Oral Human Papillomavirus Infection among Drug Users in Puerto Rico

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Objective: The prevalence of human papillomavirus (HPV) in the oral cavity has not been as well studied as genital infection and its prevalence among drug users is uncertain. This study describes the prevalence and correlates of oral HPV infection among a sample of drug users in Puerto Rico (PR).

Methods: Cross-sectional study of 271 drug users aged 18-35 years, not undergoing substance abuse treatment, living in the San Juan metropolitan area. Oral samples were collected through an oral rinse and HPV infection status was detected through PCR and HPV typing. Information on covariates was obtained through face-to-face interviews and serum analyses.

Results: A total of 34 participants were positive for any HPV type (12.5%), whereas 13 individuals (4.8%) were positive for one of the 38 type-specific HPV probes evaluated. Among those HPV positive, the most common HPV type detected was non-oncogenic HPV 72 (11.8%, n=4). Oncogenic HPV types detected were 35 (5.9%) and 56 (2.9%). Factors associated with oral HPV infection included binge drinking (OR=3.85, 95% CI=1.40, 10.58), HIV positivity (OR=4.67, 95% CI=1.58, 13.74) and ever having engaged in commercial sex (OR=3.55, 95% CI=1.46, 8.67); infection did not differ by age or gender.

Conclusion: Consistent with previous studies in the genital and oral tract, HIV infection, alcohol abuse and commercial sex practices were strongly associated with oral HPV infection. Future studies should assess the implications of oral HPV infection on oral cancer risk in this population. [*P R Health Sci J 2014;33:190-196*]

Key words: HPV, Drug users, Oral cavity, HIV, Puerto Rico

Oral HPV infection constitutes an emerging research area and a newly appreciated public health problem (1). Although HPV has been long known to be an important cause of anogenital cancer, only more recently it has been recognized as a cause of a subset of oropharyngeal squamous cell carcinomas (1, 2). In the US, 63% of oropharyngeal cancer cases are attributed to HPV, representing, approximately 11,726 new cases attributable to HPV each year (3). The epidemiology of oropharyngeal HPV infection is not well understood and has not been as well studied as infection in the genital tract (4). A recent international review determined a prevalence of oral HPV infection of 4.5% (95% CI=3.9%-5.1%) among healthy individuals (5). Oral sex, open-mouthed kissing and HIV-positivity are associated with oral HPV infection (6, 7). Although evidence for the efficacy of the HPV vaccines in the prevention of oral infection with oncogenic HPV types is still limited, there is biologic plausibility of potential effectiveness of these vaccines against head and neck cancers (8). A clinical trial in Costa Rica showed lower oral HPV prevalence four years after vaccination with the bivalent HPV16/18 vaccine among women in the vaccine arm compared to the control arm, suggesting that the vaccine offers protection against oral infection with these HPV types, with potentially important implications for prevention of HPV-associated oral cancers (9). Meanwhile, data from the United States (US), National Health and Nutrition Examination Survey (NHANES) recently showed that despite low vaccination uptake among women in the US, the prevalence of quadrivalent HPV vaccine types (6,11,16,18) among women (cervical infection) aged 14-19 years has decreased (2003-2006: 11.5% vs. 2007-2010: 5.1%), with high estimated vaccine effectiveness (10). This reduction evidences vaccine impact in the population.

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In Puerto Rico (PR), the burden of oral cavity and pharyngeal cancer is higher than among other racial/ethnic groups in the US (particularly in men) (11), with excess risk of disease among persons living with AIDS (12), highlighting the importance of evaluating the prevalence of oral cancer risk factors in this population. PR is also one of the top US states and territories in terms of HIV/AIDS incidence and prevalence (13) and drug abuse and dependence (14). Furthermore, a high prevalence of HIV/AIDS among drug users in PR has been documented, as well as lack of utilization of health care services (15). Drug users have increased risk for acquiring HIV and other STIs, mainly because of their high prevalence of risky sexual behaviors such as exchange of sex for drugs and money, unprotected sex while under the influence of drugs, and their greater likelihood of exposure to social networks with high STI prevalence (16). In the case of HPV, its seroprevalence has been observed to be high among drug users (17, 18). Furthermore, studies of HPV infection are of interest in PR, as this population still has a low HPV vaccine uptake (20% and 13% for girls and boys aged 11-18 years), although eight years have passed since the introduction of the first HPV vaccine. The HPV vaccine is approved for girls and boys aged 9-26 years, with routine vaccination recommended for children aged 11-12 years (19). Legal mandatory health care-coverage of the vaccine (Law #255 - September 15, 2012) exists in PR for girls and boys 11-18 years of age (20).

To date, risk factors for oral HPV infection are not clear (21), and studies among Hispanics are scarce (22) and non-existent among chronic drug users. Previous evidence supports that drug users may be at increased risk for oral HPV infection and potentially HPV related malignancies. Given that the epidemiology of HPV infection among drug users is not well understood, this study describes the prevalence and correlates of oral HPV infection among a sample of drug users in PR.

Methods

Study design and population

This cross-sectional study was approved by the Institutional Review Board of the Medical Sciences Campus, University of PR. The study population consisted of drug users recruited at the PR Drug Abuse Research Development Program II Study conducted from January 2008-December 2010. Ethnographic mapping strategies were used to locate outdoor drug markets in the San Juan metropolitan area of PR. The recruitment methodology and procedures used in this study have been described in more detail elsewhere (23). Subjects were recruited based on a schedule of randomized visits to the identified sites. Eligible subjects were drug users, 18-35 years of age, residing within the catchment area and not having enrolled in drug treatment during the previous 30 days. Of 390 persons recruited, the last 290 (74.4%) were asked to provide an oral sample for HPV typing. Of these, adequate samples for PCR processing were collected for 271 (93.4%) individuals, who were included in this analysis. No significant differences ($p>0.05$) were observed between those who provided oral samples and those who didn't with regard to demographic characteristics (age, gender, education), drug-use (cocaine, heroin, marihuana and crack use during the last 12 months) and stressors (PERI-stressful life events scale).

Data collection

Data collection procedures included: 1) structured face-to-face interview that collected information on demographics and lifestyles, 2) short interview to assess stressors and patterns of drug use, and 3) blood sample (serum and plasma) to test for HIV and HCV antibodies, and ascertain CD4+ T cell counts.

HPV sampling

A mouthwash method was used to collect information of oral HPV infection. A collection cup filled with 15ml of Scope was given to study participants. If participants had gum or dentures they were asked to remove them. The interviewer wore gloves and gave them the following instructions: "1) Take a gulp of "Scope" mouthwash and make gargles with it for about 1 minute (first, rinse mouth for 30 seconds and then gargle for about 30 additional seconds). 2) Spit the mouthwash carefully in the provided container, trying not to spill it. 3) Hand the container to the study interviewer. 4) Take the toothbrush provided and brush the areas of the gums, tongue, cheeks and throat. 5) Give the toothbrush to the study interviewer." Afterwards, the interviewer agitated the toothbrush for about 10 seconds in the container with mouthwash, and proceeded to close the container and properly identify it. After arrival from the field, samples were homogenized, transferred to conical 15ml tubes and centrifuged at 3000g for 10 minutes, twice. The supernatant was discarded and the button re-suspended in 10ml and 1ml of saline solution, respectively, in the first and second centrifugation. The samples were transferred to cryovial tubes, stored in low temperature freezer, -150°C, until sent for HPV typing.

DNA extraction and HPV detection and typing

HPV typing was performed by dot-blot hybridization and polymerase chain reaction (PCR) with modified L1 consensus primers (MY09/MY11) was used for amplification. After thawing, the samples were processed for DNA using the Gentra Puregene Buccal Cell Kit (Qiagen) following manufacturer's instructions. Five microliters of sample were used for PCR amplification using the standard 40 cycle protocol (24). PCR products were typed by dot-blot hybridization using 38 individual type-specific probes, including oncogenic HPV types as defined by IARC (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66) and non-oncogenic types (6/11, 26/69, 30, 32/42, 34, 53, 54, 57/2/27, 61, 62, 67, 68, 70, 71, 72, 73, 81, 82, 83, 84, 85, 86/87, 90/106, 97,102/89, and 2 separate

mixtures: mix1 (7/13/40/43/44/55/74/91) and mix2 (3/10/28/29/77/78/94) (1). A sample was considered HPV positive when it was positive for the consensus probes or any specific HPV type probes. Specimens negative for beta globin gene amplification were excluded from analysis. Controls consisted of amplification of solution containing all the above components except for sample DNA, or DNA from cell lines with and without HPV.

Study variables

Variables analyzed included HPV infection status, sociodemographic characteristics (age, gender, education, family arrangement), clinical characteristics (HPV, HIV and HCV infection status, CD4 count), injection and sex-related HIV risk behaviors, substance use (alcohol, heroin, cocaine, crack, crack/cocaine, THC and speedball-mixed heroin and cocaine) and history of incarceration.

Statistical analysis

Descriptive statistics were used to describe the overall and type-specific prevalence of HPV infection in the oral cavity. Contingency tables and chi-square statistics were used to assess the relationship of demographic and lifestyle factors with oral HPV infection. Factors at least marginally associated ($p<0.10$) to oral HPV in bivariate analyses, were included in the multivariate logistic regression model. Logistic regression models were used to estimate the crude and covariate-adjusted odds ratio [with 95% Confidence Intervals (CI)]. Age and gender were also included in the final model, given their relevance in the literature. Interactions terms of all covariates, including gender and HIV status, were evaluated within the logistic regression model.

Results

Overall, 81.2% of participants were males, 52.7% had less than high school education, 34.3% had ever been homeless, 76.4% had history of incarceration, 61.3% were intravenous drug users and 32.5% had ever been paid to have sex. The prevalence of HIV and HCV among participants was 9.7% and 48.5%, respectively. A total of 34 participants were positive for any HPV type (12.5%), whereas 13 individuals (4.8%) were positive for one of the 38 type-specific probes. Among those HPV positive, the most common HPV type detected was non-oncogenic HPV 72 (11.8%, n=4). The other non-oncogenic types detected were 32/42, 53, 62, 71, 81, 82, and 84, each with prevalence of 2.9%. Oncogenic HPV types detected were 35 (5.9%) and 56 (2.9%) (Table 1).

Although the prevalence of oral HPV infection was higher in women (17.6%) than in men (11.4%), this result was not statistically significant ($p>0.1$) (Table 2). While no differences in the prevalence of oral HPV infection were observed by age or education, the prevalence was higher among binge drinkers (21.1%) than among participants who reported not having engaged in this behavior (11.2%); this difference was marginally significant ($p=0.09$). Meanwhile, a higher prevalence of oral HPV infection was observed among HIV-positive individuals (31.8% vs. 10.2%, $p=0.003$) and among individuals ever having engaged in commercial sex (22.7% vs. 7.7%, $p<0.0001$) as compared to their counterparts. The prevalence of infection was also higher among participants with higher number of lifetime and past 6 months sexual partners, although these results were not statistically significant ($p>0.10$).

No differences in oral HPV prevalence were observed by gender or age in the multivariate logistic regression model, although a strong confounding effect was observed for gender (Table 3). Nonetheless, binge drinkers were close to 4 times more likely to have oral HPV infection (OR adjusted: 3.85, 95% CI=1.40, 10.58). Participants who reported ever having engaged in commercial sex (OR adjusted: 3.55, 95% CI=1.46, 8.67) and those HIV-positive (OR adjusted: 4.67, 95% CI=1.58, 13.74) were more likely to have oral HPV infection as compared to their counterparts. Results for Likelihood Ratio test were not statistically significant ($p=0.46$). No significant interaction terms were identified within the logistic regression models ($p>0.05$).

Discussion

Studies of HPV infection among drugs users are limited (25), and none has focused on oral infection. This study evaluates for the first time the prevalence and correlates of oral HPV infection among a sample of chronic drug-users, using data from a Hispanic population in PR. Our study evidences a high

Table 1. Prevalence of specific HPV types detected in oral rinse among a sample of drug users in Puerto Rico (n=271)

	n	Prevalence among all screened participants (%)	Proportion of positives among those with any HPV (%)
Any HPV*	34	12.50	--
Any of 38 type-specific HPV probes	13	4.80	--
>1 HPV type	1	0.34	2.94
Low Risk HPV types			
32/42	1	0.34	2.94
53	1	0.34	2.94
62	1	0.34	2.94
71	1	0.34	2.94
72	4	1.48	11.76
81	1	0.34	2.94
82	1	0.34	2.94
84	1	0.34	2.94
*High-risk HPV types***			
35	2	0.74	5.88
56	1	0.34	2.94

*HPV types detectable by PCR; **As defined by IARC

Table 2. Factors associated to oral HPV infection status among drug users in Puerto Rico (n=271).

	HPV- n (%)	HPV+ n (%)	p-value
Gender			>0.10
Men	195 (88.6)	25 (11.4)	
Females	42 (82.4)	9 (17.6)	
Age (years)			>0.10
18-29	113 (88.3)	15 (11.7)	
30-35	124 (86.7)	19 (13.3)	
Education			>0.10
Less than high school	139 (89.7)	16 (10.3)	
High school or more	98 (84.5)	18 (15.5)	
Homeless (ever)			>0.10
Yes	81 (87.1)	12 (12.9)	
No	156 (87.6)	22 (12.4)	
Type of drug user			>0.10
IDU	147 (88.6)	19 (11.4)	
Non-IDU	90 (85.7)	15 (14.3)	
History of incarceration			>0.10
Yes	182 (87.9)	25 (12.1)	
No	55 (85.9)	9 (14.1)	
Binge drinking			0.09
Yes	30 (78.9)	8 (21.1)	
No	207 (88.8)	26 (11.2)	
Commercial Sex (ever)			<0.0001
Ever	68 (77.3)	20 (22.7)	
Never	169 (92.3)	14 (7.7)	
Sexual partners (#, lifetime)			>0.10
1-10	110 (90.2)	12 (9.8)	
11+	127 (85.2)	22 (14.8)	
Sexual partners (#, past 6 months)			>0.10
0-1	162 (89.5)	19 (10.5)	
2+	75 (83.3)	15 (16.7)	
HIV status*			0.003
Positive	15 (68.2)	7 (31.8)	
Negative	184 (89.8)	21 (10.2)	
HIV status by CD4 count**			0.047
Negative	184 (89.8)	21 (10.2)	
CD4>500	8 (72.7)	3 (27.3)	
CD4≤500	7 (70.0)	3 (30.0)	
HCV Status***			>0.10
Positive	103 (89.6)	12 (10.4)	
Negative	105 (86.1)	17 (13.9)	
Marihuana (past 12 months)			>0.10
Yes	161 (88.5)	21 (11.5)	
No	76 (85.4)	13 (14.6)	
Heroine (past 12 months)			>0.10
Yes	116 (85.3)	20 (14.7)	
No	121 (89.6)	14 (10.4)	
Cocaine (past 12 months)			>0.10
Yes	134 (87.0)	20 (13.0)	
No	103 (88.0)	14 (12.0)	
Crack (past 12 months)			>0.10
Yes	90 (84.1)	17 (15.9)	
No	147 (89.6)	17 (10.4)	
Speedball (past 12 months)			>0.10
Yes	142 (89.3)	17 (10.7)	
No	95 (84.8)	17 (15.2)	
Crack/cocaine (past 12 months)			>0.10
Yes	200 (86.6)	31 (13.4)	
No	37 (92.5)	3 (7.5)	

*n=227, ** n=226, *** n=237

Table 3. Magnitude of the association between oral HPV infection status and different factors among drug users in Puerto Rico.

	OR crude (95% CI)	OR adjusted (95% CI)
Gender		
Men	1.00	1.00
Females	0.60 (0.26, 1.37)	1.51 (0.51, 4.50)
Age (years)		
18-29	1.00	1.00
30-35	1.15 (0.56, 2.38)	1.91 (0.80, 4.50)
Binge Drinking (past 30 days)		
Yes	2.12 (0.88, 5.12)	3.85 (1.40, 10.58)*
No	1.00	1.00
Commercial Sex		
Ever	3.55 (1.70, 7.43)*	3.55 (1.46, 8.67)*
Never	1.00	1.00
HIV status		
Positive	4.09 (1.50, 11.16)*	4.67 (1.58, 13.74)*
Negative	1.00	1.00

*p<0.05

prevalence of oral HPV infection in the oral cavity of evaluated drug users in PR (12.5%). Our estimate is higher than that for cancer-free individuals worldwide (4.5%, 95% CI=3.9%-5.1%), based on a recent review of 18 international studies (5). Nonetheless, our estimate is lower than that for men attending an STI clinic in PR (20.0%) (26).

Contrary to previous studies (5, 26), no participant in our study was infected with any HPV type included in current available vaccines (HPV-6, -11, -16, -18). This contrasts to a systematic review of published studies performed by Kreimer et al., (5) where oral HPV-16 accounted for 28% of all HPV detected in the oral cavity. However, HPV-16 was not detected in another study in Brazil (27) and had a low prevalence in the previous study among men in an STI clinic in PR (2.4%) (26). Although higher prevalence of oral HPV infection was observed for women than men (18% vs. 11%), this results was not statistically significant. This is contrary to results from the US NHANES 2009-2010, where prevalence estimates for any oral HPV infection where 10.1% for men and 3.6% for women (28); this pattern was also observed among a clinic-based sample of control patients (men: 6.0%, women: 1.2%) (6). Meanwhile, the pooled international study by Kreimer observed a lower similar prevalence of oral infection in both men (4.6%) and women (4.4%) (5). The higher prevalence of oral HPV infection in women in our study may be related to the fact that more of these women are engaging in high-risk sexual behaviors, including commercial sex.

Although oral HPV prevalence in drug users in our study did not significantly vary among individuals aged 18-29 (11.7%) and 30-35 years (13.3%), it was higher than prevalence estimates among young adults from the general population. Results from NHANES document that the age-specific prevalence of oral HPV infection in the general US population follows a bimodal pattern, with peak prevalence among individuals aged

30-34 years (7.3%) and 60-64 years (11.4%) (28). Similarly, a multinational study conducted among men found that the prevalence of infection non-significantly increased with age, with lower prevalence estimates among men aged 18-24 (3.2%) and highest estimates among those aged 55-74 years (6.1%) (29). Oral HPV prevalence also significantly increased over increasing age categories in the study among men attending an STI clinic in PR (26).

Consistent to previous studies (21, 30), we observed a higher prevalence of oral HPV infection among HIV-positive individuals. We also observed strong associations between oral HPV infection and both, binge drinking and history of commercial sex. These results are also consistent with studies that show heavy alcohol consumption (22) is associated with oral HPV prevalence and that female sex workers have a high prevalence of infection (73.3%) (31). Given that HIV-positive individuals and those who abuse alcohol may also be at increased risk of oropharyngeal cancers (12, 32, 33), these high-risk groups should be the target of HPV-related cancer prevention and control efforts.

We observed no association between any of the individual drugs evaluated (except alcohol) and oral HPV infection. The study by Colón-López et al. found associations between ever and recent marihuana use and oral HPV infection in bivariate analysis ($0.05<p<0.1$) (26). Meanwhile, an Australian study found a marginally significant association between illicit drug use and oral HPV prevalence (34). Thus, results are inconclusive as studies for oral HPV infection and drug use are limited in amount and sample size (35). Nonetheless, in cervix, a previous study found a positive association between recent crack use and cervical HPV detection, and an association with recent marijuana use just among HIV-uninfected women in the US (36). Meanwhile, the Women's Interagency HIV Study observed increased risk of cervicovaginal HPV infection in women with crack/cocaine use but not in those with heroin use, supporting immunologic effects of cocaine (37). Further research is warranted to elucidate these associations. The fact that ours is a relatively homogenous high-risk population of chronic drug-users may be limiting our ability to determine the exact impact of specific drugs on oral HPV infection status in this group.

Our study had some limitations. For forty-four participants HIV status was unknown, given that their veins were too deteriorated for venipuncture. Despite the exclusion of these individuals from multivariate analyses, no significant difference in the prevalence of HPV infection was observed between these and those included ($p>0.05$). Also, tobacco use was not assessed. Nonetheless, previous data have shown that the prevalence of tobacco use among drug users in PR is more than 90% (38). Finally, the reduced sample size may have limited the power of our study to detect some associations. Furthermore, the reduced number of female participants in our study limited our ability to further explore gender differences in oral HPV infection in this study. This gender difference in the study population is related to the fact that there are much more males than females attending the outdoor drug markets in the San Juan metropolitan area of PR.

Nonetheless, we conclude that surveyed drug users have a high prevalence of oral HPV infection and consistent with previous studies in the genital (1, 31, 39, 40) and oral tract (21, 28, 30, 31), HIV-positivity, commercial sex and heavy alcohol consumption are strong determinants of oral HPV infection. Results highlight the need for additional studies that assess the implications of oral HPV infection on oral cancer risk among drug users and HIV-positive individuals in PR. On both of these high-risk populations, primary prevention efforts, such as HPV vaccination, might be delayed and screening practices might be nonexistent.

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Resumen

Objetivo: La prevalencia del virus del papiloma humano (VPH) en la cavidad oral no ha sido igual de estudiada como la infección anogenital, y su prevalencia en usuarios de drogas es incierta. El siguiente estudio describe la prevalencia y los factores de riesgo asociados a la infección oral con el VPH en una muestra de usuarios de drogas en Puerto Rico (PR). Métodos: Estudio transversal de 271 usuarios de drogas entre las edades de 18-35 años, no recibiendo tratamiento y residentes del área metropolitana de San Juan. Las muestras orales fueron obtenidas mediante un enjuague bucal y la infección con VPH fue detectada por medio de PCR. Información sobre otras variables de interés fue recopilada a través de entrevistas personales y análisis de suero. Resultados: Un total de 34 participantes resultaron positivos a cualquier tipo de VPH (12.5%) y 13 de los mismos (4.8%) arrojaron positivo para alguna de las 38 sondas específicas de VPH evaluadas. Entre los participantes positivos a VPH, el tipo más común detectado fue el tipo no-oncogénico VPH 72 (11.8%, n=4). De los tipos del virus de alto riesgo el VPH 35 (5.9%) y el VPH 56 (2.9%) fueron detectados en la muestra. Factores asociados a la infección oral con VPH incluyeron abuso de alcohol (OR=3.85, 95% CI=1.40, 10.58), ser VIH positivo (OR=4.67,

95% CI=1.58, 13.74) y haber tenido sexo comercial alguna vez en la vida (OR=3.55, 95% CI=1.46, 8.67); la infección no varió por edad o género. Conclusión: Consistente con estudios previos, la infección con VIH, el abuso de alcohol y el haber tenido sexo comercial se asociaron fuertemente a la infección oral con VPH. Estudios adicionales deben realizarse con el propósito de evaluar las implicaciones que tiene la infección con VPH en el riesgo de padecer cáncer oral en esta población.

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