doencas Sexualmente Transmissiveis e AIDS, São Paulo, Brazil, and the National Institute of Public Health of Mexico, Cuernavaca, Mexico, approved all study procedures. Men who provided consent had a clinical examination two weeks prior to enrollment visit and every 6 months thereafter. Only men who returned for the enrollment visit were included in this study.

### Risk Factor Questionnaire

An extensive 88-item computer-assisted self-interview sexual history and health questionnaire were given at enrollment to assess sociodemographic characteristics and risk factors. The questionnaire required approximately 20 minutes to complete, has been previously shown to elicit reliable responses,[19] and was written in the region's primary language (Portuguese, Spanish, or English). Never smokers were defined as men who had smoked less than 100 cigarettes in their lifetime. Former smokers were defined as men who had smoked at least 100 cigarettes in their lifetime but quit smoking at least 1 year before the baseline interview. Current smokers were defined as men who smoked at least 100 cigarettes in their lifetime and were currently smoking at the time of the visit. Pack-years smoked were calculated using the average number of cigarette packs smoked per day and the numbers of years smoked.

### HPV Penile and Scrotal Sampling

Samples were obtained from the external genitalia at each visit by use of Dacron (Digene, Gaithersburg, MD, USA) swabs prewetted with saline. Three separate samples were obtained: corona of glans penis (1 sample), penile shaft (1 sample), and scrotum (1 sample). The samples were placed in 450 μL of Specimen Transport Medium and then combined into one sample before DNA extraction (described below). The specimens were stored at -70°C until PCR analyses and HPV genotyping was performed. We have previously shown the validity of these three anatomical sites in the assessment of HPV status, and high sampling reproducibility for the detection of HPV DNA by use of this method.[20]

### DNA extraction and HPV genotyping

DNA extraction was conducted with QIAamp DNA Mini Kit (Qiagen, Valencia, CA, USA) on a robotic system according to the manufacturer's instructions and DNA was stored at 4°C until use. The extracted DNA samples were tested for the presence of HPV types by amplification of 30 ng of DNA with the PGMY09/11 L1 consensus primer system.[21] HPV genotyping was performed with the linear array method on all samples irrespective of the HPV PCR result (Roche Molecular Diagnostics, Alameda, CA, USA). Only samples that tested positive for beta-globin (99% at enrollment) were judged to be adequate and included in the analysis. Before genotyping, the amplification products were run on 2% agarose gels to visualize a 450 base pair band corresponding to HPV amplification for identification of samples that might have an HPV type other than the 37 types analyzed in the genotyping assay. Samples for which HPV was amplified on PCR but did not hybridize with a specific HPV type during the genotyping assay (e.g., unclassified infections) were classified as HPV negative. Across the ten visits the frequency of these unclassified infections that were classified as HPV negative ranged from 1.25% to 4.0%. The HPV types that were classified as oncogenic were 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68[22] and non-oncogenic

types were 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73, 81, 82, 83, 84, 89, and IS39. The classification of 'any HPV' was defined as a positive test result for at least one of 37 HPV genotypes. HPV infections with single or multiple oncogenic virus types were classified as 'oncogenic'. Similarly, HPV infections with at least one non-oncogenic HPV type were classified as 'non-oncogenic'.

### Statistical analysis

Smoking status was categorized by current-, former, and never smokers and then smoking status was analyzed with two different approaches: 1) by baseline only status and 2) among men who reported the same smoking status at both the baseline and their last follow-up (LFU). Sociodemographic and sexual behavioral characteristics by smoking status (never, former, and current) were compared using the Monte Carlo estimation of exact Pearson chi-square test for categorical variables. For each individual time a newly acquired HPV infection was estimated by use of the time from study entry to the date of the first HPV detected. For estimates of any- or type-specific HPV incidence, only those men at enrollment who were free of any- or a specific HPV type, respectively, were included.

For the incidence analyses (i.e., acquisition) the analytical unit is an individual. For the grouped analysis any HPV incidence was defined as a positive test result for at least one of 37 HPV genotypes, oncogenic HPV incidence was defined as testing positive for at least one oncogenic HPV type, and non-oncogenic was defined as a positivity for at least one non-oncogenic HPV type. For the type-specific and grouped HPV incidence analyses, only the first acquired infection was considered and thus the analytical unit is an individual. Cumulative risk of HPV incidence was estimated using the Kaplan-Meier method and the log-rank test was used to identify differences by smoking status. Twelve-month HPV incidence was also estimated using the Kaplan-Meier method and the association between smoking status and HPV incidence was assessed with multivariable Cox proportional hazards regression adjusting for age, race, ethnicity, country, circumcision, total number of female partners in the last 3 months, total number of female partners, and total number of male sex partners.

HPV clearance (i.e., persistence) was defined as a participant who tested HPV negative at two consecutive visits after testing positive, excluding infections detected for the first time at a participant's final visit. Men with HPV infections, regardless of HPV status at baseline, were included in the clearance analyses. The analytical unit for the clearance analyses was an infection with each individual genotype considered as a separate infection. Thus, since men could have been infected with multiple HPV types within a defined group (e.g., HPV16 and HPV18 are both oncogenic), we adjusted for within-subject correlation in the grouped HPV clearance analyses. The median time to HPV clearance among all men with an incident infection was estimated using the clustered Kaplan-Meier method and men whose infections did not clear were censored in the analysis. We utilized multivariable Cox proportional hazards regression with the robust covariance matrix estimator to model the association between smoking status and HPV clearance. Since HPV infection status at baseline had significant impact on HPV clearance, we included this covariate in the multivariable models of HPV clearance in addition to the factors that were adjusted for in the incidence analyses. All analyses were conducted with SAS (version 9.3) and tests were two-sided with a significance level of 0.05.

## Results

The total sample sizes with complete available data were 4,026 for the baseline only smoking status analyses and 3,548 for the men who were concordant with smoking status at baseline and last follow-up. Statistically significant differences were observed for the

distribution of the study population characteristics by smoking status for the baseline only smoking status (Table 1) and among men who reported the same smoking status at baseline and last follow-up (Supplemental Table 1). The concordance of men who reported the same smoking status at both baseline and last follow-up was 83.4%, 83.3%, and 89.2% for current-, former, and never smokers, respectively.

The twelve-month incidence, the rate of a man acquiring an infection during within twelve months in the HIM study, for any-, oncogenic-, and non-oncogenic HPV infections was significantly higher among current smokers compared to former and never smokers (Table 2). Consistent findings were generally observed when examining the baseline smoking status only and the baseline and last follow-up. When we analyzed the entire available follow-up data (Figure 1a), current smoking was also associated with a statistically significantly higher probability of acquiring any- (P = 0.0084) and oncogenic (P = 0.0051) HPV infections. Current smoking was associated with borderline significant higher probability of acquiring a non-oncogenic infection (P = 0.0811).

Multivariable Cox models (Table 3) were used to adjust for potential confounding factors which revealed that current smoking exhibited significantly increased risks for any- (HR = 1.23; 95% CI 1.02-1.50) and non-oncogenic (HR = 1.21; 95% CI 1.00-1.45) incident HPV infections. When the baseline only smoking status was examined, a statistically significant association among current smokers was observed for incident oncogenic HPV infections (HR = 1.17%; 95% CI 1.00 – 1.38). Current smoking was also significantly associated with an increased incidence of HPV11 infection (HR = 4.90; 95% CI 1.40 – 17.2). No other individual type specific associations were statistically significant.

The median duration of infection (months) was generally longer among current smokers for any-, oncogenic-, and non-oncogenic HPV infections (Table 4); however, current smoking was only significantly longer for any- and non-oncogenic infections for the baseline only data. When we analyzed the entire available follow-up data (Figure 1b), current smoking was associated with a statistically significantly lower probability of clearing any- (P = 0.022) and non-oncogenic (P = 0.0319) HPV infections. In the multivariable analyses none of the hazard ratios were statistically significant for the clearance (Table 5). We also explored stratified multivariable analyses by number of lifetime female partners and pack-years smoked but these analyses did not reveal any appreciable differences in the point estimates (*data not shown*).

## Discussion

In this multinational cohort study of HPV in men, our analyses revealed that current smoking was associated with a statistically significantly higher incidence of any-, oncogenic-, and non-oncogenic HPV infections. We also found that for current smokers the median duration of any- and non-oncogenic infections infection was generally longer and associated with a lower probability of clearing of any- and non-oncogenic infections. However, none of the multivariable point estimates for clearance for current smoking were statistically significant.

In a previous report[18] we found that current smoking was associated with an increased risk of any prevalent HPV infection and prevalent oncogenic HPV infection and that these associations were restricted to men who self-reported the fewest lifetime female sexual partners. Additionally, Nielson *et al*.[23] reported an increased risk of prevalent HPV infection among men who were current smokers and among those who smoked ≥ 10 cigarettes per day. To the best of our knowledge this analysis is the first to investigate the role of smoking on the incidence and clearance of genital HPV infections among men. Our results are

generally consistent with prior findings in women that showed smoking is associated with a higher probability of incident infections.[14,15] As observed in previously published studies of the cervix,[16,17] the median duration of infection was generally longer among current smokers (Table 4); however, when we adjusted for potential confounding factors (Table 5) none of the point estimates were statistically significant for clearance.

At present, it is unclear how smoking influences HPV infection in men, but smoking has many systemic affects that could impact HPV incidence. For instance, laboratory studies have shown that smoking increases cellular proliferation and metaplasia in various tissues and cell types[24-28], which in turn could result in an increase in replication or production of HPV due to smoking-induced cell proliferation. Specific compounds in cigarette smoke have also been shown to modify the function of immune cells, affect neutrophil function,[29] cause DNA damage,[30] and suppress resistance to infections.[31] Any one of these features could result in an increased susceptibility to the acquisition of HPV. Further, studies have demonstrated that smoking has deleterious effects on both systemic and local immunity,[24,26,32,33] which are important in the detection, elimination, and immunity to viruses. Experimental evidence suggests that smoking acts as an immunosuppressant for the function of immune cells and causes the release of a variety of inflammatory factors including cytokines, oxygen radicals and proteases which can ultimately alter the function of immune cells.[34] Additionally, nicotine, the addictive component of tobacco responsible for the dependence-forming properties of smoking, has been shown to be immunosuppressive.[35,36] Thus, the increased incidence of HPV infection associated with current smoking in our analysis could be due an attenuated host immune response due to the deleterious effects attributed to smoking.

Since current smoking has potent and immediate effects on systemic and local immune function compared to those who quit smoking or never smoked, we assessed smoking status by using the baseline smoking status as well as by those individuals who self-reported the same smoking status at both baseline and the last available follow-up. We included the latter method in order to avoid misclassification of current smokers at baseline who quit smoking during follow-up and to avoid misclassification for former and never smokers who began smoking after baseline. We were concerned that current smokers at baseline who quit smoking during follow-up would be misclassified and ultimately dilute any potential smoking-related associations. Likewise, former- and never smokers who started smoking after the baseline visit would be misclassified since the long-term systemic effects of smoking could be attenuated compared to consistent current smokers. Although the concordance of men who reported the same smoking status at both baseline and last available follow-up was quite high (83.4%, 83.3%, and 89.2% for current-, former-, and never smokers, respectively), we do acknowledge the possibility that men could have changed smoking status several times. Thus there still may be some misclassification, but this misclassification is likely very minor and by reporting the results among those men who reported the same smoking status at baseline and last follow-up, we are likely more conservative with our interpretation. Although the twelve-month incidence and median duration data were generally consistent by the two approaches we employed, the P-values were not always consistent which is likely attributed to small incremental differences in the values between the two approaches and reduced statistical power because of smaller sample size in the more restrictive analysis.

There are many strengths and some limitations of this analysis that should be noted. First, the *HIM Study* is a unique resource since it is the only multi-national prospective study of the natural history of HPV infection in men. This international cohort is well-characterized,[8,18,37-41] includes men of a wide age range and extensive and previously validated participant information.[42] Another strength of the study is the large sample size

with follow-up; although we do acknowledge that stratification by smoking and sexual behavior did result in smaller subgroups. We acknowledge that we cannot account for bias due to unmeasured or unknown confounding. Sexual behavior is potentially an important confounder in the association between smoking and HPV infection. Although we accounted for potential confounding by adjusting for and stratifying by self-reported sexual behavior, residual confounding still may exist which could potentially inflate the observed point estimates. Another possible limitation is that there may be concordance of smoking and HPV among partners of the men in this study;[43,44] however, we do not have data on the partners. We also acknowledge that the men in the HIM cohort may not be a representative of the general male populations of the participating countries which may limit the generalizability of our findings. Thus, we caution overinterpretation of our results, but these data are important and novel as there is limited information on the association between smoking and HPV in men. Furthermore, since smoking is a modifiable risk factor, these data have public health implications for reducing HPV incidence.

Overall, these results demonstrated that current smokers exhibited the highest incidence and highest probability of acquiring genital HPV infections. Although the median duration of HPV infection was generally longer among current smokers, we found no statistically significant associations in the multivariable analyses. The biological role that smoking plays in HPV infection in men remains understudied, and limited epidemiology data exist on the association between smoking and HPV infection. To the best of our knowledge these are the first epidemiologic data to demonstrate an association between current smoking and incidence of genital HPV infections among men.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

| | |
|---|---|
| **HPV** | human papillomavirus |
| **HIM** | The HPV in Men Study |
| **HR** | Hazard Ratio |
| **CI** | confidence interval |
| **LFU** | last follow-up |

## Novelty and Impact

HPV infection can cause cancer in men and women. Revealing factors that have an influence on HPV incidence (acquisition) and clearance (persistence) may reveal new underpinnings of this infection. These results demonstrated that current smoking was associated with the highest probability of acquiring genital HPV infections in men. To the best of our knowledge these are the first epidemiologic data to demonstrate an association between current smoking and incidence of genital HPV infections among men.

Figure 1a

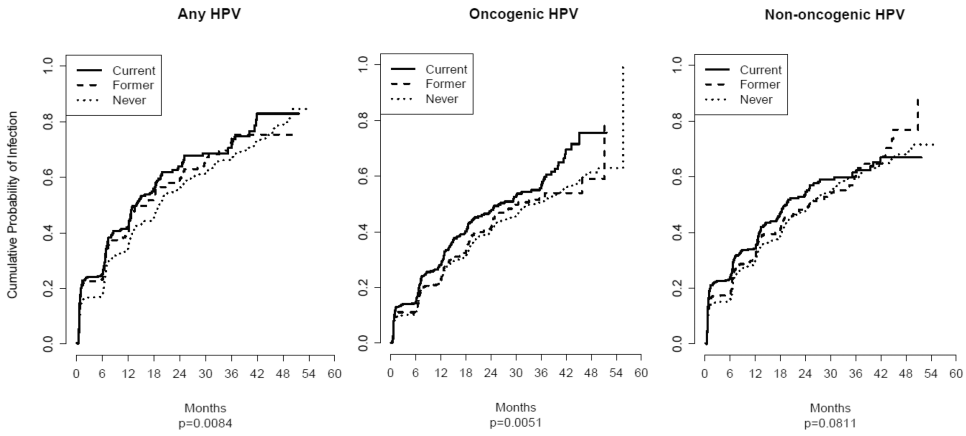


Figure 1b

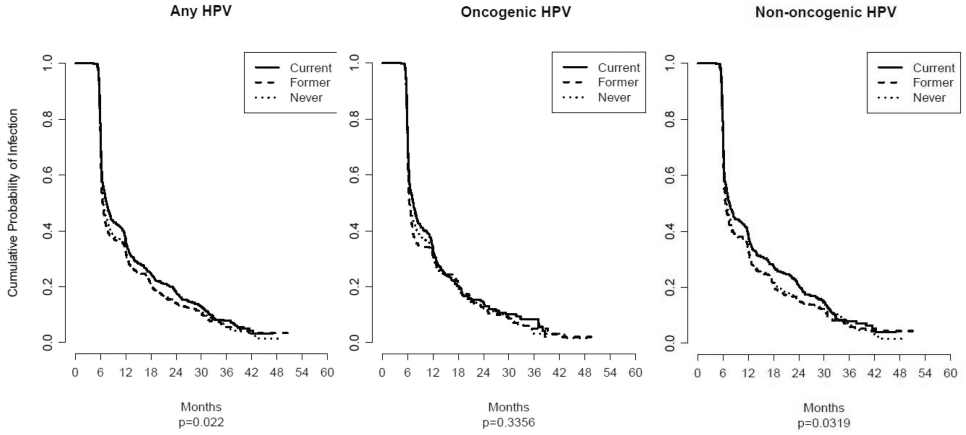


**Figure 1.**

**A) The cumulative probability for acquiring (i.e., incidence) an HPV infection for baseline only smoking status among men in the HIM study.** Current smoking was associated with a statistically significantly higher probability of acquiring any- and oncogenic HPV infections and borderline significant for non-oncogenic infections (P = 0.0811). **B) The cumulative probability for clearing an HPV infection for baseline only smoking status among men in the HIM study.** Current smoking was associated with a statistically significantly lower probability of clearing any- and non-oncogenic HPV infections.

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**Table 1**

**Distribution of select baseline characteristics of men in the HIM study by smoking status**

| | Baseline only[1] | | | | |
|---|---|---|---|---|---|
| **Characteristic** | **Overall** | **Current Smokers** | **Former Smokers** | **Never Smokers** | **P-value[2]** |
| **Age** | | | | | **< 0.001** |
| 18 to 30 | 1960 (48.7%) | 463 (48.8%) | 249 (33.2%) | 1248 (53.7%) | |
| 31 to 44 | 1544 (38.4%) | 375 (39.6%) | 317 (42.2%) | 852 (36.6%) | |
| 45 to 70 | 521 (12.9%) | 110 (11.6%) | 185 (24.6%) | 226 (9.7%) | |
| Total | 4025 (100%) | 948 (100%) | 751 (100%) | 2326 (100%) | |
| **Race** | | | | | **< 0.001** |
| White | 1803 (45.4%) | 373 (39.9%) | 341 (46.0%) | 1089 (47.5%) | |
| Black | 628 (15.8%) | 129 (13.8%) | 77 (10.4%) | 422 (18.4%) | |
| Asian/PI | 110 (2.8%) | 12 (1.3%) | 8 (1.1%) | 90 (3.9%) | |
| Other | 1428 (36.0%) | 422 (45.1%) | 315 (42.5%) | 691 (30.1%) | |
| Total | 3969 (100%) | 936 (100%) | 741 (100%) | 2292 (100%) | |
| **Ethnicity** | | | | | **< 0.001** |
| Hispanic | 1818 (45.6%) | 519 (55.2%) | 375 (50.2%) | 924 (40.1%) | |
| Non – Hispanic | 2173 (54.4%) | 421 (44.8%) | 372 (49.8%) | 1380 (59.9%) | |
| Total | 3991 (100%) | 940 (100%) | 747 (100%) | 2304 (100%) | |
| **Clinic Site/Country** | | | | | **< 0.001** |
| United States | 1312 (32.6%) | 269 (28.4%) | 207 (27.6%) | 836 (35.9%) | |
| Brazil | 1396 (34.7%) | 259 (27.3%) | 252 (33.6%) | 885 (38.0%) | |
| Mexico | 1318 (32.7%) | 420 (44.3%) | 292 (38.9%) | 606 (26.0%) | |
| Total | 4026 (100%) | 948 (100%) | 751 (100%) | 2327 (100%) | |
| **Circumcision status** | | | | | **< 0.001** |
| Not Circumcised | 2558 (63.6%) | 628 (66.2%) | 483 (64.3%) | 1447 (62.2%) | |
| Circumcised | 1467 (36.4%) | 320 (33.8%) | 268 (35.7%) | 879 (37.8%) | |
| Total | 4025 (100%) | 948 (100%) | 751 ((100%) | 2326 (100%) | |
| **Lifetime No. of Female Partners** | | | | | **< 0. 001** |
| 0 to 1 | 711 (17.7%) | 116 (12.2%) | 71 (9.5%) | 524 (22.5%) | |
| 2 to 9 | 1606 (39.9%) | 347 (36.6%) | 292 (38.9%) | 967 (41.6%) | |

| | Baseline only[1] | | | | |
|---|---|---|---|---|---|
| **Characteristic** | **Overall** | **Current Smokers** | **Former Smokers** | **Never Smokers** | **P-value[2]** |
| 10 to 49 | 1263 (31.4%) | 348 (36.7%) | 294 (39.1%) | 621 (26.7%) | |
| 50+ | 225 (5.6%) | 67 (7.1%) | 50 (6.7%) | 108 (4.6%) | |
| Refused | 220 (5.5%) | 70 (7.4%) | 44 (5.9%) | 106 (4.6%) | |
| Total | 4025 (100%) | 948 (100%) | 751 (100%) | 2326 (100%) | |
| **No. of Female Partners in Past 3 or 6 Months** | | | | | **< 0.001** |
| None | 836 (20.8%) | 204 (21.5%) | 192 (25.6%) | 440 (18.9%) | |
| 1 | 1636 (40.6%) | 368 (38.8%) | 333 (44.3%) | 935 (40.2%) | |
| 2 | 515 (12.8%) | 128 (13.5%) | 86 (11.5%) | 301 (12.9%) | |
| 3+ | 525 (13.0%) | 139 (14.7%) | 80 (10.7%) | 306 (13.2%) | |
| Refused | 513 (12.7%) | 109 (11.5%) | 60 (8.0%) | 344 (14.8%) | |
| Total | 4025 (100%) | 948 (23.6%) | 751 (18.7%) | 2326 (57.8%) | |
| **Lifetime No. of Male Partners** | | | | | 0.136 |
| 0 to 1 | 3607 (90.3%) | 832 (88.6%) | 673 (90.2%) | 2102 (91.0%) | |
| 2 to 9 | 228 (5.7%) | 58 (6.2%) | 48 (6.4%) | 122 (5.3%) | |
| 10+ | 160 (4.0%) | 49 (5.2%) | 25 (3.4%) | 86 (3.7%) | |
| Total | 3995 (100%) | 939 (23.5%) | 746 (18.7%) | 2310 (57.8%) | |

[1] The demographic features were analyzed by baseline smoking status

[2] P-value Pearson's chi-square test comparing demographics by smoking status for Baseline only

**Table 2**

**Twelve-incidence rate of HPV infection by smoking status among men in the HIM study**

| | | Twelve-Month Incidence[1] | | | | |
|---|---|---|---|---|---|---|
| **HPV Status** | **Smoking Status[3]** | **Overall** | **Current Smokers** | **Former Smokers** | **Never Smokers** | **Log Rank *p* Value[2]** |
| Any HPV | Baseline | 37.3% (35.0% – 39.8%) | 42.1% (36.8% – 47.9%) | 40.2% (34.8% – 46.2%) | 34.9% (32.0% – 38.0%) | **0.008** |
| Any HPV | Baseline & last follow-up | 37.4% (34.9% – 40.0%) | 44.7% (38.6% – 51.3%) | 40.1% (34.2% – 46.5%) | 34.6% (31.5% – 37.8%) | **0.003** |
| Non-oncogenic | Baseline | 31.1% (29.1% – 33.2%) | 34.4% (30.0% – 39.3%) | 30.9% (26.4% – 35.9%) | 30.0% (27.5% – 32.7%) | 0.079 |
| Non-oncogenic | Baseline & last follow-up | 31.1% (29.0% – 33.3%) | 36.0% (31.0% – 41.5%) | 30.5% (25.7% – 36.0%) | 29.7% (27.1% – 32.5%) | **0.030** |
| Oncogenic | Baseline | 23.5% (21.9% – 25.3%) | 28.1% (24.2% – 32.4%) | 23.0% (19.3% – 27.3%) | 22.2% (20.1% – 24.4%) | **0.005** |
| Oncogenic | Baseline & last follow-up | 23.3% (21.5% – 25.3%) | 28.8% (24.4% – 33.7%) | 22.9% (18.8% – 27.7%) | 21.9% (19.7% – 24.3%) | **0.009** |
| HPV6 | Baseline | 4.8% (4.2% – 5.6%) | 6.3% (4.7% – 8.4%) | 5.5% (4.0% – 7.6%) | 4.1% (3.3% – 5.1%) | 0.448 |
| HPV6 | Baseline & last follow-up | 4.8% (4.1% – 5.7%) | 6.2% (4.5% – 8.6%) | 5.2% (3.6% – 7.5%) | 4.3% (3.4% – 5.3%) | 0.361 |
| HPV11 | Baseline | 1.1% (0.8% – 1.6%) | 1.7% (1.0% – 3.0%) | 1.0% (0.4% – 2.1%) | 1.0% (0.6% – 1.5%) | 0.901 |
| HPV11 | Baseline & last follow-up | 1.1% (0.8% – 1.6%) | 2.0% (1.1% – 3.6%) | 0.7% (0.3% – 1.9%) | 1.0% (0.6% – 1.5%) | 0.873 |
| HPV16 | Baseline | 5.5% (4.8% – 6.4%) | 6.9% (5.2% – 9.1%) | 6.0% (4.3% – 8.2%) | 4.9% (4.0% – 6.0%) | 0.655 |
| HPV16 | Baseline & last follow-up | 5.5% (4.7% – 6.4%) | 7.2% (5.3% – 9.8%) | 5.8% (4.1% – 8.3%) | 4.9% (3.9% – 6.0%) | 0.485 |
| HPV18 | Baseline | 2.4% (1.9% – 2.9%) | 2.7% (1.7% – 4.2%) | 1.9% (1.1% – 3.4%) | 2.4% (1.8% – 3.2%) | **0.045** |
| HPV18 | Baseline & last follow-up | 2.4% (1.9% – 3.1%) | 2.9% (1.8% – 4.7%) | 2.4% (1.3% – 4.2%) | 2.3% (1.7% – 3.1%) | **0.034** |

[1] Twelve-month incidence is the rate of male acquiring an infection during any given twelve month period (i.e., year) in the HIM study

[2] P-value from log-rank test for HPV incidence by smoking status

[3] Smoking status was analyzed by two different approaches: 1) among baseline only status and 2) among men who reported the same smoking status at both the baseline and their last follow-up (LFU)

## Table 3

**Hazard ratios for HPV incidence by smoking status among men in the HIM study[1]**

| | | Baseline | Baseline & Last Follow-up |
|---|---|---|---|
| **HPV Status** | **Smoking Status** | **mHR (95% CI)[2]** | **mHR (95% CI)[2]** |
| Any HPV | Never | 1.00 | 1.00 |
| | Former | 1.09 (0.91 – 1.32) | 1.12 (0.92 – 1.37) |
| | Current | 1.13 (0.95 – 1.34) | **1.23 (1.02 – 1.50)** |
| Oncogenic | Never | 1.00 | 1.00 |
| | Former | 1.05 (0.88 – 1.27) | 1.08 (0.88 – 1.32) |
| | Current | **1.17 (1.00 – 1.38)** | 1.18 (0.98 – 1.42) |
| Non–oncogenic | Never | 1.00 | 1.00 |
| | Former | 0.94 (0.81 – 1.09) | 1.01 (0.83 – 1.22) |
| | Current | 0.88 (0.71 – 1.08) | **1.21 (1.00 – 1.45)** |
| HPV6 | Never | 1.00 | 1.00 |
| | Former | 1.10 (0.8 – 1.51) | 1.18 (0.79 – 1.75) |
| | Current | 1.12 (0.84 – 1.49) | 0.99 (0.57 – 1.71) |
| HPV11 | Never | 1.00 | 1.00 |
| | Former | 0.95 (0.51 – 1.77) | 1.48 (0.67 – 3.27) |
| | Current | 0.89 (0.51 – 1.56) | **4.90 (1.40 – 17.2)** |
| HPV16 | Never | 1.00 | 1.00 |
| | Former | 1.06 (0.78 – 1.42) | 0.89 (0.62 – 1.27) |
| | Current | 0.99 (0.75 – 1.31) | 1.31 (0.74 – 2.31) |
| HPV18 | Never | 1.00 | 1.00 |
| | Former | 0.75 (0.45 – 1.23) | 0.89 (0.54 – 1.49) |
| | Current | 1.17 (0.80 – 1.69) | 1.19 (0.50 – 2.83) |

[1] Smoking status was analyzed by two different approaches: 1) among baseline only status and 2) among men who reported the same smoking status at both the baseline and their last follow-up (LFU)

[2] Multivariable hazard ratio (mHR) adjusted for age, race, ethnicity, country, circumcision, total number of female partners in the last 3 months, total number of female partners, and total number of male sex partners

**Table 4**

**Median duration of HPV Infection by smoking status among men in the HIM Study**

| | | Median Duration of Infection (Months) | | | | |
|---|---|---|---|---|---|---|
| **HPV Status** | **Smoking Status[1]** | **Overall** | **Current Smokers** | **Former Smokers** | **Never Smokers** | ***p* Value[2]** |
| Any HPV | Baseline | 6.8 (6.6 – 7.0) | 7.4 (6.9 – 8.2) | 6.5 (6.3 – 6.9) | 6.7 (6.5 – 7.0) | **0.023** |
| Any HPV | Baseline & last follow-up | 6.7 (6.5 – 6.9) | 7.2 (6.7 – 7.9) | 6.6 (6.3 – 6.9) | 6.6 (6.4 – 6.9) | 0.109 |
| Non-oncogenic | Baseline | 6.9 (6.6 – 7.2) | 7.6 (6.9 – 8.5) | 6.7 (6.4 – 7.1) | 6.8 (6.5 – 7.1) | **0.033** |
| Non-oncogenic | Baseline & last follow-up | 6.8 (6.6 – 7.1) | 7.3 (6.8 – 8.4) | 6.7 (6.3 – 7.1) | 6.7 (6.5 – 7.2) | 0.154 |
| Oncogenic | Baseline | 6.6 (6.4 – 6.9) | 7.4 (6.6 – 8.1) | 6.4 (6.2 – 6.8) | 6.5 (6.3 – 6.9) | 0.335 |
| Oncogenic | Baseline & last follow-up | 6.5 (6.4 – 6.7) | 7.1 (6.4 – 8.0) | 6.4 (6.2 – 6.9) | 6.5 (6.3 – 6.7) | 0.551 |
| HPV6 | Baseline | 6.4 (6.2 – 6.8) | 6.2 (6.1 – 10.5) | 6.4 (6.0 – 10.6) | 6.3 (6.1 – 6.8) | 0.348 |
| HPV6 | Baseline & last follow-up | 6.3 (6.1 – 6.8) | 6.2 (6.0 – 11.9) | 6.4 (5.9 – 12.2) | 6.3 (6.1 – 6.8) | 0.368 |
| HPV11 | Baseline | 6.9 (6.2 – 11.8) | 11.8 (5.7 – 18.0) | 6.2 (5.8 – 18.1) | 7.1 (6.2 – 11.8) | 0.884 |
| HPV11 | Baseline & last follow-up | 6.6 (6.0 – 8.5) | 11.8 (5.7 – 17.1) | 6.3 (5.9 – 18.1) | 6.6 (6.0 – 8.5) | 0.981 |
| HPV16 | Baseline | 7.4 (6.5 – 10.3) | 8.0 (6.3 – 14.0) | 7.2 (6.1 – 12.2) | 7.8 (6.5 – 11.5) | 0.769 |
| HPV16 | Baseline & last follow-up | 7.4 (6.4 – 10.3) | 7.8 (6.3 – 14.7) | 7.2 (6.0 – 12.2) | 7.8 (6.3 – 11.9) | 0.706 |
| HPV18 | Baseline | 6.4 (6.2 – 6.9) | 6.5 (6.2 – 11.2) | 6.6 (5.9 – 7.0) | 6.2 (6.0 – 7.8) | 0.849 |
| HPV18 | Baseline & last follow-up | 6.4 (6.2 – 6.9) | 6.4 (6.1 – 11.2) | 6.6 (5.9 – 7.0) | 6.2 (6.0 – 7.8) | 0.992 |

[1] Smoking status was analyzed by two different approaches: 1) among baseline only status and 2) among men who reported the same smoking status at both the baseline and their last follow-up (LFU)

[2] p-value of the univariate Cox model with the robust covariance matrix estimator for HPV clearance across entire follow-up period by smoking status

## Table 5

**Hazard ratios for clearance of HPV Infection by smoking status among men in the HIM Study**

| | | Baseline | Baseline & Last Follow–up |
|---|---|---|---|
| **HPV Status** | **Smoking Status[1]** | **mHR (95% CI)[1]** | **mHR (95% CI)[2]** |
| Any HPV | Never | 1.00 | 1.00 |
| | Former | 0.94 (0.87 – 1.01) | 0.95 (0.87 – 1.03) |
| | Current | 0.93 (0.86 – 1.01) | 0.93 (0.85 – 1.01) |
| Oncogenic | Never | 1.00 | 1.00 |
| | Former | 0.96 (0.86 – 1.07) | 0.95 (0.85 – 1.06) |
| | Current | 0.94 (0.85 – 1.05) | 0.94 (0.83 – 1.06) |
| Non–oncogenic | Never | 1.00 | 1.00 |
| | Former | 0.93 (0.85 – 1.02) | 0.95 (0.85 – 1.06) |
| | Current | 0.93 (0.84 – 1.02) | 0.94 (0.83 – 1.06) |
| HPV6 | Never | 1.00 | 1.00 |
| | Former | 0.93 (0.70 – 1.23) | 0.95 (0.85 – 1.06) |
| | Current | 0.91 (0.70 – 1.19) | 0.94 (0.83 – 1.06) |
| HPV11 | Never | 1.00 | 1.00 |
| | Former | 1.02 (0.54 – 1.94) | 1.00 (0.50 – 1.97) |
| | Current | 0.83 (0.49 – 1.43) | 0.80 (0.43 – 1.46) |
| HPV16 | Never | 1.00 | 1.00 |
| | Former | 0.98 (0.74 – 1.29) | 0.96 (0.71 – 1.30) |
| | Current | 0.92 (0.71 – 1.20) | 0.86 (0.64 – 1.14) |
| HPV18 | Never | 1.00 | 1.00 |
| | Former | 0.80 (0.49 – 1.30) | 0.68 (0.40 – 1.18) |
| | Current | 0.82 (0.54 – 1.25) | 0.87 (0.55 – 1.36) |

[1] Smoking status was analyzed by two different approaches: 1) among baseline only status and 2) among men who reported the same smoking status at both the baseline and their last follow-up (LFU)

[2] Multivariable hazard ratio (mHR) adjusted for HPV status at baseline, age, race, ethnicity, country, circumcision, total number of female partners in the last 3 months, total number of female partners, and total number of male sex partners.