

Oral Sexual Behaviors Associated with Prevalent Oral Human Papillomavirus Infection

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(See the editorial commentary by Kreimer, on pages 1253–4.)

Oral human papillomavirus (HPV) infection is a cause of oropharyngeal cancer. We investigated whether sexual behaviors that elevated the odds of oropharyngeal cancer developing in a case-control study similarly elevated the odds of oral HPV infection developing among control patients. HPV infection was detected in 4.8% of 332 control patients from an outpatient clinic and in 2.9% of 210 college-aged men (age range, 18–23 years). Among control patients, the odds of infection developing independently increased with increases in the lifetime number of oral ($P = .007$, for trend) or vaginal sex partners ($P = .003$, for trend). Among college-aged men, the odds of oral HPV infection developing increased with increases in the number of recent oral sex partners ($P = .046$, for trend) or open-mouthed kissing partners ($P = .023$, for trend) but not vaginal sex partners. Oral sex and open-mouthed kissing are associated with the development of oral HPV infection.

Oral human papillomavirus (HPV) infection is newly appreciated as an important cause of head and neck squamous cell carcinoma (HNSCC) [1, 2]. Multiple case-control studies have

consistently associated oral HPV infection with HNSCC [1–4] and, in particular, oropharyngeal cancer [1, 3].

Despite this risk, little is known about oral HPV infection in the general population. In population-based, case-control studies of oral cancer, the prevalence of oral HPV infection among control patients varied from 5.0% to 9.2% [3, 5]. In initial studies, sexual behavior, HIV and HIV-related immunosuppression, increasing age, and smoking were associated with oral HPV infection [6–8].

We recently demonstrated strong associations between sexual behavior and both oropharyngeal cancer [1] and HPV16-positive HNSCC [2]. In these case-control studies, the lifetime number of vaginal or oral sex partners was strongly associated with cancer. We hypothesized that these measurements of sexual behavior serve as surrogates for exposure to oral HPV infection. We therefore explored whether these same sexual behaviors were associated with the odds of oral HPV infection developing among the control patient population in our case-control studies, and we extended this analysis to an additional population of college-aged men.

Methods. Two distinct populations were used for this cross-sectional study. One study population consisted of the control patient group enrolled in 2 case-control studies nested within a prospective cohort with HNSCC [1, 2]. From 2000 through 2006, the study enrolled control patients from among patients at the Johns Hopkins outpatient otolaryngology clinic (Baltimore, MD) who were ≥ 18 years of age and had no history of cancer.

A second population comprised students recruited at the campuses of Towson University (Towson, MD) and the University of Maryland (College Park, MD) in May 2007. Study eligibility criteria included age >17 years and male sex (young women were not included, because some might have received the human papillomavirus quadrivalent vaccine [Gardasil; Merck]).

The study protocols were approved by the institutional review boards of the Johns Hopkins Hospital, Towson University, and the University of Maryland. Written informed consent was obtained from all study participants.

As described elsewhere [1], detailed behavioral information was obtained from control patients by use of an audio computer-assisted self-interview (ACASI). The abbreviated ACASI for college-aged men included age, race, history of sexually transmitted infections, sexual preference, and recent (i.e., in the past 12 months) and lifetime numbers of sex partners.

In both risk behavior surveys, oral sex was defined as “putting your mouth or tongue on a woman’s vagina (or man’s penis).”

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Table 1. Associations between factors of interest and oral human papillomavirus (HPV) infection in 332 adult outpatient controls assessed for the presence of HPV.

Factor	Prevalence of HPV, ^b total no. (%) ^c	Univariate analysis		Multivariate analysis ^a	
		OR (95% CI) ^d	<i>P</i> ^e	OR (95% CI) ^d	<i>P</i> ^e
Demographic					
Sex					
Female	81 (1.2)	1.00		1.00	
Male	251 (6.0)	5.08 (0.66–39.1)		4.53 (0.54–37.8)	
Race and ethnicity					
Non-Hispanic					
White	276 (4.7)	1.00		...	
Black	34 (8.8)	2.00 (0.53–7.3)		...	
Asian or Middle Eastern	13 (0.0)	
Hispanic	9 (0.0)	
Age, years			.04		.13
<40	31 (6.5)	1.00		1.00	
40–54	120 (6.7)	1.04 (0.21–5.1)		0.75 (0.14–4.1)	
55–64	95 (4.2)	0.64 (0.11–3.7)		0.51 (0.08–3.3)	
≥65	86 (2.3)	0.35 (0.05–2.6)		0.37 (0.05–3.0)	
Risk per each year after age >30 years	...	0.94 (0.90–0.99)		0.97 (0.92–1.02)	
Sexual behavior					
Sexual orientation					
Heterosexual	318 (4.7)	1.00		...	
Homo- or bisexual	14 (7.1)	1.50 (0.19–12.7)		...	
Oral sex partners, ^f lifetime no.			.002		.007
0–1	156 (1.9)	1.00		1.00 ^g	
2–10	136 (5.9)	3.19 (0.83–12.3)		2.37 (0.52–9.5)	
≥11	40 (12.5)	7.29 (1.7–31.9)		5.20 (1.13–24.7)	
Barrier use^h					
Yes or no oral sex					
Yes	100 (3.0)	1.00		...	
No	232 (5.6)	1.92 (0.54–6.9)		...	
Sex partners, lifetime no.			.001		.003
0–5	193 (3.1)	1.00		1.00 ^g	
6–25	98 (5.1)	1.67 (0.50–5.6)		1.23 (0.35–4.3)	
≥26	40 (12.5)	4.48 (1.29–15.5)		3.91 (1.05–14.6)	
HSV-2 antibodies					
No					
No	258 (3.5)	1.00		1.00 ^g	
Yes	67 (9.0)	2.71 (0.93–7.9)		2.65 (0.86–8.1)	
Tobacco and alcohol use					
Ever smoked tobacco					
No					
No	184 (4.9)	1.00		1.00	
Yes					
Former user	105 (1.0)	0.19 (0.02–1.5)		0.21 (0.03–1.9)	
Current user	44 (13.6)	3.05 (1.03–9.1)		3.86 (1.17–12.7)	
Intensity of current smoking, cigs/day			.52		...
<20	33 (12.1)	1.00		...	
20–39	7 (14.3)	0.41 (0.03–5.0)		...	
≥40	4 (25.0)	0.50 (0.02–11.1)		...	
Ever drank					
No					
No	80 (3.8)	1.00		...	
Yes					
Former user	46 (6.5)	1.77 (0.34–9.1)		...	
Current user	207 (4.8)	1.29 (0.34–4.8)		...	

(continued)

Table 1. (Continued.)

Factor	Prevalence of HPV, ^b total no. (%) ^c	Univariate analysis		Multivariate analysis ^a	
		OR (95% CI) ^d	<i>P</i> ^e	OR (95% CI) ^d	<i>P</i> ^e
Days of drinking per week, ⁱ no.			.92		...
<1	74 (5.4)	1.00		...	
1–6	101 (5.0)	1.02 (0.26–3.9)		...	
All	24 (4.2)	0.84 (0.09–8.0)		...	
Ever used marijuana					
No	284 (4.2)	1.00		...	
Yes	50 (8.0)	2.00 (0.60–6.3)		...	

NOTE. A total of 4.8% of the 332 outpatient controls were found to be HPV positive (HPV+). CI, confidence interval; cigs, cigarettes; HSV-2, herpes simplex virus type 2; OR, odds ratio.

^a Unless otherwise indicated, multivariate models included age (continuous variable), sex, lifetime no. of oral sexual partners (categories of 0, 1, 2–5, 6–10, 11–15, 16–25, 26–50, 51–100, or >100 partners), and current tobacco use (yes or no).

^b In oral exfoliated cells.

^c Data are the total no. of outpatient controls assessed (% of outpatient controls in each factor group who were found to be HPV+).

^d Data are the odds ratio (OR) and the 95% confidence interval (CI), unless otherwise indicated, and are derived from logistic regression models.

^e For trend. Trends in odds were tested by modeling each ordinal variable as a single continuous independent variable. Trend *P* values were calculated for the finest data categories available, with use of data categories smaller than those displayed in the table.

^f Partners on whom oral sex was performed.

^g Models for sexual behaviors were each adjusted for age (continuous variable), sex, and current tobacco use (yes or no) but were not adjusted for other sexual behaviors because of colinearity in these behaviors.

^h During oral sex.

ⁱ Among current drinkers.

Open-mouthed kissing was defined as follows: “French kissing, also known as open-mouthed kissing, means putting your tongue into a women’s (or man’s) mouth.”

Oral samples were collected from control patients by use of a 30-s oral rinse and gargle with 10 mL of sterile saline and were combined with samples collected from the posterior oropharyngeal wall by means of 5–10 strokes of a cytology brush (Oral CDx; CDx Labs). DNA was purified from oral samples by use of a phenol-chloroform–based protocol [9].

Oral samples were collected from college-aged men by use of a 30-s oral rinse and gargle with 10 mL of mouthwash (Scope; Procter & Gamble). DNA was purified from mouthwash oral rinses by use of a Puregene-based protocol (Qiagen) [9].

Purified DNA (10 μ L) was analyzed for 37 HPV types by use of a multiplex polymerase chain reaction assay targeted (via PGYM09/11 primer pools) to the conserved L1 region of the viral genome, followed by type specification by line-blot hybridization (Roche Molecular Systems), as described elsewhere [9].

Whole-blood samples were collected, and serum samples were separated by centrifugation and stored at -70°C . The presence of herpes simplex virus type 2 (HSV-2) antibodies was evaluated using HerpeSelect-2 ELISA IgG (Focus Technologies).

Individuals who had any of the 37 types of HPV detected in the oral rinse sample were classified as “HPV positive,” whereas all other subjects were classified as “HPV negative.”

Recent sexual behavior was defined as behavior occurring in the past 12 months. The category “ever” defined a history of substance use occurring at least once per month for 1 year (for

alcohol and marijuana) and once per day for 1 year (for tobacco). “Current tobacco use” was defined as use occurring in the past 12 months.

Prevalence rates were compared using an equality of proportions test. Median values were compared using a nonparametric equality of medians test. Univariate and multivariate logistic regression estimated the odds ratios (ORs) and 95% confidence intervals (CIs) for risk factors for oral HPV infection. Factors of importance in univariate analysis were included in multivariate models. For outpatient controls, final multivariate models included sex, age, lifetime number of oral sex partners (0, 1, 2–5, 6–10, 11–15, 16–25, 26–50, 51–100, or >100), and current smoking (yes or no). Multivariate models for college-aged men included age and the lifetime number of vaginal sexual partners (0–2, 3–9, or ≥ 10). Trends in ORs were tested by modeling each ordinal variable as a single continuous independent variable. All calculations were performed using Stata software (version 9.0; Stata).

Results. The characteristics of the outpatient controls are shown in table 1. Control patients were originally selected to match the age and sex of case patients with HNSCC and had a median age of 57 years (range, 25–87 years); most were male (76%). Control patients were primarily non-Hispanic and white (84%), and most were residents of Maryland (69%). Twenty-four percent of control patients had never performed oral sex, 2.6% had never had vaginal sex, and the median lifetime number of partners was 2–5 (interquartile range [IQR], 1 to 2–5 partners) for oral sex and 2–5 (IQR, 2–5 to 11–15 partners) for vaginal sex.

Table 2. Associations between factors of interest and oral human papillomavirus (HPV) infection among 210 college-aged men.

Factor	Prevalance of HPV, ^b total no. (%) ^c	Univariate analysis		Multivariate analysis ^a	
		OR (95% CI) ^d	<i>P</i> ^e	OR (95% CI) ^d	<i>P</i> ^e
Demographic					
Race					
White	145 (3.5)	1.0			
Black	45 (2.2)	0.63 (0.07–5.5)			
Asian, Native American, or other	22 (0.0)	...			
Ethnicity					
Non-Hispanic	198 (3.0)	1.0			
Hispanic	12 (0.0)	...			
Age, years			.009		.021
18–19	110 (0.9)	1.0		1.0	
20–23	100 (5.0)	5.7 (0.65–50.0)		4.5 (0.51–41.0)	
Sexual behavior					
Sexual orientation					
Heterosexual	200 (2.5)	1.0		1.0	
Homo- or bisexual	10 (9.1)	4.3 (0.46–41.0)		15.6 (0.83–129.0)	
Oral sex partners, ^f no.					
In lifetime			.029		.031
0–9	203 (2.0)	1.0		1.0	
≥10	7 (28.6)	20.0 (2.9–135.0)		7.4 (0.82–66.0)	
In past year			.033		.046
0–5	199 (2.0)	1.0		1.0	
≥6	11 (18.2)	10.8 (1.7–67.0)		7.9 (1.05–59.0)	
Barrier use ^g					
Usually/always or no oral sex	97 (1.0)	1.0		1.0	
Rarely/ never	113 (4.4)	4.4 (0.51–39.0)		7.4 (0.65–85.0)	
People open-mouthed kissed, no.					
In lifetime			.083		.067
0–9	129 (0.8)	1.0		1.0	
≥10	81 (6.2)	8.4 (0.97–73.0)		9.5 (0.76–118.0)	
In past year			.037		.023
0–5	144 (0.7)	1.0		1.0	
≥6	66 (7.6)	11.7 (1.3–102.0)		17.4 (1.5–198.0)	
Vaginal sex partners, no.					
In lifetime			.44		.91
0–9	181 (2.2)	1.0		1.0	
≥10	29 (6.9)	2.1 (0.24–19.0)		0.70 ^h (0.07–7.6)	
In past year			.063		.27
0–5	184 (2.2)	1.0		1.0	
≥6	26 (7.7)	3.8 (0.6–21.6)		1.5 ^g (0.19–11.0)	
HSV-2 antibodies					
No	199 (3.0)	1.00		1.00	
Yes	11 (0.0)	

NOTE. A total of 2.9% of the 210 college-aged men were found to be HPV positive (HPV+).

^a The multivariate model was adjusted for age (continuous variable) and the lifetime no. of vaginal sex partners (0–2, 3–9, and ≥10 partners), unless otherwise indicated.

^b In oral rinse.

^c Data are the total no. of college-aged men assessed (% of college-aged men in each factor group who were found to be HPV+).

^d Data are the odds ratio (OR) and the 95% confidence interval (CI), unless otherwise indicated, and are derived from logistic regression models.

^e For trend. Trends in odds were tested by modeling each ordinal variable as a single continuous independent variable. Trend *P* values were calculated using the categories 0–2, 3–9, and ≥10 for the lifetime no. of partners for each sexual behavior and the categories 0–2, 3–5, and ≥6 for the no. of partners for each sexual behavior occurring in the past year.

^f Partners on whom oral sex was performed.

^g During oral sex.

^h Vaginal sex behaviors adjusted for age (continuous variables) and lifetime no. of oral sex partners (0–2, 3–9, and ≥10 partners).

Table 3. Age at first occurrence of sexual behaviors among a total of 332 adult outpatient controls and 210 college-aged men assessed for the presence of HPV.

Behavior	Persons assessed, no.		Age at first occurrence, median (IQR), years	
	Outpatient controls	College-aged men	Outpatient controls	College-aged men
Open-mouthed kiss	NA	192	NA	14 (13–16)
Vaginal sex	316	147	18 (16–21)	17 (16–18)
Performed oral sex	245	151	21 (18–26)	17 (16–18)

NOTE. IQR, interquartile.

Oral HPV infections were detected in 4.8% (95% CI, 2.8%–7.7%) of outpatient controls. Three individuals had multiple infections. Of the oral HPV infections that were detected, 10 were considered to be high risk (2 were caused by HPV58, and 1 each was caused by HPV16, 51, 56, 59, 66, 68, 73, and 83) and 9 were considered to be low risk (3 were caused by HPV62, and 1 each was caused by HPV6, 11, 42, 52, 61, and 89) [10].

Factors associated with a prevalent oral HPV infection in univariate analysis included age, sexual behavior, and tobacco use (table 1). The odds of oral HPV infection developing significantly increased with increases in the lifetime number of oral ($P = 0.002$, for trend) or vaginal ($P = .001$, for trend) sex partners and decreased by 6% per year after age 30 years ($P = .04$, for trend) (table 1). The odds of oral HPV infection developing were significantly elevated among current smokers (OR, 3.1; 95% CI, 1.03–9.1). However, intensity of tobacco use (table 1) and cumulative tobacco use (data not shown) were not associated with oral infection. Oral HPV infection tended to be more common among men than women (OR, 5.1; 95% CI, 0.66–39) (table 1).

In multivariate analysis, the odds of oral HPV infection were significantly elevated among current tobacco smokers (OR, 3.9; 95% CI, 1.2–12.7) and individuals who reported having either >10 oral (OR, 5.2; 95% CI, 1.1–25) or >25 vaginal (OR, 3.9; 95% CI, 1.1–15) sex partners during their lifetime (table 1).

Male college students (median age, 19 years) were studied to further explore associations between sexual behaviors and oral HPV infection (table 2). Nine percent of college-aged men had never engaged in open-mouthed kissing, 28% had never performed oral sex, and 30% had never had vaginal sex. Among all college-aged men, the median number of open-mouthed kissing partners (8; IQR, 4 to ≥ 10 partners) was higher than the number of oral sex partners (2; IQR, 0–4 partners) ($P < .001$) or vaginal sex partners (3; IQR, 0–6 partners). Age at initiation of open-mouthed kissing was significantly younger than age at initiation of oral sex ($P < .001$) or vaginal sex ($P < .001$) (table 3).

The prevalence of oral HPV infection in college-aged men was 2.9% (95% CI, 1.1%–6.1%). Five high-risk HPV infections (one

each caused by HPV16, 35, 39, 51, and 66) and one low-risk HPV infection (caused by HPV84) were detected.

As was observed for outpatient controls, age and lifetime sexual behaviors were associated with oral HPV infection among college-aged men, in univariate and multivariate analysis (table 2). In univariate analysis, the odds of oral HPV infection developing significantly increased with increases in the lifetime number of oral sex ($P = .029$, for trend) or open-mouthed kissing ($P = .083$, for trend) partners but not vaginal sex partners ($P = .44$, for trend). The odds of oral HPV infection developing remained significantly associated with these oral behaviors after adjustment for age and the lifetime number of vaginal sex partners (table 1).

Associations between oral HPV and recent sexual behaviors (i.e., those occurring in the previous 12 months) were also investigated. In univariate analysis, oral HPV infection was more strongly associated with the number of recent oral sex ($P = .046$, for trend) and open-mouthed kissing ($P = .023$, for trend) partners than with recent vaginal sex partners ($P = .27$, for trend). In multivariate analysis, ≥ 6 recent oral sex (OR, 7.9; 95% CI, 1.1–59.0) or open-mouthed kissing (OR, 17; 95% CI, 1.5–198.0) partners and older age ($P = .02$, for trend) significantly elevated the odds of oral HPV infection developing, after adjustment for the lifetime number of vaginal sex partners (table 2).

To further evaluate the independent effect of open-mouthed kissing, a subset analysis was performed for the 59 college-aged men who reported no history of performing oral sex. Among these men, oral HPV infection was significantly more common among those with ≥ 10 lifetime (25% vs. 0%; $P = .0002$) and those with ≥ 5 recent (17% vs. 0%; $P = .003$) open-mouthed kissing partners.

Discussion. The data from the present study indicate that the same sexual behaviors associated with oropharyngeal cancer in case-control studies [1] are associated with oral HPV infection among control patients. Thus, measurements of sexual behavior likely serve as surrogates for oral HPV infection, explaining our previous associations of these behaviors with oropharyngeal cancer [1, 2]. The odds of oral HPV infection in-

creased with the increase in the number of oral sex partners or open-mouthed kissing partners, indicating that oral HPV infection is sexually acquired and is transmitted by behaviors as common as open-mouthed kissing.

Oral sexual behaviors have been associated with oral HPV infection [6, 11] and transmission of other viral infections, such as HSV [11]. Because sexual behaviors are often highly correlated, we acknowledge that it is difficult to identify which behaviors are independently responsible for viral transmission. However, in the present study, oral HPV infection was detected among individuals without a history of performing oral sex but with a high number of open-mouthed kissing partners. Furthermore, the number of recent open-mouthed kissing or oral sex partners was more strongly associated with oral HPV infection than was the number of vaginal sex partners, and it remained important after adjustment for vaginal sex partners, indicating that these behaviors likely play a larger role in transmission of virus to the oral cavity. Prospective studies are needed to further evaluate the risk of incident oral HPV infection associated with each specific type of sexual behavior.

To our knowledge, this is the first study to report an association between open-mouthed kissing and oral HPV infection. Transmission of other DNA tumor viruses through open-mouthed kissing has been hypothesized but not well demonstrated. Human herpesvirus 8 (HHV8) [12] and Epstein-Barr virus (EBV) replicate in oral epithelial cells and are detectable in saliva [13]. The increasing seroprevalence of EBV during adolescence and young adulthood supports the possibility of oral-to-oral transmission of EBV. Transmission of HHV8 during familial exchange of saliva (e.g., through washing a child's face with saliva) [14] is thought to explain the high seroprevalence of HHV8 (18%–30%) [12] in populations with limited access to water. Similar horizontal, nonsexual transmission could, in theory, account for the detection of oral HPV infection in children [8]. Given that open-mouthed kissing is common, this behavior may contribute to the circulation of HPV in populations and may increase the risk of oral HPV infection among individuals who might not otherwise be exposed.

Possible interactions between tobacco smoking and oral HPV infection are of interest, because both are major risk factors for oral cancer. In the present study, current tobacco use, but not cumulative tobacco use, was associated with prevalent oral HPV infection, and, in our previous study [7], it was associated with the persistence of infection. However, paradoxically, cumulative tobacco exposure was not associated with the risk of HPV-positive HNSCC in our recent case-control study [2]. These data suggest that tobacco exposure may not independently increase the risk of HPV-positive HNSCC but, instead, may modulate risk by promoting infection among those exposed to HPV and/or persistence among infected individuals, possibly via effects on local oral mucosal

immunity. Prospective data on natural history are needed to clarify these possible interactions.

A limitation of this study is that it was not population based; therefore, extrapolation of the findings to the general population may not be possible. However, the levels of sexual risk in our study populations were comparable to those reported in similar age groups in the National Health and Nutrition Examination Survey (NHANES). The lifetime number of sex partners was similar among 40- to 49-year-old outpatient controls and NHANES participants: 26% vs. 30% of men and 7.7% vs. 10% of women reported having ≥ 15 sex partners during their lifetime, respectively.

HSV-2 seroprevalence, a biomarker for sexual risk-taking, was also comparable among outpatient controls and NHANES participants (21% vs. 24% among 30–49 year olds) [15] and among college-aged men (5.2%), compared with 14- to 19-year-old men (0.9%) and 20- to 29-year-old men (5.6%) in NHANES [15].

Additional limitations of the present study include the limited sample size and the absence of data on open-mouthed kissing (for control patients) and smoking (for college-aged men). In addition, oral rinse collection media and purification methods varied in the 2 study populations; however, the groups were analyzed separately [9]. Although our research suggests a strong association between sexual behavior and the development of oral HPV infection, a temporal association between sexual behavior and incident oral HPV infection remains to be demonstrated. Despite these limitations, our data suggest that oral sex contact, inclusive of oral-to-oral and oral-to-genital contact, may play a role in human-to-human transmission of HPV infection, a finding that may have implications for the timing of administration of prophylactic vaccines to children.

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