

Sexual Transmission of Oral Human Papillomavirus Infection among Men

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Abstract

We estimated the prevalence of oral human papillomavirus (HPV) and assessed risk factors among young heterosexual men participating in the HPV Infection and Transmission among Couples through Heterosexual Activity (HITCH) study. Oral and genital HPV samples were collected from 222 men and their female partners who were participating in the HITCH study, a longitudinal cohort on HPV transmission among heterosexual couples. Demographic and behavioral data were collected through self-administered computer questionnaires and biologic samples were tested with the Linear Array for HPV. Outcome measures were overall and type-specific prevalence of oral HPV. The prevalence of oral HPV among men was 7.2% and was higher among men who were ever smokers (12.2%), in nonmonogamous relationships (17.9%), or had a partner with oral (28.6%) and/or genital (11.5%) HPV infection. Moreover, prevalence increased with frequency of oral sex among men whose partner who had a genital infection with the same HPV type. Our results provide further evidence that oral HPV may be transmitted through either oral–oral or oral–genital routes. *Cancer Epidemiol Biomarkers Prev*; 23(12); 2959–64. ©2014 AACR.

Introduction

Human papillomavirus (HPV) is a major risk factor for several types of cancer including oropharyngeal cancer. Despite the availability of a prophylactic vaccine, the incidence of HPV-driven oropharyngeal cancer continues to increase (1).

Currently, the natural history of HPV is well understood in the genital tract; however, more remains to be learned about HPV infection in the oral tract. Oral HPV prevalence is at least 5-fold lower than in the genital tract, with a recent cross-sectional study of the National Health and Nutrition Examination Survey (NHANES) data reporting approximately 7% prevalence among U.S. adults (2). This same study also found a 2-fold higher prevalence among men than women (10.1% vs. 3.6%). Risk factors for oral HPV infection include smoking and sexual behaviors as well as demographic characteristics (2–4). Moreover, immunosuppressed individuals are at an increased risk of oral HPV infection (5). Although HPV is sexually transmitted and several large studies have

found a strong association with oral sexual behaviors (2, 4, 6), some studies have failed to find this association (3, 7). Therefore, further studies are needed to clarify the natural history of oral HPV infection. The goal of this study was to estimate the prevalence and assess risk factors of oral HPV infection among young men participating in the HPV Infection and Transmission among Couples through Heterosexual Activity (HITCH) cohort study.

Materials and Methods

Study design and population

This study included participants from the HITCH study. Study procedures have been described previously (8). Briefly, this is a longitudinal cohort study conducted at McGill University from May 2005 through January 2011 that enrolled young female university or junior college students (aged 18–24) and their male partners (at least 18 years old).

Data collection

Participants completed self-administered computer questionnaires and provided biologic samples for HPV assessment. Participants were asked to abstain from oral, vaginal, and anal sex for 24 hours before clinic visits. Oral samples were collected using a soft toothbrush and mouthwash at the initial and 4-month visit starting in July 2008. Women self-collected vaginal specimens using a Dacron swab and a clinic nurse collected penile and scrotal samples at each clinic visit for the men. The Linear Array HPV genotyping assay (LA-HPV; Roche Molecular Systems) was used to detect 36 mucosal HPV genotypes

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(6, 11, 16, 18, 26, 31, 33, 34, 35, 39, 40, 42, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, and 89). β -Globin DNA was coamplified to assess DNA integrity. The ethical review committees of McGill University, Concordia University, and Montreal University Hospital Center approved the study. All participants provided written informed consent.

Statistical analyses

Stata 12.0 (Stata Corp.) was used for all statistical analyses. A result was considered statistically significant at $P < 0.05$ and all tests were two-sided. A participant was considered an ever smoker if he had smoked at least 100 cigarettes in his lifetime. Concurrent partner status was defined as none if neither partner reported having partners other than their HITCH partner, either if one reported other partners, and both if both reported other partners. The average of both partners' reports was used for couple-related characteristics. Prevalence ratios (PR) with 95% confidence intervals (CI) were calculated using Poisson regression with robust error variances (9). For type-specific comparisons between couples, each HPV type was counted as its own observation, such that each individual could have 36 HPV-type outcomes. Poisson regression within a generalized estimating equations framework with an exchangeable correlation structure was used to adjust standard errors and CIs for the actual number of participants (10). Multivariable models were adjusted for age, which was dichotomized based on median age.

Results

Overall HPV prevalence

A total of 222 men were included in the analysis, 130 of whom had a partner with a genital HPV infection. The overall prevalence of oral HPV was 7.2% (16/222) among all men and 11.5% (15/130) among men with a genital HPV-positive HITCH partner. The prevalence of HPV16 was 2.3% (5/222) among all men and among the 33 men who had a partner with a genital HPV16 infection it was 6.1% (2/33). Among women, oral HPV prevalence was 3.2% (7/220). Because of the low number of outcomes, we were unable to perform any meaningful analyses and therefore only the results for men are shown.

Overall oral HPV prevalence was higher among ever smokers, men with more than 9 lifetime sex partners (oral, vaginal, anal), men in nonmonogamous relationships, and men who either themselves had a prevalent genital infection or had a partner with either an oral or genital HPV infection (Table 1). Among the 52 men who had never smoked, were in a monogamous relationship, and had a partner without oral or genital HPV, none had a prevalent infection.

Type-specific HPV prevalence

To account for multiple HPV types, we also performed type-specific analysis to determine whether the presence of one specific type in a man corresponded to the presence of the same type in his partner. Significant factors affecting

type-specific prevalence were infection status of the man himself or his partner as well as frequency of oral sex on the female partner and being in a nonmonogamous relationship (Table 1). In particular, there was a more than 2-fold increase in prevalence for each unit increase in frequency of oral sex on the female partner among men who had a partner that was infected with the same HPV type in the genitals.

Discussion

The prevalence of oral HPV infection among men in the HITCH cohort was 7.2%. To our knowledge, this is the first study to demonstrate higher oral HPV prevalence among men whose female partner had a prevalent genital or oral HPV infection suggesting that transmission may occur through oral or genital routes. Prevalence was also significantly higher among men who had ever smoked, had a high number of lifetime sex partners, or were in nonmonogamous relationships. Our results are largely consistent with previous studies that have found male sex, smoking, and sexual behaviors to be the most significant risk factors for oral HPV infection (2–4, 6, 7, 11).

We found that overall prevalence of oral HPV infection was higher among ever smokers. Others have found that current smoking increases the risk for both prevalent and incident HPV infection (2, 4, 7). Among men in the HPV Infection in Men (HIM) cohort study, the odds of a prevalent infection were increased among current smokers as was the risk of incident infection (3, 7). In addition, the prevalence of oral HPV infection increased with increasing intensity of smoking among participants in the NHANES cohort (2). The adverse effects of tobacco smoking on human health are well known, including immunosuppression and increased susceptibility to viral infections (12), and the local immunosuppressive effects of smoking may modulate the risk for oral HPV infection.

HPV is thought to be sexually transmitted to the oral tract although results have been conflicting (2–4, 7, 11). The higher prevalence among men with an oral HPV-positive partner suggests an oral–oral route as a mode of transmission. This is supported by evidence from previous studies that have found an association between deep-mouth kissing and oral HPV infection (4, 6, 11). For example, D'Souza and colleagues reported higher prevalence of oral HPV infection among college-aged men with increasing number of open mouth kissing partners in the past year, while Pickard and colleagues found an association between lifetime number of open-mouth kissing partners (4, 6).

We observed increased prevalence of oral HPV infection among men with a genital HPV-positive partner suggesting oral sex as a mode of transmission to the oral tract. Moreover, type-specific oral prevalence increased with frequency of oral sex on the female partner among men whose partner was infected with the same type. Previous studies have found an association between both

Table 1. Prevalence of oral HPV infection among male participants in the HITCH cohort study

	Overall (n = 222)				Type-specific (n = 7992) ^a			
	Total, n (%)	Prevalence, n (%)	Unadjusted PR (95% CI)	Adjusted PR (95% CI) ^b	Prevalence, n (%)	Unadjusted PR (95% CI)	Adjusted PR (95% CI) ^b	Adjusted PR (95% CI) ^b
Age, years								
≤21	100 (45.1)	5 (5.0)	1.00 (ref)	–	8 (0.10)	1.00 (ref)	–	–
>21	122 (54.9)	11 (9.0)	1.80 (0.65–5.03)	–	13 (0.16)	1.33 (0.43–4.13)	–	–
Smoking								
Never	124 (55.9)	4 (3.2)	1.00 (ref)	1.00 (ref)	8 (0.10)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Ever	98 (44.1)	12 (12.2)	3.80 (1.26–11.43)	3.72 (1.23–11.23)	13 (0.16)	2.06 (0.64–6.59)	2.04 (0.64–6.51)	2.04 (0.64–6.51)
Lifetime no. any sex partners ^c								
1–4	76 (34.2)	2 (2.6)	1.00 (ref)	1.00 (ref)	4 (0.05)	1.00 (ref)	1.00 (ref)	1.00 (ref)
5–9	70 (31.5)	4 (5.7)	2.17 (0.41–11.53)	2.09 (0.40–10.83)	5 (0.06)	1.36 (0.22–8.55)	1.38 (0.23–8.42)	1.38 (0.23–8.42)
>9	76 (34.2)	10 (13.2)	5.00 (1.13–22.14)	4.69 (1.17–18.89)	12 (0.15)	3.00 (2.53–15.70)	3.09 (0.71–13.50)	3.09 (0.71–13.50)
Frequency of oral sex on female partner								
Never/rarely	48 (21.6)	1 (2.1)	1.00 (ref)	1.00 (ref)	1 (0.01)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Sometimes	126 (56.8)	10 (7.9)	3.81 (0.50–29.10)	3.76 (0.49–28.59)	13 (0.16)	4.95 (0.64–38.27)	4.92 (0.64–38.00)	4.92 (0.64–38.00)
Most times/always	48 (21.6)	5 (10.4)	5.00 (0.60–41.41)	4.84 (0.59–39.94)	7 (0.09)	7.00 (0.80–61.49)	6.89 (0.77–61.71)	6.89 (0.77–61.71)
Average effect of each additional increase in frequency			1.49 (0.78–2.86)	1.46 (0.78–2.74)		1.64 (0.86–3.13)	1.62 (0.84–3.15)	1.62 (0.84–3.15)
If HITCH partner is: genital HPV-positive								
Never/rarely/sometimes ^d	97 (74.6)	10 (10.3)	1.00 (ref)	1.00 (ref)	6 (2.40)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Most times/always	33 (25.4)	5 (15.2)	1.47 (0.54–4.00)	1.42 (0.52–3.85)	5 (6.41)	2.69 (0.71–10.22)	2.72 (0.71–10.33)	2.72 (0.71–10.33)
Average effect of each additional increase in frequency			1.32 (0.64–2.70)	1.27 (0.62–2.62)		2.26 (1.01–5.08)	2.33 (1.00–5.43)	2.33 (1.00–5.43)
If HITCH partner is: genital HPV-negative								
Never/rarely/sometimes ^d	76 (83.5)	1 (1.3)	1.00 (ref)	1.00 (ref)	8 (0.13)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Most times/always	15 (16.48)	0	NC	NC	2 (0.12)	0.91 (0.19–4.51)	0.89 (0.18–4.46)	0.89 (0.18–4.46)
Average effect of each additional increase in frequency			1.32 (1.01–1.73)	1.16 (0.79–1.69)		1.08 (0.49–2.39)	1.06 (0.49–2.31)	1.06 (0.49–2.31)
Total episodes of vaginal sex								
<35	60 (27.4)	4 (6.7)	1.00 (ref)	1.00 (ref)	4 (0.05)	1.00 (ref)	1.00 (ref)	1.00 (ref)
35–60	46 (21.0)	2 (4.4)	0.65 (0.12–3.42)	0.61 (0.12–3.08)	2 (0.03)	0.65 (0.12–3.42)	0.63 (0.12–3.20)	0.63 (0.12–3.20)
>60–100	64 (29.2)	2 (3.1)	0.47 (0.09–2.48)	0.40 (0.07–2.20)	5 (0.06)	1.17 (0.22–6.33)	1.06 (0.17–6.61)	1.06 (0.17–6.61)
>100	49 (22.4)	7 (14.3)	2.14 (0.66–6.92)	1.87 (0.59–5.91)	8 (0.10)	2.45 (0.74–8.08)	2.25 (0.69–7.32)	2.25 (0.69–7.32)

(Continued on the following page)

Table 1. Prevalence of oral HPV infection among male participants in the HITCH cohort study (Cont'd)

	Overall (n = 222)				Type-specific (n = 7992) ^a			
	Total, n (%)	Prevalence, n (%)	Unadjusted PR (95% CI)	Adjusted PR (95% CI) ^b	Prevalence, n (%)	Unadjusted PR (95% CI)	Adjusted PR (95% CI) ^b	Adjusted PR (95% CI) ^b
Frequency of vaginal sex per week								
<3	63 (28.6)	3 (4.8)	1.00 (ref)	1.00 (ref)	3 (0.04)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3-4	60 (27.3)	4 (6.7)	1.40 (0.33-6.02)	1.35 (0.32-5.77)	5 (0.06)	1.75 (0.39-7.82)	1.72 (0.39-7.59)	1.72 (0.39-7.59)
>4-6	54 (24.6)	2 (3.7)	0.78 (0.13-4.50)	0.76 (0.13-4.44)	2 (0.03)	0.78 (0.13-4.50)	0.77 (0.13-4.47)	0.77 (0.13-4.47)
>6	43 (19.6)	6 (14.0)	2.93 (0.77-11.12)	2.59 (0.68-9.92)	9 (0.11)	4.40 (1.09-17.73)	4.10 (0.92-18.27)	4.10 (0.92-18.27)
Days since last vaginal sex								
<2	34 (15.5)	3 (8.8)	1.00 (ref)	1.00 (ref)	5 (0.06)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2-2.5	83 (37.9)	5 (6.0)	0.68 (0.17-2.71)	0.69 (0.17-2.77)	6 (0.08)	0.49 (0.10-2.31)	0.49 (0.10-2.37)	0.49 (0.10-2.37)
>2.5-5	55 (25.1)	5 (9.1)	1.03 (0.26-4.05)	1.11 (0.27-4.58)	6 (0.08)	0.74 (0.16-3.46)	0.78 (0.15-4.01)	0.78 (0.15-4.01)
>5	47 (21.5)	2 (4.3)	0.48 (0.08-2.74)	0.49 (0.08-2.88)	2 (0.03)	0.29 (0.05-1.84)	0.29 (0.04-1.95)	0.29 (0.04-1.95)
Concurrent partner status								
None	183 (82.4)	9 (4.9)	1.00 (ref)	1.00 (ref)	13 (0.16)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Either	29 (13.1)	2 (6.9)	1.40 (0.32-6.19)	1.34 (0.30-6.09)	3 (0.04)	1.46 (0.30-7.11)	1.43 (0.28-7.22)	1.43 (0.28-7.22)
Both	10 (4.5)	5 (50.0)	10.17 (4.17-24.78)	9.85 (3.95-24.57)	5 (0.06)	7.04 (2.74-18.08)	6.94 (2.69-7.22)	6.94 (2.69-7.22)
Oral infection in partner								
No	213 (96.8)	14 (6.6)	1.00 (ref)	1.00 (ref)	18 (0.23)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	7 (3.2)	2 (28.6)	4.35 (1.21-15.62)	5.29 (1.35-20.75)	3 (0.04)	144.32 (30.58-681.13)	167.58 (34.40-816.28)	167.58 (34.40-816.28)
Genital infection in partner								
No	91 (41.2)	1 (1.1)	1.00 (ref)	1.00 (ref)	10 (0.13)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	130 (58.8)	15 (11.5)	10.50 (1.41-78.44)	9.91 (1.39-70.88)	11 (0.14)	25.14 (9.79-64.58)	25.28 (9.61-66.45)	25.28 (9.61-66.45)
Genital infection in self								
No	94 (42.5)	2 (2.1)	1.00 (ref)	1.00 (ref)	9 (0.11)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	127 (57.5)	14 (11.0)	5.18 (1.20-22.33)	4.83 (1.21-19.19)	12 (0.15)	26.93 (11.33-64.03)	27.17 (11.40-64.80)	27.17 (11.40-64.80)

Abbreviation: NC, not calculable due to zero cells.
^aBased on Poisson regression analysis for which each HPV-type outcome represented an individual observation, resulting in 36 outcomes per person. Among men, 0.26% (217,992) oral HPV-type outcomes were positive. Generalized estimating equations were used to account for multiple observations per individual.
^bAdjusted for age (≤ 21 vs. > 21).
^cAny sex includes vaginal, oral, and anal.
^dCategories collapsed due to zero cells.

incidence and prevalence of oral HPV infection and number of recent and lifetime number of oral sex partners as well as frequency of oral sex (2, 4, 6, 11), although results from the HIM study have failed to confirm this association (3, 7). We observed high point estimates for the prevalence ratios for the effect of frequency of oral sex on oral HPV infection and this was especially apparent among men with a genital HPV-positive partner; however, these results require confirmation in a larger sample.

We also found that oral HPV prevalence was higher among men who had a concurrent genital HPV infection; however, it is unknown whether autoinoculation is a mode of oral HPV transmission (13, 14). It is plausible that these men acquired infections at both sites from their infected partner. Moreover, increased susceptibility to HPV infection among some individuals could account for this finding.

Men in nonmonogamous relationships had higher oral HPV prevalence than those in monogamous relationships. Others have found a strong association between being married and decreased risk of oral HPV although this was limited to women in one study (2, 3). Our finding that prevalence was significantly higher among nonmonogamous men supports the results of these studies. Couples with multiple partners would have increased exposure to new HPV infections while those who were married, and supposedly monogamous, would limit this exposure.

The main strength of our study included having the type-specific HPV status of the female partner available. This enabled us to determine the association between prevalence and oral and genital infections in the partner thus furthering the understanding of possible modes of transmission. Another strength included having concurrent partner status available for the couples. This is an important indicator of possible new infections being introduced into the partnership.

There are additional limitations that merit consideration. First, although the HITCH cohort study includes more than 500 couples, oral specimens were only available for 256 men. This lower sample size may have reduced our power to detect significant associations. We did not collect data on lifetime or recent number of oral sex partners because the study was designed to investigate genital transmission between newly formed couples. Recall error is always a possibility in sexual behavior reporting in observational studies. This was mitigated by the fact that enrolled couples had been together for no more than 6 months. In addition, we averaged responses by the male and female partner regarding their sexual activity as a couple, such as frequency of oral sex, to maximize accuracy. Answer agreement between couples was moderate for these measures, which included frequency of oral sex on the female partner ($\kappa = 0.46$), total episodes of vaginal sex ($\kappa = 0.51$), frequency of vaginal sex per week ($\kappa = 0.39$), and days since last vaginal sex ($\kappa = 0.53$). Misclassification of sexual behavior features due to errors in

reporting may have introduced bias toward the null, thus limiting our ability to observe associations with HPV infection.

Our results provide further evidence that oral HPV may be transmitted through either oral–oral or oral–genital routes. The current conflicting evidence for the strength of association between oral sex and oral HPV infection needs to be clarified. Future studies would benefit from knowing partner HPV status at multiple anatomic sites as well as more detailed data on oral sexual behaviors (such as length of partnership and concurrent sexual partner status) in natural history studies of oral HPV.

Disclosure of Potential Conflicts of Interest

P.-P. Tellier has received speakers' bureau honoraria from Merck Canada. F. Coutlée received speakers' bureau honoraria from Merck Sharp & Dohme. E.L. Franco is a consultant/advisory board member for Merck and Roche. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

None of the authors have been paid to write this manuscript by any source, commercial or otherwise. As corresponding author and PI for the study, E.L. Franco had full access to all the data in the HITCH cohort study.

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