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Incidence and clearance of oral human papillomavirus infection in men: the HIM cohort study

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Abstract

Background—Oral human papillomavirus (HPV) infection causes a subset of oropharyngeal cancers. These cancers disproportionately affect men, are increasing in incidence, and have no proven prevention methods. We aimed to establish the natural history of oral HPV infection in men.

Methods—To estimate incidence and clearance of HPV infections, men residing in Brazil, Mexico, and the USA who were HIV negative and reported no history of anogenital cancer were recruited into the *HPV Infection in Men (HIM)* cohort study. A subset of the cohort who provided two or more oral rinse-and-gargle samples with valid HPV results and who completed a minimum of 2 weeks of follow-up were included in this analysis. Oral rinse-and-gargle samples and questionnaire data were obtained every 6 months for up to 4 years. Samples were analysed for the presence of oncogenic and non-oncogenic HPV infections by the linear array method.

Findings—1626 men aged 18–73 years and with a median follow-up of 12.7 months (IQR 12.1–14.7) were included in the analysis. During the first 12 months of follow-up, 4.4% (95% CI 3.5–5.6; n=115 incident infections) of men acquired an incident oral HPV infection, 1.7% (1.2–2.5; n=53 incident infections) an oral oncogenic HPV infection, and 0.6% (0.3–1.1; n=18 incident infections) an oral HPV 16 infection. Acquisition of oral oncogenic HPV was significantly associated with smoking and not being married or cohabiting, but was similar across countries, age groups, and reported sexual behaviours. Median duration of infection was 6.9 months (95 %

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Contributors: ARG designed and leads the *HIM Study* as the principal investigator. LLV and EL-P contributed to the design and implementation of the *HIM Study* at their respective country sites. ARK, ARG, MRP, and MA incorporated the oral HPV substudy within the HIM infrastructure and were responsible for data collection. ARK, CMPC, and ARG designed the analysis. H-YL and WF did the statistical analysis under the direction of ARK, CMPC, and ARG. ARK, CMPC, AH, and ARG interpreted the data. ARK, CMPC, and ARG wrote the report. H-YL, WF, MRP, MA, AH, LLV, JJS, and EL-P reviewed all material for important intellectual content. ARK, CMPC, and ARG are the guarantors of all material in the report.

CI 6.2–9.3; n=45 cleared infections) for any HPV, 6.3 months (6.0–9.9; n=18 cleared infections) for oncogenic HPV, and 7.3 months (6.0–not estimable; n=5 cleared infections) for HPV 16. Eight of the 18 incident oral HPV 16 infections persisted for two or more study visits.

Interpretation—Newly acquired oral oncogenic HPV infections in healthy men were rare and most were cleared within 1 year. Additional studies into the natural history of HPV are needed to inform development of infection-related prevention efforts.

Keywords

oral human papillomavirus; natural history; acquisition

Introduction

Human papillomavirus type 16 (HPV16) is associated with the rapid increase in incidence of oropharyngeal cancer in some world regions, most notably in the USA, Sweden, and Australia, where it causes more than 50% of cases.^{1–4} However, no proven methods exist to prevent or detect these cancers at an early stage. Detection of prevalent infection with HPV16 in oral exfoliated cells is significantly associated with oropharyngeal cancer.⁵ However, prevalent oral HPV 16 infection is rare, present in only 1.0% of cancer-free individuals.^{6,7} In recent population-based studies of oral HPV infection in the USA,^{6,7} prevalence was three times higher in men than in women, which is a similar gender ratio to that reported for oropharyngeal cancer.⁸ A bimodal age distribution in HPV infection has been noted, with peak prevalence at ages 30–34 and 60–64 years.⁷ Whether these peaks are caused by increased duration of infection over an individual's lifespan or whether they are caused by an increase in acquisition at older ages (a pattern contrary to that established for cervical HPV infection) is an important epidemiological question.

Because prevalence is the product of acquisition and duration of infection, some oral HPV16 infections detected cross-sectionally are likely to have persisted for some time. Persistent oral HPV16 infection might be a precursor to oropharyngeal cancer, similar to how persistent cervical HPV infections lead to cervical precancer and, in the absence of screening, to cancer.^{9,10} Although understanding the rates of HPV acquisition and persistence in the oral region is essential to inform potential prevention efforts for HPV-related oropharyngeal cancers, to do a prospective oral HPV infection study with oropharyngeal cancer as an endpoint is not feasible, since oral HPV16 infection and the resultant HPV-induced oropharyngeal cancer are rare (1.8 per 100000 women and 8.2 per 100000 men),^{3,11,12} and a long latency period typically occurs between infection and cancer (at least 10–20 years).¹³ Thus, we made use of the *HPV Infection in Men (HIM) Study* (a prospective cohort study to assess the natural history of genital HPV infections in healthy men residing in Brazil, Mexico, and the USA) to examine the acquisition and clearance of oral HPV infection, the presumed obligate precursor to HPV-related oropharyngeal cancer.

Methods

Study population

This work was nested within the *HIM Study*, which is in progress and has been previously described.^{14,15} Briefly, men were recruited from Brazil, Mexico, and the USA beginning in 2005; the oral component of this research was started in 2007.¹² The complete *HIM Study* cohort consists of 4072 men aged 18–70 years who reported no previous diagnosis of penile or anal cancers, had never been diagnosed with genital or anal warts, and reported no symptoms of or treatment for a sexually transmitted infection, including HIV/AIDS. No exclusion criteria were based on history of head and neck cancer. Men were recruited from

different population sources to increase access to a broad range of ages, sexual behaviors, and HPV risk.¹⁴ Men from this cohort were included in our analysis if they provided two or more oral rinse-and-gargle samples with valid HPV results. The human subjects committees of the University of South Florida (Tampa, FL, USA), Ludwig Institute for Cancer Research (São Paulo, Brazil), Centro de Referência e Treinamento em Doenças Sexualmente Transmissíveis e AIDS (São Paulo, Brazil), and Instituto Nacional de Salud Pública de México (Cuernavaca, Mexico) approved all study procedures. All participants provided written informed consent.

Procedures

HIM Study participants completed a pre-enrollment (baseline) visit, and were enrolled on completion of their first follow-up visit (2 weeks post-baseline). Patients were then followed up every 6 months for up to 4 years. Because the oral component was started roughly 2 years after enrollment into the *HIM Study* cohort began, the first oral rinse-and-gargle sample obtained was used as a baseline (although it will not necessarily have been from the participant's baseline study visit). At each visit, patients completed a computer-assisted self-interview with questions about sociodemographic characteristics, smoking status, alcohol use, and sexual history (eg, recent oral sex and lifetime numbers of sex partners).

Each oral rinse-and-gargle sample was obtained by use of a 30 s rinse and gargle with 15 mL of locally available mouthwash.¹² The sample was centrifuged at 3000g for 15 min at 4°C, the supernatant was decanted, and the pellet was resuspended in 20 mL of sterile normal saline. Centrifugation was repeated, and the pellet was resuspended in 1.2 mL of saline with repeated pipetting and vortexing to ensure even sample distribution. Samples were then stored at –80°C for PCR analysis and genotyping.

Methods for extraction and genotyping of HPV DNA were optimized for the detection of oral HPV infection as previously described.¹² DNA extraction was done with the robotic MDx Media Kit (Qiagen, Valencia, CA, USA) in accordance with the manufacturer's instructions. Samples that were β -globin negative were manually re-extracted. Briefly, 200 μ L samples of clinical material were digested with 20 μ L of proteinase K solution and lysed with 200 μ L of lysis buffer at 56°C. Samples were tested for the presence of HPV by amplification of 50 ng of total DNA with the PGMY09/11 L1 consensus primer system. HPV genotyping was done with Linear Array (Roche Molecular Diagnostics, Alameda, CA, USA) for all samples, irrespective of HPV PCR results.^{16,17} Samples were amplified in a PTC-200 thermocycler (MJ Research, Saint-Bruno-de-Montarville, QC, Canada). 13 HPV types were classified as oncogenic: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.¹⁸ Other (non-oncogenic) HPV types detected with the Roche Linear Array system were: 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73, 81, 82, 83, 84, CP6108, and IS39.

Statistical analysis

Genotype-specific HPV infections were reported individually and in groups (any, oncogenic, non-oncogenic, and vaccine types). The classification of any HPV type was defined as a positive test result for at least one of the 37 HPV genotypes included in the assay. Infection with one or more than one oncogenic HPV type defined an oncogenic infection. Independently, infection with at least one non-oncogenic HPV type defined a non-oncogenic infection.

For incidence analyses, only the first-acquired genotype-specific infection was considered, and only men who tested negative for any or type-specific HPV infection at the baseline oral visit were included. Person-time for a newly acquired HPV infection was calculated from

the baseline oral visit to the date of first detection of HPV DNA—ie, with the assumption that a new infection arose on the date of detection. A second method was used to estimate incidence in which new infections were assumed to have arisen at the midpoint between detection and the preceding study visit. The calculation of exact 95% confidence intervals (CIs) for incidence estimates was based on the number of events modeled as a Poisson variable for the total person-months. Cumulative risk of acquiring a new HPV infection in the first 12 months of follow-up was estimated by the Kaplan-Meier method, with log-rank tests used to identify differences across age groups.

HPV genotype-specific clearance was defined as a participant testing HPV negative after having previously tested positive, excluding prevalent infections and those detected for the first time at a participant's final visit. Median time to clearance was estimated from all men with an incident infection by the Kaplan-Meier method for individual HPV types and by the clustered Kaplan-Meier method for grouped types to account for within-subject correlation.¹⁹ Since men could have been infected with more than one HPV type from within a defined group (eg, HPV16 and HPV18 are both oncogenic types), grouped HPV clearance analyses were adjusted for within-subject correlation. Men whose infections did not clear by the final visit were censored in the Kaplan-Meier analysis.

Factors associated with incidence of any and oncogenic HPV infections were assessed by Cox proportional-hazards regression. Univariate models were adjusted for design factors (country and age). For multivariable models, candidate variables consisted of those that were significant in univariate models (marital status, education, smoking status, sexual orientation, lifetime number of sex partners, and ever having participated in oral sex with a man), design variables (age and country), and variables that were believed to be relevant on the basis of previous work. We assessed potential interactions between variables. Continuous variables, with the exception of age, were classified into tertiles or quartiles. Because of low numbers of oral HPV infections, factors associated with clearance could not be examined. All analyses were done with SAS version 9.3 (SAS Institute, Cary, NC, USA). All statistical tests were two-sided and attained significance at $\alpha=0.05$.

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Results

The analyzed cohort consisted of 1626 men (499 from Brazil, 557 from Mexico, and 570 from the USA) who were the first to have provided oral rinse-and-gargle samples at two or more study visits. These men completed a minimum of 2 weeks of follow-up (median 12.7 months, IQR 12.1–14.7; range 0.5–37.2). 161 (10%) men completed two follow-up visits, 953 (59%) completed three visits, 485 (30%) completed four visits, and 27 (2%) completed five visits. Men in the analyzed cohort were similar to men in the full *HIM Study* cohort ($n=4072$), with respect to various sociodemographic and behavioral characteristics (table 1). At the oral baseline visit, men in the analyzed cohort ranged in age from 18 to 73 years with a median age of 32 years (IQR 24–41).

Acquisition of oral HPV infection was uncommon in healthy men overall (table 2). When we assumed that a new infection arose on the date of detection, the rate of oral HPV acquisition was 5.6 per 1000 person-months and for oncogenic HPV was 2.5 per 1000 person-months. During the first 12 months of follow-up, 4.4% (95% CI 3.5–5.6; $n=115$ incident infections) of men acquired an incident oral HPV infection, 1.7% (95% CI 1.2–2.5; $n=53$ incident infections) acquired oncogenic HPV, 0.6% (95% CI 0.3–1.1; $n=18$ incident

infections) acquired HPV 16, and 3.4% (95% CI 2.6–4.5; n=80 incident infections) acquired non-oncogenic HPV. Oral HPV 16 was the most frequently acquired oncogenic HPV genotype, followed by types 59 and 39, which were detected in 0.5% (n=11 incident infections) and 0.3% (n=7 incident infections) of the population, respectively. All other oncogenic HPV types were acquired in the oral region in less than 0.1% of healthy men. HPV55 was the most common non-oncogenic oral infection, acquired in 2.0% (n=38 incident infections) of men. Of the 115 men with an incident oral HPV infection, 17 (15%) were co-infected with more than one type of HPV; HPV16 was present in 5 (29%) of these co-infections. When we assumed that a new infection arose at the midpoint between study visits, the incidence rate of oral HPV was 5.7 per 1000 person-months and for oncogenic HPV types remained 2.5 per 1000 person-months. The 12-month cumulative incidence of oral HPV acquisition was 7.0% (95% CI 5.8–8.4) and for oncogenic HPV types was 3.1% (95% CI 2.4–4.2).

Most incident oral HPV infections cleared within 1 year (table 2). Median duration of infections was similar for oral oncogenic HPV infections (6.3 months, 95% CI 6.0–9.9; n=18 cleared infections) and for HPV 16 infections (7.3 months, 95% CI 6.0–NE; n=5 cleared infections). Furthermore, eight of the 18 incident oral HPV 16 infections persisted for two or more study visits; infections that occurred for the first time at the final study visit (n=12) were excluded. Graphical estimates of the cumulative incidence and time to clearance of type 16, oncogenic, and any oral HPV infections show the rarity of oral HPV infections and their propensity to clear with time (figure 1).

The risk of acquiring oncogenic oral HPV or any type of oral HPV was similar across age groups (figure 2). Within the first 12 months of follow-up, the risk of acquiring any oral HPV was highest in men aged 31–50 years; however, this pattern did not persist throughout the follow-up period. In our multivariable analyses, acquisition of a new oral oncogenic HPV infection was significantly higher in men who were single, divorced, separated, or widowed than in those who were married or cohabiting, and was higher in current and former cigarette smokers than in those who had never smoked (table 3). Acquisition of any new oral HPV infection was significantly higher in men who were living in Mexico than in those who were living in the USA, in those who were divorced, separated, or widowed than in those who were married or cohabiting, in those who reported current cigarette smoking than in those who had never smoked, in bisexual than in heterosexual men, and in those who had completed 16 years of education than in those with less than 12 years of education (table 3). Other variables were not significantly associated with oral HPV infection (any or oncogenic): alcohol intake, ever having had oral sex, having had recent oral sex (within the past 6 months), recent number of oral sexual encounters, and time elapsed since last oral sex encounter (table 3). The increase in the risk (OR 2.32; 95% CI 1.30–4.12) of any oral HPV associated with reporting 20 or more lifetime sexual partners was not significant after adjustment for covariates (adjusted OR 1.73, 0.87–3.45). None of the interaction terms were significant.

Discussion

Our findings show that acquisition of an oral oncogenic HPV infection in healthy men is a rare event (2.5 per 1000 person-months) compared with genital (22.2 per 1000 person-months)¹⁵ and, to a lesser extent, anal (3.7 per 1000 person-months)²⁰ HPV infection, and that incidence is fairly stable across countries and age groups. We have also shown that, similar to patterns of clearance in the genital epithelium in men and women, most newly acquired oral oncogenic HPV infections in men clear within 1 year, and that smoking and marital status affect the acquisition of oral HPV infections (panel).

Most of our knowledge about HPV epidemiology relates to the cervix, where HPV acquisition occurs shortly after sexual debut,²¹ most infections clear within 1–2 years,²² and infections at older ages are uncommon.²³ Our findings suggest different epidemiological characteristics for oral HPV infection in men. Our results were consistent with those of two prospective studies of oral HPV incidence,^{24,25} and our findings suggest that acquisition of oral oncogenic HPV infection is rarer than acquisition of genital infection, although infections at both sites seem to clear at roughly the same rate. In a recent population-based study of oral HPV prevalence, a bimodal age distribution was noted in men, with peak prevalence at older ages.⁷ However, acquisition of oral HPV in our study was constant across age groups. Together these data suggest that higher oral HPV prevalence at older ages could be caused by increased duration of infections at older ages, rather than increased acquisition.

Although epidemiologic data suggest that tobacco use is the main cause of head and neck cancers overall, it is not a strong risk factor for HPV-driven oropharyngeal cancer,^{5,26} the incidence rates and population burden of which are roughly equivalent in current and former smokers and in those who had never smoked.²⁷ However, in our study, cigarette smoking was significantly associated with acquisition of oral HPV in healthy men; the risk of acquiring an oncogenic oral HPV infection was nearly three times higher in current smokers (HR=2.80) and more than two times higher in former smokers (HR=2.31) than in those who had never smoked, after adjustment for potential confounders. Current smoking has previously been associated with increased prevalence of oral HPV,^{7,12,28} however, the exact biological mechanism has yet to be established. Tobacco exposure induces proinflammatory and immunosuppressive effects,^{29,30} which might increase the likelihood of HPV infection and persistence, particularly at the oral cavity where tobacco carcinogens have direct contact with the oral epithelium.

Marital status was strongly associated with risk of acquiring any and oncogenic oral HPV infections, with married or cohabiting men at a significantly reduced risk in both categories. Marital status seems to be more predictive of oral HPV acquisition than does lifetime number of sexual partners, a finding that is consistent with our previous analysis of oral HPV prevalence.¹² In our multivariable models, the effect estimates for marital status remained unchanged after adjustment for lifetime number of sexual partners. These findings contrast with those of the largest study of oral HPV prevalence,⁷ in which lifetime and recent numbers of partners for any type of sex were more strongly associated with oral HPV detection than was marital status.

Sexual orientation was also associated with risk of oral HPV infection in our study, with bisexual men at the highest risk. These findings suggest that marital status and sexual orientation could reflect a participant's likelihood of engaging in risky sexual behaviors and partnerships, or differences in a participant's sexual network, and that these characteristics might be more predictive of risk than lifetime number of sexual partners. Finally, men who spent a greater number of years in education had an increased risk of acquiring an oral HPV infection, possibly because they had been exposed to more sexual opportunities than those with fewer years in education.

No significant association was seen between any measure of oral sexual behavior and acquisition of oral oncogenic HPV after adjustment for potential confounders, a finding consistent with our study of oral HPV prevalence.¹² Two prospective studies^{24,25} have previously investigated associations between oral sex and acquisition of oral HPV, with inconsistent results. In one study of young men and women,²⁵ no significant association between oral sex and incidence of oral HPV was noted; however, in another study, which was in young men only,²⁴ performing oral sex on a woman more than once per week was

associated with a significantly increased risk of an incident oral HPV infection. In studies that do not show an association with oral sex, this finding might be due to insufficient power, inadequate detail in the questionnaire, or recall bias. This information bias could have led to exposure misclassification and therefore attenuation of risk estimates to the null. Alternatively, other sexual behaviors might account for the increased risk of oral HPV infection. More adequately-powered prospective studies in diverse populations are needed to clarify these associations.

Ours is the largest prospective study to examine the natural history of oral HPV infection, and it covers the at-risk population for HPV-related oropharyngeal cancer (ie, otherwise healthy men of a wide age range). However, limitations need to be considered in the interpretation of these results. First, because of the methods of recruitment and rigors of study participation, the analyzed cohort might not be representative of the wider population. However, the issue of generalizability would have only a small effect on the assessment of factors associated with oral HPV acquisition. Second, although we used the accepted gold standard method for oral sample collection (oral rinse and gargle) this method does not provide a targeted sample of the biologically relevant cancer site (the oropharynx). Furthermore, the quantitative association between HPV detection in oral exfoliated cells and risk of future HPV-driven oropharyngeal cancer is unknown. Third, we were restricted in our ability to fully assess rates and predictors of clearance. As a result, we were unable to use a more rigorous definition of clearance (eg, two consecutive visits with negative HPV DNA results). Additionally, if oral HPV viral load was below the lower limit of detection of the assay,³¹ we could have misclassified a low-copy-number infection as cleared; in such a case, we would have underestimated the true duration of infection. Finally, despite a very large population sample size, our ability to report rates of HPV type-specific acquisition and clearance was limited by the rarity of oral HPV infection.

HPV infection causes cancer at several anatomical sites; however, the natural history of the infection at non-cervical sites has been understudied, especially at the oral epithelium. From our analyses of the *HIM Study* cohort of men, we now understand that the natural history of HPV infection differs across anatomical sites. Furthermore, in the oral region, vaccine-preventable oral HPV types that are associated with oropharyngeal cancer (HPV 16 and 18) represented 17% of newly acquired oral HPV infections in men without cancer in our study population. To inform prevention efforts for HPV-related oropharyngeal cancers, further investigation of the natural history of oral HPV is needed, with factors associated with oral HPV persistence and clearance as the focus.

Panel: Research in context

Systematic review—Data from epidemiological studies¹⁻⁵ suggest that human papillomavirus (HPV) has an important causal role in some oropharyngeal squamous cell carcinomas, and in the increasing incidence of this cancer in men. We searched PubMed using terms related to oral HPV acquisition, incidence, clearance, and natural history, and identified two relevant reports. Edelstein and colleagues²⁴ studied 212 men aged 18–24 years, who were followed up for 12 months, and estimated that the 12-month cumulative incidence of any oral HPV infection was 12%. Pickard and colleagues²⁵ studied 1000 men and women aged 18–30 years, who were followed up for 3 months, and reported that the incidence of any oral HPV was 5.7 per 1000 person-months.

Interpretation—Our analysis showed that newly acquired oral oncogenic HPV infections in healthy men were rare and constant across age groups. These findings suggest that the increased prevalence of oral HPV at older ages reported in a population-based study⁷ might be caused by increased duration of infections at older ages, rather than increased incidence.

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Figure 1. Kaplan-Meier estimates of the cumulative incidence and time to clearance of any, oncogenic, and type 16 oral human papillomavirus (HPV) infections
 (A) Incidence of any oral HPV, (B) Incidence of oncogenic oral HPV, (C) Incidence of oral HPV16, (D) Clearance of any incident oral HPV, (E) Clearance of incident oncogenic oral HPV, (F) Clearance of incident oral HPV16

Figure 2. Age-stratified Kaplan-Meier estimates of the cumulative incidence of any and oncogenic oral human papillomavirus (HPV) infections

(A) Incidence of any oral HPV, (B) Incidence of oral oncogenic HPV

Table 1
Baseline characteristics of men included and not included in the analysis

	Included (n=1626)	Not included (n=2446)	Full cohort (n=4072)
Country			
USA	570 (35%)	773 (32%)	1343 (33%)
Brazil	499 (31%)	900 (37%)	1399 (34%)
Mexico	557 (34%)	773 (32%)	1330 (33%)
Age (years)			
18–30	759 (47%)	1165 (48%)	1924 (47%)
31–44	592 (36%)	957 (39%)	1549 (38%)
45–73	275 (17%)	324 (13%)	599 (15%)
Race			
White	751 (46%)	1072 (44%)	1823 (45%)
Black	229 (14%)	407 (17%)	636 (16%)
Asian/Pacific Islander	39 (2%)	73 (3%)	112 (3%)
Mixed race	585 (36%)	853 (35%)	1438 (35%)
Missing data	22 (1%)	41 (2%)	63 (2%)
Ethnicity			
Hispanic	748 (46%)	1087 (44%)	1835 (45%)
Non-Hispanic	867 (53%)	1335 (55%)	2202 (54%)
Missing data	11 (1%)	24 (1%)	63 (1%)
Marital status			
Single	702 (43%)	1103 (45%)	1805 (44%)
Married or cohabiting	774 (48%)	1121 (46%)	1895 (47%)
Divorced, separated, or widowed	145 (9%)	214 (9%)	359 (9%)
Missing data	5 (<1%)	8 (<1%)	13 (<1%)
Education (years)			
12	724 (45%)	1210 (49%)	1934 (47%)
13–15	458 (28%)	591 (24%)	1049 (26%)
16	436 (267%)	634 (26%)	1070 (26%)
Missing data	8 (<1%)	11 (<1%)	19 (<1%)
Smoking status			
Never	962 (59%)	1385 (57%)	2347 (58%)
Former	300 (18%)	435 (18%)	735 (18%)
Current	359 (22%)	618 (25%)	977 (24%)
Missing data	5 (<1%)	8 (<1%)	13 (<1%)
Alcohol intake (drinks per month)			
0	406 (25%)	576 (24%)	982 (24%)
1–30	725 (45%)	1110 (45%)	1835 (45%)
31	464 (29%)	686 (28%)	1150 (28%)
Missing data	31 (2%)	74 (3%)	105 (3%)
Sexual orientation			

	Included (n=1626)	Not included (n=2446)	Full cohort (n=4072)
MSW	1392 (86%)	2010 (82%)	3402 (84%)
MSM	54 (3%)	106 (4%)	160 (4%)
MSWM	93 (6%)	178 (7%)	271 (7%)
Missing data	87 (5%)	152 (6%)	239 (6%)
Lifetime number of sex partners			
0–2	348 (21%)	646 (26%)	994 (24%)
3–7	450 (28%)	634 (26%)	1084 (27%)
8–19	413 (25%)	592 (24%)	1005 (25%)
20	400 (25%)	557 (23%)	957 (24%)
Missing data	15 (1%)	17 (1%)	32 (1%)
Ever had oral sex			
No	195 (12%)	317 (13%)	512 (13%)
Yes	1422 (87%)	2096 (86%)	3518 (86%)
Missing data	9 (1%)	33 (1%)	42 (1%)
Ever had oral sex with a man			
No	1290 (79%)	2010 (82%)	3300 (81%)
Yes	223 (14%)	401 (16%)	624 (15%)
Missing data	113 (7%)	35 (1%)	148 (4%)
Had oral sex in the past 6 months			
No	469 (29%)	456 (19%)	925 (23%)
Yes	1085 (67%)	793 (32%)	1878 (46%)
Missing data	72 (4%)	14 (<1%)	86 (2%)
Question not asked*	0	1183 (48%)	1183 (29%)
Number of oral sex acts in the past 6 months			
0	488 (30%)	473 (19%)	961 (24%)
1–6	282 (17%)	213 (9%)	495 (12%)
7–24	377 (23%)	236 (10%)	613 (15%)
25	366 (23%)	296 (12%)	662 (16%)
Missing data	113 (7%)	43 (2%)	156 (4%)
Question not asked*	0	1185 (48%)	1185 (29%)
Time since last oral sex (days)			
0–3	323 (20%)	244 (10%)	567 (14%)
>3–10	290 (18%)	185 (8%)	475 (12%)
>10–30	288 (18%)	199 (8%)	487 (12%)
>30	416 (26%)	263 (11%)	679 (17%)
Never	195 (12%)	317 (13%)	512 (13%)
Missing data	114 (7%)	51 (2%)	165 (4%)
Question not asked*	0	1187 (49%)	1187 (29%)

Data are n (%).

MSW=men who have sex with women. MSM=men who have sex with men. MSWM=men who have sex with women and men.

* The study questionnaire was revised in 2007 after oral sample collection began.

Table 2
Prevalence at baseline and incidence and clearance of oral human papillomavirus (HPV) infection in men

	Incidence				Clearance		
	Prevalence (n=1626)	Incident infections*	Person-months*	Incidence per 1000 person-months (95% CI)*	12-month incidence (95% CI)*	New infections†	Median time to clearance (months; 95% CI)*
Any HPV type	71 (4.4%)	115	20565	5.6 (4.6-6.7)	4.4% (3.5-5.6)	81	6.9 (6.2-9.3)
Oncogenic	22 (1.4%)	53	21556	2.5 (1.8-3.2)	1.7% (1.2-2.5)	24	6.3 (6.0-9.9)
16	10 (0.6%)	18	21851	0.8 (0.5-1.3)	0.6% (0.3-1.1)	6	7.3 (6.0-NE)
18	0 (0%)	1	22013	0 (0-0.3)	0% (0-0)	0	NE
31	0 (0%)	1	22001	0 (0-0.3)	0.1% (0-0.4)	1	6.5 (NE)
33	0 (0%)	0	22013	0 (0-0.2)	0% (0-0)	0	NE
35	1 (0.1%)	5	21988	0.2 (0.1-0.5)	0.1% (0-0.5)	3	5.7 (5.6-NE)
39	1 (0.1%)	7	21968	0.3 (0.1-0.7)	0.3% (0.1-0.7)	4	9.9 (5.9-NE)
45	0 (0%)	3	22013	0.1 (0-0.4)	0.1% (0-0.5)	0	NE
51	4 (0.2%)	2	21946	0.1 (0-0.3)	0.1% (0-0.5)	1	5.7 (NE)
52	1 (0.1%)	1	21999	0 (0-0.3)	0% (0-0)	0	NE
56	2 (0.1%)	4	21998	0.2 (0-0.5)	0.1% (0-0.5)	1	6.1 (NE)
58	1 (0.1%)	3	21987	0.1 (0-0.4)	0.1% (0-0.5)	1	5.2 (NE)
59	2 (0.1%)	11	21918	0.5 (0.3-0.9)	0.5% (0.2-1.0)	7	6.3 (6.0-NE)
68	0 (0%)	1	22013	0 (0-0.3)	0% (0-0)	0	NE
Non-oncogenic	53 (3.3%)	80	20918	3.8 (3-4.8)	3.4% (2.6-4.5)	57	7.7 (6.4-9.8)
6	4 (0.2%)	7	21926	0.3 (0.1-0.7)	0.3% (0.1-0.8)	6	7.7 (7.6-NE)
11	2 (0.1%)	0	21983	0 (0-0.2)	0% (0-0)	0	NE
26	0 (0%)	2	22013	0.1 (0-0.3)	0% (0-0)	0	NE
40	0 (0%)	0	22013	0 (0-0.2)	0% (0-0)	0	NE
42	0 (0%)	2	22007	0.1 (0-0.3)	0.1% (0-0.5)	1	5.8 (NE)
53	1 (0.1%)	4	21995	0.2 (0-0.5)	0% (0-0)	0	NE
54	0 (0%)	1	21999	0 (0-0.3)	0.1% (0-0.4)	1	8.3 (NE)
55	16 (1.0%)	38	21585	1.8 (1.2-2.4)	2.0% (1.4-2.8)	31	10.3 (6.5-NE)
61	5 (0.3%)	6	21918	0.3 (0.1-0.6)	0.3% (0.1-0.7)	4	9.3 (6.0-NE)

	Incidence				Clearance			
	Prevalence (n=1626)	Incident infections*	Person-months*	Incidence per 1000 person-months (95% CI)*	12-month incidence (95% CI)*	New infections†	Cleared Infections*	Median time to clearance (months; 95% CI)*
62	5 (0.3%)	7	21938	0.3 (0.1-0.7)	0.3% (0.1-0.7)	3	2	6.3 (6.0-NE)
64	1 (0.1%)	0	22001	0 (0-0.2)	0% (0-0)	0	0	NE
66	5 (0.3%)	6	21944	0.3 (0.1-0.6)	0.1% (0-0.4)	1	1	6.1 (NE)
67	0 (0%)	0	22013	0 (0-0.2)	0% (0-0)	0	0	NE
69	1 (0.1%)	1	21996	0 (0-0.3)	0% (0-0)	0	0	NE
70	2 (0.1%)	3	21974	0.1 (0-0.4)	0.1% (0-0.5)	1	1	6.1 (NE)
71	3 (0.2%)	2	21969	0.1 (0-0.3)	0.1% (0-0.5)	1	1	6.0 (NE)
72	3 (0.2%)	3	21957	0.1 (0-0.4)	0.2% (0.1-0.7)	2	1	14.0 (NE)
73	0 (0%)	1	22013	0 (0-0.3)	0% (0-0)	0	0	NE
81	0 (0%)	0	22013	0 (0-0.2)	0% (0-0)	0	0	NE
82	2 (0.1%)	0	21988	0 (0-0.2)	0% (0-0)	0	0	NE
83	1 (0.1%)	0	21993	0 (0-0.2)	0% (0-0)	0	0	NE
84	4 (0.2%)	5	21943	0.2 (0.1-0.5)	0.2% (0.1-0.6)	3	3	8.0 (5.7-NE)
CP6108	1 (0.1%)	4	21969	0.2 (0-0.5)	0.2% (0.1-0.6)	3	2	6.0 (5.9-NE)
IS39	0 (0%)	0	22013	0 (0-0.2)	0% (0-0)	0	0	NE
Vaccine types (6, 11, 16, or 18)	16 (1.0%)	25	21734	1.2 (0.7-1.7)	0.9% (0.5-1.5)	12	7	7.6 (6.3-19.1)

Data are n (%), unless otherwise indicated. NE=not estimable.

* Analysis based on newly acquired incident infections.

† Number of new infections was different from the number of incident infections because multiple infections were judged individually in the clearance analysis, and new infections detected at a participant's final visit were not analyzed for clearance.

Table 3
Factors associated with oral human papillomavirus (HPV) incidence

	Number of men (%; n=1626)	Oncogenic HPV			Any HPV		
		No. infections/person-months	Univariate* HR (95% CI)	Multivariable† HR (95% CI)	No. infections/person-months	Univariate* HR (95% CI)	Multivariable‡ HR (95% CI)
Country							
USA	570 (35.1)	19/7177	1.00	1.00	23/6950	1.00	1.00
Brazil	499 (30.7)	14/6705	0.70 (0.35–1.40)	0.74 (0.35–1.55)	34/6496	1.46 (0.86–2.48)	1.76 (0.94–3.27)
Mexico	557 (34.3)	20/7674	0.92 (0.49–1.73)	1.39 (0.67–2.87)	58/7118	2.40 (1.48–3.89)	3.88 (2.08–7.22)
Age (years)							
Median (IQR)	32 (24–41)	..	1.00 (0.97–1.02)	1.01 (0.98–1.04)	..	1.01 (0.99–1.02)	1.00 (0.98–1.02)
18–30	759 (46.7)	25/10001	1.00	NA	48/9632	1.00	NA
31–44	592 (36.4)	20/7917	1.00 (0.56–1.80)	NA	48/7553	1.26 (0.85–1.88)	NA
45–73	275 (16.9)	8/3638	0.93 (0.42–2.06)	NA	19/3380	1.18 (0.70–2.01)	NA
Marital status							
Married or cohabiting	702 (43.3)	16/10677	1.00	1.00	51/10069	1.00	1.00
Single	774 (47.7)	28/9031	2.78 (1.30–5.96)	2.72 (1.26–5.90)	48/8730	1.77 (1.08–2.89)	1.35 (0.79–2.30)
Divorced, separated, or widowed	145 (8.9)	9/1782	4.20 (1.76–10.03)	3.89 (1.58–9.61)	16/1699	2.71 (1.49–4.91)	2.56 (1.36–4.81)
Missing data	5 (<1%)	..	..	..	..	..	..
Education (years)							
12	724 (44.7)	21/9764	1.00	NA	48/9319	1.00	1.00
13–15	458 (28.3)	18/5783	1.61 (0.74–3.47)	NA	29/5587	1.90 (1.12–3.22)	1.94 (1.13–3.33)
16	436 (26.9)	14/5888	1.16 (0.57–2.34)	NA	37/5545	1.74 (1.12–2.7)	1.74 (1.08–2.80)
Missing data	8 (<1%)	..	..	..	..	..	..
Smoking status							
Never	962 (59.3)	18/12687	1.00	1.00	52/12194	1.00	1.00
Former	300 (18.5)	12/3968	2.12 (1.02–4.40)	2.31 (1.10–4.88)	22/3791	1.30 (0.79–2.14)	1.32 (0.77–2.26)
Current	359 (22.1)	22/4834	3.09 (1.64–5.81)	2.80 (1.45–5.42)	40/4512	1.78 (1.17–2.71)	1.81 (1.15–2.86)
Missing data	5 (<1%)	..	..	..	..	..	..
Alcohol intake (drinks/month)							

	Number of men (%; n=1626)	Oncogenic HPV				Any HPV			
		No. infections/person-months		Univariate* HR (95% CI)	Multivariable† HR (95% CI)	No. infections/person-months		Univariate* HR (95% CI)	Multivariable‡ HR (95% CI)
0	406 (25.5)	9/5392	1.00	NA	NA	24/5149	1.00	NA	NA
1-30	725 (45.5)	23/9671	1.42 (0.66-3.07)	NA	NA	56/9214	1.33 (0.82-2.14)	NA	NA
31	464 (29.1)	21/6120	2.05 (0.93-4.53)	NA	NA	34/5830	1.42 (0.84-2.41)	NA	NA
Missing data	31 (2%)	..	..	..	..	..	..	..	..
Sexual orientation									
MSW	1392 (90.4)	44/18435	1.00	NA	NA	89/17621	1.00	1.00	1.00
MSM	54 (3.5)	2/737	1.34 (0.32-5.64)	NA	NA	3/731	0.91 (0.28-2.91)	0.65 (0.20-2.11)	0.65 (0.20-2.11)
MSWM	93 (6.0)	6/1191	2.62 (1.08-6.37)	NA	NA	15/1063	2.72 (1.55-4.79)	2.29 (1.26-4.19)	2.29 (1.26-4.19)
Missing data	87(5%)	..	..	..	..	..	..	..	..
Lifetime number of any sex partners									
0-2	348 (21.6)	8/4682	1.00	1.00	1.00	19/4514	1.00	1.00	1.00
3-7	450 (27.9)	14/6049	1.30 (0.54-3.10)	0.98 (0.39-2.46)	0.98 (0.39-2.46)	28/5814	1.12 (0.63-2.01)	1.20 (0.62-2.33)	1.20 (0.62-2.33)
8-19	413 (25.6)	16/5394	1.85 (0.78-4.35)	1.22 (0.49-3.04)	1.22 (0.49-3.04)	27/5127	1.37 (0.76-2.48)	1.21 (0.61-2.40)	1.21 (0.61-2.40)
20	400 (24.8)	15/5228	1.90 (0.78-4.64)	1.08 (0.41-2.84)	1.08 (0.41-2.84)	38/4936	2.32 (1.30-4.12)	1.73 (0.87-3.45)	1.73 (0.87-3.45)
Missing data	15 (1%)	..	..	..	..	..	..	..	..
Ever had oral sex									
No	195 (12.1)	3/2609	1.00	NA	NA	14/2509	1.00	NA	NA
Yes	1422 (87.9)	50/18812	2.37 (0.73-7.69)	NA	NA	101/17921	1.15 (0.65-2.04)	NA	NA
Missing data		..	..	..	..	..	..	..	..
Ever had oral sex with a man	9 (1%)								
No	1290 (85.3)	43/17272	1.00	NA	NA	82/16543	1.00	NA	NA
Yes	223 (14.7)	8/2830	1.40 (0.64-3.08)	NA	NA	22/2665	1.95 (1.19-3.21)	NA	NA
Missing data	113 (7%)	..	..	..	..	..	..	..	..
Had oral sex in the past 6 months									
No	469 (30.2)	12/6201	1.00	NA	NA	29/5918	1.00	NA	NA
Yes	1085 (69.8)	39/14356	1.45 (0.75-2.82)	NA	NA	78/13693	1.25 (0.80-1.93)	NA	NA
Missing data	72 (4%)	..	..	..	..	..	..	..	..

	Oncogenic HPV				Any HPV		
	Number of men (%; n=1626)	No. infections/person-months		Multivariable [†] HR (95% CI)	No. infections/person-months		
		Univariate* HR (95% CI)			Univariate* HR (95% CI)		Multivariable [‡] HR (95% CI)
Number of oral sex acts in the past 6 months							
0	488 (32.3)	15/6439	1.00	NA	33/6147	1.00	NA
1–6	282 (18.6)	3/3835	0.33 (0.09–1.14)	NA	12/3669	0.62 (0.32–1.20)	NA
7–24	377 (24.9)	21/4969	1.81 (0.92–3.56)	NA	35/4732	1.43 (0.88–2.33)	NA
25	366 (24.2)	11/4742	1.00 (0.45–2.23)	NA	24/4505	1.13 (0.66–1.94)	NA
Missing data	113 (7%)	..	..	..	..	..	..
Time since last oral sex (days)							
0–3	323 (21.3)	14/4290	1.00	NA	26/4169	1.00	NA
>3–10	290 (19.1)	13/3839	1.02 (0.48–2.18)	NA	25/3591	1.04 (0.60–1.81)	NA
>10–30	288 (19.0)	8/3769	0.64 (0.27–1.52)	NA	18/3594	0.75 (0.41–1.36)	NA
>30	416 (27.5)	12/5459	0.64 (0.29–1.40)	NA	22/5179	0.62 (0.35–1.10)	NA
Never	195 (12.9)	3/2609	0.32 (0.09–1.15)	NA	14/2509	0.72 (0.37–1.40)	NA
Missing data	114 (7%)	..	..	..	..	..	..

Data are hazard ratios (95% CI), unless otherwise indicated. MSW=men who have sex with women. MSM=men who have sex with men. MSWM=men who have sex with women and men.

* Univariate models, apart from for country and age, are adjusted for design factors (country and age [continuous]).

† Adjusted for country, age (continuous), marital status, smoking status, and lifetime number of sexual partners.

‡ Adjusted for country, age (continuous), marital status, education, smoking status, sexual orientation, and lifetime number of sexual partners.