Association of Periodontitis and Human Papillomavirus in Oral Rinse Specimens NHANES 2009–2012

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Abstract

Background—Human papillomavirus (HPV) positive oropharyngeal squamous cell carcinomas are increasing in incidence and are becoming significant public health concerns. Periodontitis is a chronic condition in which the affected tissue may facilitate oral HPV infection and persistence. The purpose of this study was to determine if an association of the presence of HPV in oral rinse specimens and periodontal disease exists.

Methods—The National Health and Nutrition Examination Survey data for years 2009–10 and 2011–12 were combined. Participants ages 30–69 years with clinically assessed periodontal and HPV data were included in the study (n=6,004). The data were analyzed with Rao Scott Chi Square and logistic regression.

Results—There were 498 participants who had the presence of HPV in oral rinse specimens. The adjusted odds ratio for the presence of HPV in oral rinse specimens with relation to periodontal disease was 1.04 (95% confidence interval: 0.63, 1.73), adjusting for sex, race/ethnicity, education, age, income to poverty ratio, smoking, alcohol use and number of lifetime sex partners.

Conclusions—The researchers failed to reject the hypothesis of no association of the presence of HPV in oral rinse specimens and periodontitis.

Practical Implications—Although oral HPV infection is a serious concern, periodontitis was not shown to be related to the presence of HPV in oral rinse specimens in adjusted analyses in this study.

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Keywords

Periodontal diseases; risk assessment; public health/community dentistry; National Health and Nutrition Examination Survey (NHANES)

Worldwide, head and neck carcinomas are the 6th most common cancer with an incidence of 400,000–500,000 annual cases,[1–5] and nearly $3.2 billion in treatment costs. Even with aggressive treatment, there is significant morbidity and mortality.[6] In 1983, human papilloma virus (HPV) was identified as a risk factor for oropharyngeal squamous cell carcinoma.[7] Between 5–20% of head and neck squamous cell carcinomas and 40–90% of oropharyngeal carcinomas are related to HPV.[1,8] There are over 150 different HPV types[9] (or strains), most of which are not considered high risk types.

The high risk types are: HPV-16, 18, 31, 33, 35, 45, 51, 52, 56, 68, 59, 68, 73, and 82.[1] High risk HPV types have been found in nearly one-fourth of oral and laryngeal squamous cell carcinomas;[10] HPV-16 was associated with 45–90% of oropharyngeal carcinomas.[1,11] In contrast to the incidence of HPV negative (HPV−) oropharyngeal squamous cell carcinomas, HPV positive (HPV+) oropharyngeal squamous cell carcinomas have been increasing in incidence in the U.S.,[12–15] from 0.8/100,000 in 1998 to 2.6/100,000 in 2004.[8] HPV is an 8,000 base-pair DNA genome in an icosahedral 55nm capsid.[16] The virus is small, non-enveloped, and epitheliotrophic.[17]

Although there is a growing awareness of the association of HPV and oropharyngeal squamous cell carcinomas, there is a lack of information about oral HPV infection and infectivity. D'Souza et al. reported that the prevalence of HPV-16 infection in exfoliated oral epithelial cells increased the odds of oropharyngeal carcinoma 13 times.[18]

Periodontitis is a complex chronic oral condition involving teeth, bone, epithelial cells, a biofilm community of bacteria, fungi, and viruses,[16,19,20] and the immune system's response to the biofilm community. Periodontitis has been associated with other chronic inflammatory diseases such as diabetes, and cardiovascular disease.[15] In periodontitis, there is a continuous release of inflammatory cytokines and biomarkers which adversely affects systemic health,[5] and is related to a modulation in epithelial barrier function protection.

It is unknown if the biofilm and chronic inflammation of periodontitis with a decrease in epithelial barrier protection may be associated with oral HPV infectivity. The purpose of this study is to determine if there is an association of the presence of HPV in oral rinse specimens and periodontitis. The null hypothesis is that the odds ratio for the presence of HPV in oral rinse specimens is equal in individuals who have periodontitis as it is in individuals who do not have periodontitis. Previous studies have been equivocal. Some were limited by the use of self-reports for identifying periodontitis, others used self-reported oral health as the periodontal variable. Other studies have also had limitations as small sample sizes, or hospital-based cases. This study adds to the literature results from a large, nationally represented sample in which clinical assessment of all teeth was performed and the definition used for periodontitis was based on the definition for population surveillance

of the Centers for Disease Control and Prevention in partnership with the American Academy of Periodontology.[21]

METHODS

Study design and data source

This study was acknowledged by the West Virginia University Institutional Review Board (protocol 1408392538). The researchers used a cross-sectional study design to determine the association of the presence of HPV in oral rinse specimens (HPV+ or HPV−) and periodontitis. The data source was the National Health and Nutrition Examination Survey (NHANES), years 2009–2012. The NHANES is a national population study of the non-institutionalized and civilian public which has a stratified, multistage probability sampling design. The National Center for Health Statistics Institutional Review Board approved the NHANES study. Participants received written informed consent. Interviewers surveyed a household member and requested a physical evaluation of the participant at an NHANES mobile examination center. Eligible participants in the NHANES were ages 14 to 69 years. Details of the NHANES are available at http://www.cdc.gov/nchs/nhanes.htm.

Study sample

The eligible sample for this study was a subset of the NHANES, years 2009–2012. It included NHANES participants with complete, clinically assessed periodontal and HPV data. Edentulous individuals, individuals with heart transplants, artificial heart valves, congenital heart disease, rheumatic fever, hemophilia, kidney disease with dialysis, a pacemaker or younger than age 30 years were not included. The data were available for participants ages 30–69 years (n= 6,004).

Outcome/Dependent Variable—The study outcome was the presence of HPV in oral rinse specimens (HPV+ or HPV−). The HPV samples were obtained during oral evaluations in which the participants swished and gargled 10 mL of a mouth rinse or saline for 30 seconds. The samples were stored at 4°C and evaluated with polymerase chain reaction for HPV at Ohio State University. Details are available at the NHANES website.

Key variable of interest/exposure

The key variable of interest was periodontal status as mild, moderate, *or* severe periodontitis (a combined category) or no periodontitis. The definition of periodontitis used in this study was based on the definition for population surveillance of the Centers for Disease Control and Prevention in partnership with the American Academy of Periodontology.[21] Their researchers defined mild periodontitis as either one periodontal site having a probing depth of 5 mm or above; or having at least 2 interproximal periodontal sites with 3 mm or more in attachment loss and at least 2 interproximal periodontal sites with at least 4mm probing depth which does not occur on the same tooth.[21] The definition for moderate periodontitis was at least 2 interproximal sites with probing depths of at least 5 mm which do not occur on the same tooth or at least 2 interproximal sites which are not on the same tooth and which have an attachment loss of at least 4 mm.[21] Severe periodontitis was defined as at least one interproximal site having a probing depth of at least 5 mm with at least 2 interproximal sites

which are on different teeth having attachment loss of at least 4 mm. The data in this study were dichotomized (mild, moderate, or severe periodontitis v. no periodontitis) due to sample size availability.

The periodontal evaluations were conducted by licensed dentists with halogen illumination and the use of a mirror and HuFriedy™ periodontal probes. Details are available at the NHANES website.

Other variables/potential confounders of Epidemiological importance

Other variables have been indicated to having had an epidemiologic role in HPV+ status. The other variables used for this study included sociodemographic and behavioral variables. The variables were self-reported to the interviewer and included: sex (male v. female); race/ethnicity (Non-Hispanic black, Mexican American, Other v. Non-Hispanic white); education (high school or less than high school v. more than high school); age (30–44 v. 45–69 years); family income to poverty ratio (less than 2 v. 2 and above); smoking (current, or former smoker v. never smoker); alcohol consumption (moderate, heavy v. no consumption); and lifetime sex partners (2–10, 11 and above v. 0–1). These variables were selected as having had previously been shown to have an association with HPV infectivity;[6,22–25] and sex, race/ethnicity, education, age, income, and smoking were also previously shown to be related to periodontal disease.[26–31]

Statistical analyses

The NHANES has a complex study design. The design and sample weights were used in the statistical analyses of this study. Statistical analyses included descriptive statistics (frequency determinations), univariate Rao Scott Chi Square, and unadjusted and adjusted logistic regression on HPV. Three models were built. The full adjusted logistic regression included sex, race/ethnicity, education, age, family income to poverty ratio, alcohol consumption, and lifetime sex partners in addition to the key variable of interest, periodontitis, as these variables were significant in the univariate analysis and are considered important in epidemiological studies. A reduced model included only the variables which were significant in the full model in addition to the periodontitis variable. These variables were sex, smoking, lifetime sex partners, and race/ethnicity. A third parsimonious model was made in which the variable, race/ethnicity, was removed as it failed to reach significance in the reduced model. Interactions of the variables with periodontitis and presence of HPV in oral rinse specimens (HPV+ or HPV−) were also analyzed, but did not significantly change the relationship and were not included in the three models presented. SAS 9.3® (Cary, NC) software was used to analyze the data.

RESULTS

Of the 6,004 participants, 50.1% were male, and 66.8% were non-Hispanic white. The participants were evenly distributed in age. Most (63.7%) had some college or above; had an income to poverty ratio above 2.0 (69.2%); and were never-smokers (56.3%). There were 28.2% who reported moderate alcohol use and 43.7% who reported having 2–10 lifetime sex partners. There were 59.7% who did not have periodontitis and 92.5% who were did not

have the presence of HPV in their oral rinse specimens (HPV−). Of the 498 participants who had the presence of HPV in their oral rinse specimens (HPV+), 66 were HPV-16 positive, 57 were HPV-55 positive, and 49 were HPV-62 positive. Details are presented in the figure.

The results of Chi Square analyses are present in Table 1. There were significant differences in the presence of HPV in oral rinse specimens (HPV+ or HPV−) with relation to periodontitis. Of the HPV+ participants, there were 41.3% who did not have periodontitis, and 58.7% who had periodontitis; whereas, 61.3% of HPV− participants did not have periodontitis, and 38.7% had periodontitis. These differences were statistically significant (p<0.0001).

Other variables with significant relationships with the presence of HPV in oral rinse specimens (HPV+ or HPV−) were male sex, less education, lower income to poverty ratio increased alcohol consumption, smoking, and higher number of lifetime sex partners.

The results of the logistic regression of periodontitis on the presence of HPV in oral rinse specimens are presented in Table 2. In unadjusted logistic regression, the odds ratio for presence of HPV in oral rinse specimens with periodontitis was 2.25 (95% confidence interval: 1.61, 3.13, p<0.001) as compared with participants who did not have periodontitis.

When sex, race/ethnicity, education, age, income to poverty ratio, smoking, alcohol use and number of lifetime sex partners were included in a full model of the variables of epidemiological importance, the adjusted odds ratio for the presence of HPV in oral rinse specimens with periodontitis was 1.04 (95% confidence interval: 0.63, 1.73, p=0.8684). (Interaction analyses of periodontitis with sex, race/ethnicity, education, income to poverty ratio, smoking, alcohol use and number of lifetime sex partners were not significant in their relationship with the presence of HPV in oral rinse specimens and were not included in the full model.)

A reduced model, retaining the periodontitis variable and the significant variables from the full model (sex, race/ethnicity, smoking, and lifetime sex partners), had an adjusted odds ratio of 1.33 (95% confidence interval: 0.88, 2.00, p=0.1715) for periodontitis. A parsimonious model retaining the periodontitis variable and removing race/ethnicity (which failed to reach significance in the reduced model) had an adjusted odds ratio of 1.38 (95% confidence interval: 0.92, 2.08, p=0.1182).

DISCUSSION

In summary, the primary result of this study is that the odds ratio for the presence of HPV in oral rinse specimens (HPV+ or HPV−) with relation to periodontitis adjusted for sex, race/ethnicity, education, age, income to poverty ratio, smoking, alcohol use and number of lifetime sex partners was 1.04 (95% confidence interval: 0.63, 1.73, p=0.8684), indicating there was no independent association between the presence of HPV in oral rinse specimens (HPV+ or HPV−) and periodontitis. Though not the focus of the study, the sex of the participant, smoking status, and number of lifetime sex partners were independently associated with the presence of HPV in oral rinse specimens. The data used were NHANES 2009–12 data which were nationally representative. There were 498 participants who had

the presence of HPV in oral rinse specimens of 6,004 participants; and of these participants, there were 66 who were HPV-16 positive.

These results are important and add to the body of subject knowledge in that the role of periodontitis in the presence of HPV in oral rinse specimens was not shown to be significant. Although periodontitis has been shown to be associated with many other chronic diseases, it was not shown to be associated with oral HPV in this cross-sectional study.

In addressing the context and related studies with the results of this study, there were similar results found by researchers in a small study of 56 participants with chronic periodontitis, 26 participants with gingivitis, and 22 controls who were healthy.[16] The researchers did not find HPV-16 in the gingival samples.[16]

Similarly, Escalona et al. conducted a study using the gingival crevicular fluid of 20 HIV+ participants who had periodontitis, 7 HIV– participants who had periodontitis, and 7 controls.[32] They found no significant difference in periodontal status in HPV-HIV infection with the patients with HIV; and HPV was found only in the crevicular fluid of HIV+ patients on antiretroviral therapy.[32]

In addition, in a study of 102 healthy participants with periodontal disease, no HPV DNA was found in the gingival biopsy specimens.[33]

However, positive associations of periodontitis and HPV were found in several other studies. Hormia, et al. studied 31 individuals with periodontitis.[20] They used polymerase chain reaction on gingival biopsy specimens and found 26% were positive for high risk type HPV, indicating that the periodontal pocket was a possible reservoir of HPV.[20] Other researchers, using the Southern blot method with 32P-radiolabeled DNA found HPV in 30% of gingival tissue with gingivitis or periodontitis, which also suggested gingival epithelium was a potential reservoir for HPV;[34] and 92.3% of 13 biopsies of gingival overgrowth lesions in renal allograft recipients were HPV +.[17]

Tezal, et al. examined tongue cancer biopsy specimens for HPV+ or HPV– status from 30 participants and determined periodontal status by panoramic radiographic alveolar bone loss and found an association with HPV+ status and alveolar bone loss.[35] Tezal, et al. also examined biopsy specimens of primary squamous cell carcinoma of the oral cavity, oropharynx, and larynx for HPV+ or HPV– status from 124 participants and determined periodontal status with the same panoramic radiographic alveolar bone loss technique.[37] They also found an association of HPV+ status and alveolar bone loss.[36] Although the positive associations were determined in the aforementioned small studies, Hang, et al. evaluated 5410 healthy adults in China and found a self-reported association of a history of oral disease and HPV infectivity;[31] and, Bui, et al. found a self-reported association of: poor or fair oral health; possibility of gum disease; use of mouthwash to treat dental problems in the previous week; and higher number of teeth lost to be significantly associated with HPV+ status in the 2009–2010 National Health and Nutrition Examination Survey.[29]

The current research results and the studies which showed positive associations had differences in study variables and methodologies. Several of the studies in which positive

associations were determined, except for the Hang, et al., and Bui, et al., studies, were very small studies in which there is a potential for type 2 (beta error) due to the small sample size. There were methodology differences in the definition of periodontitis. Researchers in two of the studies in which positive associations were found used radiographic bone loss to define periodontitis, whereas, in this study, full mouth periodontal probings were used as the basis to define periodontitis. Similarly, in the large studies of Hang, et al.[31], and Bui, et al.[29], periodontitis was either self-reported, or a self-reported proxy variable was used rather than full mouth probings to determine periodontitis. Gingival tissue samples were used in several of the studies, whereas oral rinse specimens were used in this study. These differences in study variables and methodologies explain some of the different results. This is the first study, to our knowledge, to use full mouth periodontal probings and the definition of periodontitis from the Centers for Disease Control and Prevention in partnership with the American Academy of Periodontology to identify periodontitis in HPV studies. Future research is needed using full mouth periodontal probings and the definition of periodontitis from the Centers for Disease Control and Prevention in partnership with the American Academy of Periodontology and large data sources to support the results of this study.

The study has several strengths. The researchers in this current study used clinical periodontal data from the National Health and Nutrition Examination Survey, 2009–2012, rather than self-report reported data which have the potential to be subject to social bias. The data for periodontitis included clinical evaluations of all of the teeth of the participants, rather than partial mouth evaluations, and were analyzed with an established definition. The HPV analyses were strictly conducted with polymerase chain reaction testing. The study is not hospital-based, or case-based. The sample size was large (N=6004), and nationally representative. It had a high quality data source, NHANES, and combined years to adequately develop a large sample.

Nevertheless, this study has limitations in that causal or temporal relationships cannot be determined by the study design. The variables considered were based on previous epidemiological studies and there may be other social determinants or biological factors which could confound or be effect modifiers in the relationship. Although the sample was large and used combined years of the NHANES, there were 498 participants who had the presence of HPV in oral rinse specimens and there is the potential of significant results with a larger sample.

CONCLUSION

There is an urgent need to learn more about HPV, its infectivity, persistence, remission, recurrence, and its role in malignancy.[37] The presence of HPV in oral rinse specimens is a concern and requires future studies.

The researchers failed to reject the hypothesis of no association of the presence of HPV in oral rinse specimens and periodontitis. Although oral HPV infection is a serious concern, periodontitis was not shown to be related to the presence of HPV in oral rinse specimens in adjusted analyses in this study.

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Acknowledgments

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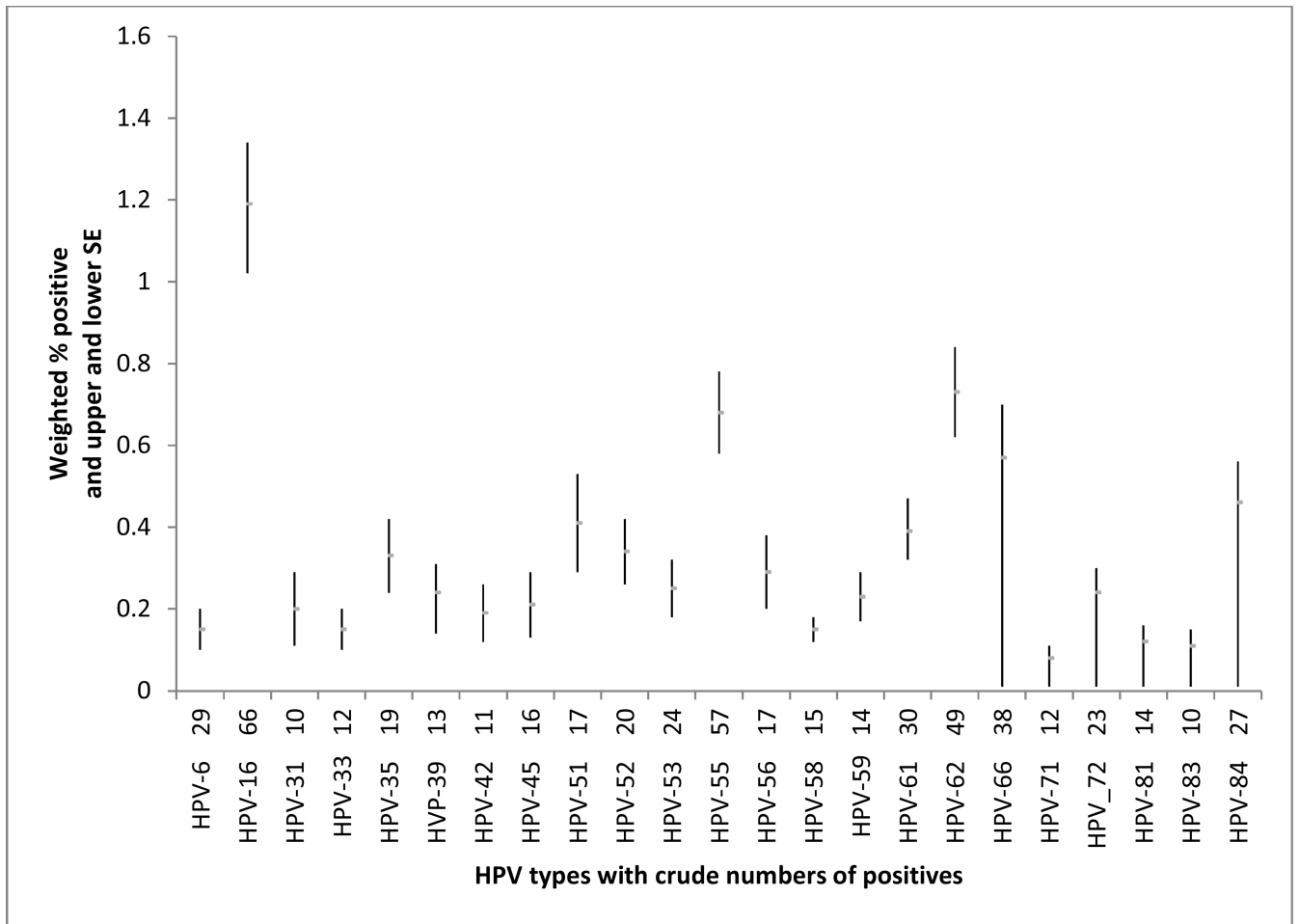
Figure.
Prevalence of oral human papillomavirus (HPV) by HPV type. HPV types with fewer than 10 were suppressed.

Table 1

Presence of HPV in oral rinse specimens (HPV+ or HPV−) versus periodontal disease and other variables of interest, NHANES 2009–12: Rao Scott Chi Square Analysis

Variable	HPV+ N	HPV+ wt N	wt column %	HPV− N	HPV− wt N	wt column %	p-value
Periodontal Disease							<.0001 *
No disease	189	7,680,364	41.3	2,870	141,244,692	61.3	
Yes disease	309	10,919,274	58.7	2,636	89,292,955	38.7	
Sex							<.0001 *
Male	384	14,682,623	78.9	2,612	109,515,598	47.5	
Female	114	3,917,016	21.1	2,894	121,022,048	52.5	
Race/ethnicity							.0568
Non-Hispanic white	176	11,765,083	63.3	2,147	154,894,716	67.2	
Non-Hispanic black	150	2,911,913	15.7	1,201	25,268,865	11.0	
Mexican American	84	1,719,076	9.2	882	19,381,458	8.4	
Other	88	2,203,567	11.8	1,276	30,992,608	13.4	
Age							.0677
30–34 years	66	2,261,033	15.5	624	25,844,936	14.1	
35–39 years	41	1,316,833	9.0	607	25,164,592	13.8	
40–44 years	41	1,859,750	12.8	640	26,580,912	14.5	
45–49 years	41	1,670,795	11.5	589	27,158,291	14.9	
50–54 years	64	2,156,027	14.8	580	25,196,983	13.8	
55–60 years	53	2,142,149	14.7	456	21,368,017	11.7	
60–64 years	74	2,214,353	15.2	575	17,631,893	9.6	
65–69 years	33	953,617	6.5	397	13,903,242	7.6	
Education							.0008 *
Less than HS	131	3,186,241	17.1	1,339	36,039,431	15.6	
HS graduate	130	4,823,129	25.9	1,137	45,888,992	19.9	
Some coll/tech	157	6,482,892	34.9	1,512	66,699,681	29.0	
Coll/tech graduate	80	4,107,376	22.1	1,512	81,744,421	35.5	
Family income to poverty ratio							.0016 *

Variable	HPV+ N	HPV+ wt N	wt column %	HPV- N	HPV- wt N	wt column %	p-value
0 to less than 1.25	167	4,280,819	24.1	1,438	36,141,939	16.8	
1.25 to less than 2.00	86	2,738,831	15.4	835	28,295,693	13.2	
2.00 to less than 4.00	103	4,717,321	26.6	1,231	58,958,012	27.4	
4.00 and above	104	5,995,035	33.8	1,519	91,557,015	42.6	
Alcohol consumption							<.0001 *
Non-use	70	1,772,617	12.0	1,277	41,425,319	21.4	
Moderate use	149	6,135,307	41.6	1,954	100,024,901	51.7	
Heavy use	170	6,826,175	46.3	1,245	51,862,437	26.8	
Smoking status							<.0001 *
Current	186	6,652,863	35.8	1,079	40,640,365	17.6	
Former	120	4,950,246	26.7	1,234	56,584,439	24.6	
Never	192	6,996,529	37.6	3,190	133,250,544	57.8	
Lifetime sex partners							<.0001 *
0	**		**	157	4,110,015	2.0	
1	11	350,645	2.1	701	29,720,647	14.3	
2–5	80	2,347,233	13.9	1,582	69,712,801	33.5	
6–10	102	3,836,682	22.7	1017	46,783,958	22.5	
11–20	82	3,383,768	20.0	662	30,383,430	14.6	
Above 20	156	6,859,791	40.6	690	34,451,329	13.2	

*
indicates significant differences in p-values between the HPV seropositive and HPV seronegative groups in relation to the specific variable.

Abbreviations: HPV + HPV seropositive; HPV - : HPV seronegative; N-number; wt-weighted; HS. high school; and coll/tech, college technical school. Tech-technical school.

**
cell has too few to report

Wt column % indicates weighted percentage to account for complex sample design. Consequentially, dividing cell size, N, by total sample will not result in weighed percentage; however dividing *wt N*, by weighted sample will provide wt column%.

Table 2

Logistic regression on presence of HPV in oral rinse specimens, NHANES 2009–12

Variable	Model 1 AOR (95%CI)	Model 2 AOR (95%CI)	Model 3 AOR (95%CI)
Periodontal disease			
Yes	**1.38 (0.92, 2.08)**	**1.33 (0.88, 2.00)**	**1.04 (0.63, 1.73)**
No	**reference**	**reference**	**reference**
Sex			
Male	3.13 (2.27, 4.31)	3.15 (2.28, 4.35)	3.35 (2.35, 4.77)
Female	reference	reference	reference
Smoking			
Current	1.90 (1.40, 2.60)	1.92 (1.41, 2.61)	2.08 (1.47, 2.95)
Former smoker	1.10 (0.76, 1.59)	1.14 (0.79, 1.66)	1.26 (0.80, 1.98)
Never smoker	reference	reference	reference
Lifetime sex partners			
2–10	3.80 (1.68, 8.60)	3.86 (1.75, 8.55)	4.04 (1.86, 8.75)
11 or more	8.57 (4.04, 18.16)	8.69 (4.21, 17.94)	8.44 (4.37, 16.30)
0–1	reference	reference	reference
Race/ethnicity			
Non-Hispanic Black		1.36 (0.95, 1.95)	1.66 (1.14, 2.43)
Mexican American		1.24 (0.85, 1.80)	1.29 (0.87, 1.91)
Other		1.36 (0.88, 2.09)	1.46 (0.96, 2.28)
Non-Hispanic White		reference	reference
Education			
High School education or less			1.03 (0.72, 1.47)
More than high school education			reference
Age			
30–44 years			0.72 (0.47, 1.12)
45 –69 years			reference
Family income to poverty ratio			
Less than 2			1.04 (0.76, 1.44)
2 and above			reference
Alcohol consumption			
Moderate			1.01(0.61, 1.67)
Heavy			1.08 (0.62, 1.90)
No consumption			reference

AOR= Adjusted odds ratio; CI=confidence interval.

Model 1 is a parsimonious model including periodontal disease, the variable of interest, and significant epidemiological variables; Model 2 additionally includes race/ethnicity; and Model 3 is the full model considered with epidemiological rationale.