

Gender differences in risk factors and natural history of oral human papillomavirus (HPV) infection

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Abstract

Oral HPV16 infection causes oropharyngeal squamous cell carcinoma (OPSCC), and prevalence is higher among men than women in the United States. In a cohort study of oral HPV infection among 409, 18-25 year-olds, risk significantly *increased* with recent (prior three months) number of oral sexual partners among men, but not women (p-interaction [p_i] = 0.05). In contrast, risk significantly *declined* with lifetime number of vaginal sexual partners among women, but not men (p_i = 0.037). Men were also significantly less likely to clear an oral HPV infection than women. Our data contribute to understanding gender differences in risk for HPV-positive OPSCC.

Brief Report

Background

Oral HPV16 infection causes a majority of OPSCC in the US, and incidence rates are higher and rising more rapidly among men than women.[1, 2] The higher risk of OPSCC among US men is explained in part by a 5-fold higher oral HPV16 prevalence,[3-5] but the factors contributing to this gender difference in prevalence are unknown.

Currently, it is unknown whether the higher oral HPV prevalence among men is attributable to increased incidence, decreased clearance or a combination of both factors. Previous studies indicate that the natural history of oral HPV infection may differ by gender, but inferences were limited by small sample size, short follow-up, inclusion of a single gender, or a focus on specific populations (e.g. HIV-infected individuals).[6-11] We investigated differences in oral HPV natural history among young adult men and women, a population known to be at high risk for sexually transmitted infections.

Methods

To gain insight into gender differences, we conducted a prospective, natural history study of oral HPV infection among young adult men and women aged 18-25 years attending two Baltimore County Health Department sexually transmitted disease clinics for routine care. Participants were enrolled into the Study of Papillomavirus in Teens and Twenties, (SPITT; ClinicalTrials.gov number: NCT00994019) between April 2010 and November 2012, as previously described [12]. Individuals who attended a second visit were considered enrolled into a prospective cohort study and were followed every three months for 18 months. Participants with persistent infection at their 18 month visit had extended follow-up up to 30 months.

At each visit, participants provided a 30-second oral rinse and gargle sample (ORS), as previously described[12], and completed a computer assisted self-interview (CASI) containing questions regarding behavioral information (including number of lifetime and recent [prior three months] partners for open-mouthed kissing, oral and vaginal sex), demographics, tobacco, alcohol and drug use. Participants were provided \$15 incentives and a gift of \$2-5 value [water-bottle, snack, cosmetic/cologne] at each follow-up visit. Oral rinse samples were processed and tested for 36 HPV genotypes by use of PGMY09/11 PCR primer pools and primers for β -globin, followed by reverse line blot hybridization to the Roche linear array.[13] “Oncogenic” HPV types included HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 and 73.

Incident infection was defined as detection of a novel HPV genotype, and clearance as detection of a type-specific HPV infection followed by two consecutive negative visits (e.g. +--). Time to clearance was defined as time from first detection to first negative sample and visualized using Kaplan-Meier curves. Risk factors for incidence and clearance of type-specific oral HPV infection were explored using WLW models with robust variance, including time-updated covariates in each model. Differences in risk factors for males versus females were tested for interaction between gender and each sexual behavior.

Results

Median age of the 409 participants was 21 years (interquartile range [IQR]=20-23), 52% were men, 73% were Black, and 39% had a history of STD. Men and women were similar with regard to age, race, recent cigarette smoking, and lifetime number of oral sexual partners. However, men were more likely to report >10 lifetime vaginal (51% vs. 32%), >1 recent vaginal (50% vs. 36%) and >1 recent oral (28% vs. 22%) sexual partners ($p<0.05$ for all). Recent cunnilingus (oral sex on a woman) was reported by

70% of men and 9% of women, and recent fellatio (oral sex on a man) was reported by 8% of men and 71% of women.

Men had higher oral HPV prevalence and incidence compared to women. At baseline, 68 prevalent, type-specific oral HPV infections were detected among 44 (11%) participants (15.4% in men vs. 5.6% in women, $p=0.001$). Median follow-up time was 18 months (IQR=10-18), with a median of 6 oral rinse samples collected per participant (IQR=3-7). Loss to follow-up was due to relocation ($n=56$), entry into a drug treatment facility ($n=28$), incarceration ($n=10$) or death ($n=2$). A total of 134 incident, type-specific oral HPV infections were detected during follow-up for an estimated incidence rate [IR] of 22.0 per 1000 person-months. The incidence of HPV16 (2.5 vs. 0.7 per 1000 person-months, $p=0.08$) and any oncogenic HPV infections (15.5 vs. 8.9 per 1000 person-months, $p=0.04$) was higher among men than women.

In univariate analysis, in addition to male gender, other risk factors for oral HPV infection included younger age, and sexual behavior. In the entire cohort, risk increased with number of recent, but not lifetime, partners for oral ($p\text{-trend}=0.007$) or vaginal sex ($p\text{-trend}<0.001$). In contrast, recent cigarette, alcohol or marijuana use, and deep-kissing (e.g. French kissing) were not associated with risk (data not shown).

As shown in Table 1, we observed significant interactions between gender, oral sexual behavior and risk of incident oral HPV infection. Notably, recent performance of oral sex significantly increased risk of oral HPV infection among men, but not women (hazard ratio [HR]: 3.15 vs 0.66, $p\text{-interaction}$ [p_i] = 0.01). Further, risk increased significantly with number of recent oral sexual partners among men, but not women (p_i = 0.052). In contrast, risk significantly *declined* with higher lifetime number of vaginal sexual partners among women but not men (p_i = 0.037), Table 1.

To better understand reasons behind the interaction of gender and oral sex, we evaluated risk of oral HPV infection associated with performing cunnilingus (oral sex on a woman) versus fellatio (oral sex on a man). This analysis also revealed differences by gender (Table 1). Cunnilingus increased risk of oral HPV infection among men but not women (HR=2.52 vs 0.77, $p_i = 0.042$), whereas fellatio was not associated with risk among men or women.

Given the gender differences in oral HPV incidence, we next evaluated the effect of gender on oral HPV clearance. There were 202 type-specific, oral HPV infections in men and women in this study, including 68 prevalent and 134 incident infections. Median follow-up time was 12.2 (IQR=6.3-18.1) months after first detection. Median time to clearance was 3.7 months, with 24% of infections persisting to 12 months. Median time to clearance was significantly longer in men than women (5.3 vs 3.0 months, $p<0.001$, Figure 1).

Factors significantly associated with reduced oral HPV clearance in unadjusted analysis included male gender (HR=0.54, 95%CI 0.37-0.78), infection category (prevalent vs. incident, HR=0.47, 95%CI 0.32-0.68), and recent alcohol use (HR=0.62, 95%CI 0.42-0.91). In adjusted analysis, men remained 37% less likely than women (adjusted HR=0.63, 95%CI=0.42-0.95) to clear an oral HPV infection (Supplemental Table 1).

Discussion

We conclude that the risk factors and natural history of oral HPV infection are significantly different among men and women. Gender appears to influence the risk of oral HPV infection when performing oral sex. Recent performance of cunnilingus by men, but not other sexual partnership combinations (i.e women performing cunnilingus,

women performing fellatio, or men performing fellatio), increased risk of oral HPV infection and that risk increased with number of partners. This is consistent with a recent population-based study showing higher oral HPV prevalence in men than women was not explained by differences in number of sexual partners[5], but instead was explained by stronger associations between oral sexual behavior and infection among men.

Notably, the inverse association between lifetime number of partners and risk of oral HPV infection among women is consistent with the leading hypothesis that women are more likely to mount a vigorous immune response to genital HPV infection, conferring subsequent protection from oral HPV infection.[5] Importantly, our data also indicate that men are at greater risk of oral HPV infection persistence than women. Given the observed rapid clearance of incident infections, it is possible that some of the detected HPV DNA represents viral deposition without establishment of epithelial infection, thus attenuating gender differences. The differences in risk factors and natural history of oral HPV infection among men and women observed here likely contribute to the higher risk of HPV-related HNC among men.

Rapid oral HPV clearance observed among most of the young adults in this study is comparable to some recent studies reporting median clearance of around 6 months among adults,[9] but more rapid than other studies which reported median clearance of 18-48 months.[14, 15] As expected, the incidence rate observed among high-risk young adults recruited from an STD clinic in this study (IR=16.5 per 1000 person-months) was higher than two studies comprised of university students with similar ages, which reported incidence rates of 5.6 per 1000 person-months [8] and 7.5 per 1000 person-months[6], respectively. Studies of adults reported lower oral HPV incidence rates than those observed among these college students/ young adults.[9]

This study had several strengths and limitations. Samples were collected every three months, allowing delineation of the rapid viral clearance, and were tested centrally. Behavioral risk factors were collected prospectively at every visit using CASI. Men and women were enrolled in the same clinic within a small age range (18-25 year olds), representing the same source population. The study may be vulnerable to bias due to losses of follow-up. Additionally, this study population was selected as a higher risk population, expected to have a higher incidence of oral HPV infection than the general population; while risk factors identified in this study would be expected to be the same in the general population, the actual incidence of infection in this study does not reflect that in the general population.

This study describes oral HPV natural history over 18 months among high-risk young adults, a group known to be at increased risk for sexually transmitted infections, including HPV. We describe, for the first time, a difference in this oral HPV natural history between men and women. Indeed, our results suggest gender influences the risk of oral HPV infection when performing oral sex, and that performing cunnilingus (oral sex on a woman) confers higher risk of oral HPV acquisition than fellatio (oral sex on a man). These natural history differences suggest that increased oral HPV16 prevalence and higher rates of HPV-related oropharyngeal cancer observed in men compared to women in the U.S. are explained both by higher oral HPV acquisition rates, as well as slower clearance once infected.

Table 1. Risk of oral HPV infection associated with each sexual behavior, by participant gender.

Characteristics*	Univariate HR (95%CI)		P-value for interaction
	Men	Women	
Recently performed any oral sex			
No	1.00	1.00	0.010
Yes	3.15 (1.42-6.98)	0.66 (0.27-1.64)	
Recent number of people performed oral sex on			
0	1.00	1.00	0.052
1	3.02 (1.34-6.80)	0.56 (0.22-1.43)	
2	3.07 (1.06-8.87)	1.13 (0.39-3.23)	
≥ 3	4.54 (1.39-14.83)	0.95 (0.19-4.80)	
P-trend	0.001	0.86	
Lifetime number of people performed oral sex on			
≤ 2	1.00	1.00	0.071
3-5	1.46 (0.68-3.12)	0.44 (0.21-0.94)	
≥6	1.00 (0.45-2.21)	0.57 (0.25-1.28)	
P-trend	0.88	0.037	
Lifetime number of vaginal sex partners			
≤ 2	1.00	1.00	0.037
3-5	0.52 (0.17-1.55)	0.37 (0.14-0.95)	
≥6	1.15 (0.54-2.44)	0.31 (0.13-0.71)	
P-trend	0.22	0.003	
Recent cunnilingus (oral sex on a woman)			
No	1.00	1.00	0.042

Yes	2.52 (1.27-5.02)	0.77 (0.31-1.95)	0.333
Recent fellatio (oral sex on a man)			
No	1.00	1.00	
Yes	0.85 (0.29-2.54)	0.43 (0.17-1.08)	0.494
Sexual Orientation			
Heterosexual	1.00	1.00	
Homosexual/ Bisexual	0.75 (0.25-2.30)	1.17 (0.53-2.54)	

^ Bolding represents statistical significance at an alpha of 0.05. For additional description of participant enrollment, characteristics and eligibility, refer to the manuscript on baseline oral HPV prevalence in this population.[12]

* Recent defined as past three months

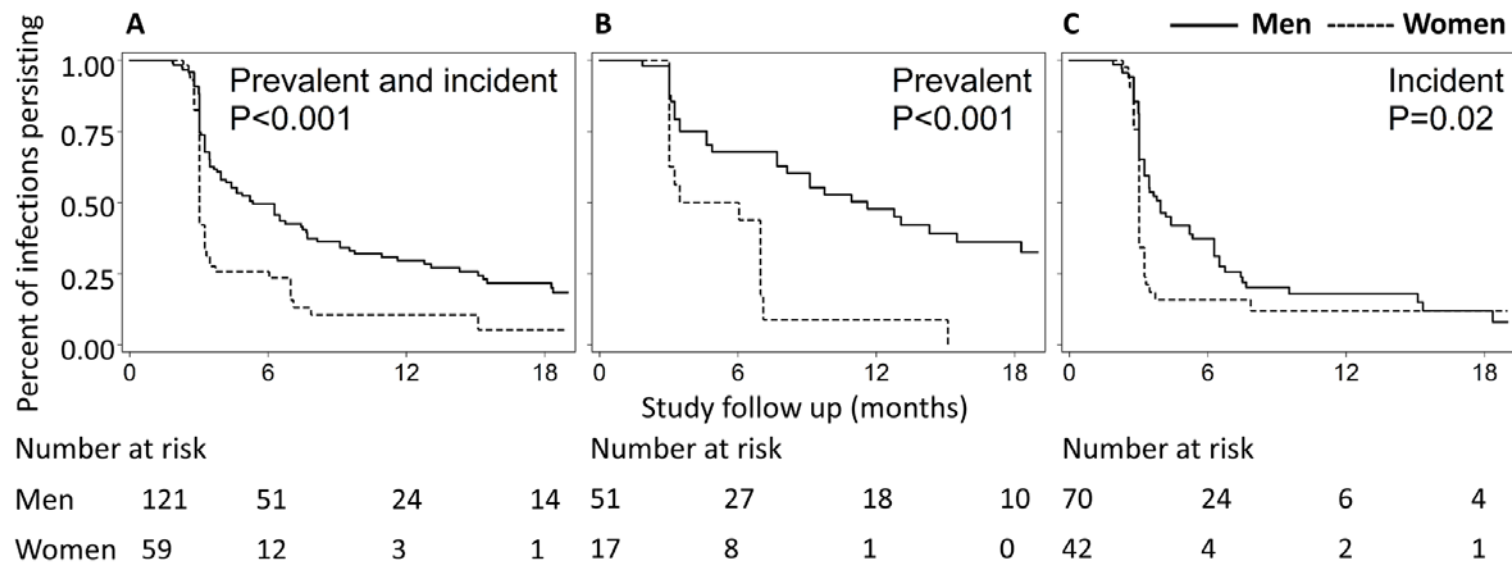


Figure 1. Kaplan Meier curves of time to clearance of type-specific oral HPV infections, stratified by gender. Shown is the natural history of: **(A)** all 180 detected oral HPV infections (prevalent and incident); **(B)** analysis restricted to 68 prevalent infections; and **(C)** analysis restricted to 112 incident infections that had follow-up after detection (out of 134 total incident infections detected). Overall 12-month clearance was 70.4% in men compared to 89.6% in women ($p < 0.001$). Median time to clearance was significantly shorter for incident versus prevalent infections (3.3 vs. 8.1 months, $p < 0.001$). Log-rank p-values for a comparison of time to clearance of oral HPV infections in men and women are shown.

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Supplemental Table 1. Unadjusted and adjusted risk factors for oral HPV clearance.

Characteristics *	HR (95% CI)	
	Unadjusted	Adjusted
Gender		
Female	1.00	1.00
Male	0.54 (0.37-0.78)	0.63 (0.42-0.95)
Sexual Orientation		
Heterosexual	1.00	
Homosexual/ Bisexual	1.13 (0.59,2.17)	
Sexual Orientation		
Heterosexual Female	1.00	
Homosexual/ Bisexual Female	0.48 (0.17-1.39)	
Homosexual/ Bisexual Male	0.98 (0.64-1.52)	
Heterosexual Male	0.45 (0.31-0.65)	
Recent daily cigarette use		
No (None/<1/day)	1.00	
Yes (≥1/day)	0.70 (0.46-1.08)	
Recent alcohol use		
No (≤1/week)	1.00	1.00
Yes (≥2/week)	0.62 (0.42-0.91)	0.65 (0.45-0.94)
Recent marijuana use		
No	1.00	
Yes	0.90 (0.60-1.36)	
Recently performed oral sex		

No	1.00	
Yes	0.90 (0.57-1.42)	
Type of infection		
Incident	1.00	1.00
Prevalent	0.47 (0.32-0.68)	0.49 (0.34-0.70)

*Recent was defined as last three months.