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Oral Human Papillomavirus Prevalence and Genotyping Among a Healthy Adult Population in the US

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IMPORTANCE In the US, oropharyngeal cancer, predominantly caused by high-risk (HR) human papillomavirus (HPV) infection, is the most frequent HPV-associated cancer, surpassing cervical cancer. However, little is known about oral HPV prevalence and genotype distribution in the general population.

OBJECTIVE To assess oral HPV prevalence and factors associated with HR and low-risk infection in a general US population.

DESIGN, SETTING, AND PARTICIPANTS PROGRESS (Prevalence of Oral HPV Infection, a Global Assessment) was a cross-sectional observational study conducted between November 2021 and March 2022 in 43 dental offices in the US (24 urban, 13 urban cluster, and 6 rural sites), spanning 21 states. Eligible participants were aged 18 to 60 years, visiting dental clinics for routine dental examination. Dental clinics used targeted sampling to recruit equal distributions of men and women and across age groups.

EXPOSURE Participants provided an oral gargle specimen for HPV DNA and genotyping and completed behavioral questionnaires, and dentists reported oral health status. Detection of HPV DNA and genotyping was performed using the SPF10/DEIA/LiPA25 system at a central laboratory.

MAIN OUTCOME Oral HPV prevalence.

RESULTS Of the 3196 participants enrolled, mean (SD) age was 39.6 (12.1) years, and 55.5% were women. Oral HPV prevalence was 6.6% (95% CI, 5.7%-7.4%) for any HPV genotype, and 2.0% (95% CI, 1.5%-2.5%), 0.7% (95% CI, 0.4%-1.0%), and 1.5% (95% CI, 1.1%-1.9%) for HR, HPV-16, and 9-valent-HPV vaccine types, respectively. Among HPV-positive participants, HPV-16 was the most prevalent genotype (12.4% among men and 8.6% among women). Prevalence of HPV was higher in men than women and highest among men aged 51 to 60 years (16.8%, 6.8%, and 2.1% for any HPV, HR HPV, and HPV-16, respectively). Factors associated with HR oral infection included being male (adjusted odds ratio [AOR], 3.1; 95% CI, 1.2-8.5), being aged 51 to 60 years (AOR, 3.3; 95% CI, 1.5-7.3), having 26 or more lifetime male sex partners (AOR, 6.5; 95% CI, 2.3-18.7), and having 6 to 25 lifetime female oral sex partners (AOR, 3.4; 95% CI, 1.3-8.7).

CONCLUSIONS AND RELEVANCE In this cross-sectional study, oral HPV burden was highest among older men who may be at higher risk of developing oropharyngeal cancer. In addition to male sex and older age, HR oral HPV infection was also associated with sexual behaviors, including increasing number of male sex partners and female oral sex partners.

Supplemental content

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Head and neck cancers (HNCs) are the seventh most common tumors worldwide, with an estimated annual burden of 870 000 new cases and 440 000 deaths in 2020.[1] In addition to being a necessary cause of cervical cancer, human papillomavirus (HPV) is a cause of a growing subset of HNC, including oropharyngeal cancer (OPC).[2] In the US, the incidence of OPC has surpassed cervical cancer and is the most common HPV-related cancer.[3] Of concern is that the incidence of HPV-related OPC continues to increase at a rate of 2.8% per year among men in the US.[4] The proportion of OPC due to HPV has significantly increased over time, with recent publications indicating that more than 80% of OPCs are attributable to HPV infection.[5] Human papillomavirus types recognized as carcinogens are HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, and as such are considered high-risk HPV types (HR HPV).[6] Human papillomavirus-16 alone is responsible for 85% to 96% of HPV-positive OPC cases.[7] Low-risk HPV types (LR HPV), most commonly 6 and 11, are responsible for anogenital and oral warts and recurrent respiratory papillomatosis, a rare and debilitating disease, both of which reduce quality of life.[5,8]

Despite the growing OPC burden, little is known of the prevalence, type distribution, and related factors associated with oral HPV among the general population, nor how these differ by sex. Furthermore, given the anatomic site of infection, several studies have identified oral health as an OPC risk factor.[9,10] This has led to an emerging hypothesis that oral health may be associated with oral HPV infection, though findings are inconclusive[9,10] and necessitate further research.

To fill gaps in knowledge, we designed the PROGRESS (Prevalence of Oral HPV Infection, a Global Assessment) study to assess oral HPV prevalence and associated factors in the general adult US population.[11] Here we report the prevalence and oral HPV type distribution among men and women attending dental clinics for routine care in the US. We also describe how HR and LR HPV prevalence differs by sociodemographic and modifiable factors, stratified by sex.

Key Points

Question What is the burden of oral human papillomavirus (HPV) in a general US population?

Findings In this cross-sectional study of 3196 participants, oral HPV prevalence was 6.6% for any detected genotype, and 2.0%, 0.7%, and 1.5% for high-risk (oncogenic), HPV-16, and 9-valent-HPV vaccine types, respectively. Among HPV-positive participants, HPV-16 was the most prevalent genotype (12.4% among men and 8.6% among women); HPV prevalence was higher in men than women and highest among men aged 51 to 60 years (16.8%, 6.8%, and 2.1% for any HPV, high-risk HPV, and HPV-16, respectively).

Meaning Oral HPV burden was highest among older men who may be more at risk of developing oropharyngeal cancer.

Methods

Study Design and Participants

PROGRESS is a cross-sectional study assessing oral HPV infection in the US. A detailed description of the study design and methodology, including data collection, HPV testing procedures, and sample size calculations, has been published previously.[11]

Eligible participants were men and women aged 18 to 60 years accessing routine dental care who could provide written informed consent. All participants diagnosed with or who were suspected to have HNC were excluded. The PROGRESS study protocol was approved by the Western Institutional Review Board in 2020 and by the corresponding institutional review board/ethics committee at dental sites when required. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Site Recruitment and Site Initiation

Study sites (n = 43) were dental clinics across 21 US states and included urban (population ≥50 000; n = 24), urban cluster (population between 2500 and 49 000; n = 13), and rural sites (population <2500; n = 6). The 2020 IQVIA OneKey database, a national database of health care providers updated on a continuous basis through government and nongovernment industry sources, was used to identify and recruit dental sites. Participating dental clinics used targeted sampling to recruit equal distributions of men and women and across age groups.[11]

Data Collection and Study Procedures

Data were collected between March 2021 and April 2022. Participants underwent HPV sampling via oral rinse and gargle and completed self-administered questionnaires to collect sociodemographics, including self-reported sex; age; race and ethnicity; medical history, including immunosuppression (if a participant reported having a blood disease/cancer, autoimmune disease, HIV, or if they are currently receive corticosteroids, chemotherapy, biologic therapy, or other immunosuppressants) and previous diagnosis of a sexually transmitted infection (STI, including HIV, syphilis, gonorrhea, genital herpes, chlamydia, or anogenital warts); and other risk factors shown or hypothesized to be associated with HPV, like tobacco use and sexual behaviors.[9] Dentists counted the number of missing teeth and identified presence of gingivitis and/or periodontitis. Dentists obtained HPV vaccination status by asking participants whether they had been vaccinated against HPV (response categories yes, no, unknown). Participants who responded yes were asked to provide vaccination dates and age when vaccinated. Participants who responded unknown or who responded yes but could not provide vaccination dates or age were asked to verify details after the study visit and dentists called these participants via telephone within 1 week to record updated information. Participants were considered vaccinated, based on US Food and Drug Administration and Advisory Committee on Immunization Practices recommendation,[12] including (1) vaccinated in 2006 or later and (2) were 26 years or younger if vaccinated prior to 2019, or up to age 45 years if vaccinated after 2019. Participants who responded yes but whose age or vaccination dates were outside the scope of recommendations were recategorized as unknown. Details of the oral rinse and gargle sampling

process and participant- and dentist-collected data are described elsewhere.[11]

HPV Testing

Samples were analyzed at the H. Lee Moffitt Cancer Center and Research Institute (Tampa, Florida) for HPV. Analysis included DNA and genotyping via SPF10 LiPA25 algorithm[13] that identified 25 HPV types: 6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 70, and 74.

Statistical Analysis

Statistical analyses were performed with SAS, version 2.0 (SAS Institute). A sample was considered positive for any HPV genotype if it tested polymerase chain reaction (PCR) positive. This includes specimens testing positive for 1 or more of the 25 HPV types included in the assay and those that tested positive by PCR but without positive genotyping for any of 25 types, which we labeled *untypable HPV* and grouped with LR HPV types.[14] A sample was considered HR HPV if any of 12 types were detected, regardless of the presence of LR HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. A sample was considered LR if 1 or more LR-only types were detected: 6, 11, 34, 40, 42, 43, 44, 53, 54, 66, 68, 70, or 74, or were PCR positive but did not hybridize to 1 of 25 probes (ie, untypable). In cases of multiple concurrent infections, this same rule was applied (eg, if HPV 6 and 16 were concurrently detected, then the specimen was considered HR HPV positive).

Oral HPV prevalence was estimated for any HPV type (PCR positive), specific HPV types, and grouped infections (HR, LR, and nonavalent-vaccine-types [9-valent]). Any oral HPV prevalence was calculated by dividing the number of study participants who were PCR positive by the total number of study participants. Genotype-specific oral HPV prevalence was calculated in this way for each of 25 individual HPV types, HR HPV, LR HPV, and HPV types included in the 9-valent HPV vaccine (6, 11, 16, 18, 31, 33, 45, 52, and 58). Prevalence estimates were stratified by age and sex. Prevalence of each of the individual 25 genotypes detected was calculated separately for men and women by dividing the number of male and female study participants positive for each genotype by the number of male and female samples positive for oral HPV infection. Prevalence of HPV was also stratified by self-reported vaccination status.

We examined how HR and LR prevalence differed by sociodemographics and behavioral characteristics. Relative risk was used for variables with 2 categories. A relative risk of 1 suggests no difference in risk between groups. A risk ratio greater than 1 suggests an increased risk of the outcome in the exposed group. A risk ratio less than 1 suggests a reduced risk in the exposed group. Cramer V was used for variables with 3 or more ordinal categories. It ranges from 0 to 1, where 0 indicates no association between the 2 variables and 1 indicates a perfect association between the 2 variables. Goodman-Kruskal γ was used for variables with 3 or more nominal categories. It ranges from −1 to 1. Values near −1 have a negative association, values near 1 have a positive association, and values near 0 have no association. Analyses were stratified by sex due to differences in HPV prevalence by sex described in the literature.[9] Analyses related to LR infection were included due to the causal role of LR infections in anogenital warts and recurrent respiratory papillomatosis and to provide a more complete understanding of factors associated with HPV infection.

Variables for adjustment in multivariable logistic regression models were selected based on variables with high HPV prevalence in bivariate analyses, as well as the a priori literature.[9] Two multivariable logistic regression models estimated adjusted odds ratios (AORs) and 95% CIs for factors associated with HR and LR oral infection. Due to sample size limitations, male and female participants were combined in each multivariable model. Sexual behavior (ie, heterosexual, bisexual, same-sex engagement) was omitted from models due to collinearity with other sexual health variables.

Results

A total of 43 dental sites recruited 3196 participants between November 2021 and March 2022. Participant characteristics are described in **Table 1**; 1773 (55.5%) were female and 1423 (44.5%) were male, and the mean (SD) age was 39.6 (12.1) years. More women than men reported having never smoked tobacco (77.6% vs 68.3%). More men than women had gingivitis/periodontitis (27.4% vs 20.2%). Among male participants, 47.7% reported more than 5 lifetime female sex partners, and 6.3% reported more than 5 lifetime male sex partners. Among female participants, 2.8% reported more than 5 lifetime female sex partners, and 39.7% reported more than 5 lifetime male sex partners. Ninety-one participants (2.9%) were HPV vaccinated based on self-reported data.

Oral HPV Infection Prevalence

Figure 1 presents HPV prevalence stratified by sex and age. Prevalence of 1 or more of 25 typable oral HPV infections was 6.6% (95% CI, 5.7%-7.4%), 2.0% for HR types (95% CI, 1.5%-2.5%), 0.7% for HPV-16 (95% CI, 0.4%-1.0%), and 1.5% for HPV types the 9-valent HPV vaccine is directed against (95% CI, 1.1%-1.9%). Multiple concurrent infections were detected in 15 participants (0.5%), most of which (14 of 15) included an HR genotype. Among men, prevalence of 1 or more of 25 typable oral HPV infections was 9.1% (95% CI, 7.6%-10.6%), 3.3% for HR types (95% CI, 2.4%-4.2%), 1.1% for HPV-16 (95% CI, 0.6%-1.7%), and 2.5% for HPV types the 9-valent HPV vaccine is directed against (95% CI, 1.7%-3.3%). Compared with men, HPV prevalence among women was significantly lower for any HPV type (4.6%; 95% CI, 3.6%-5.5%) and HR HPV (1.0%; 95% CI, 0.5%-1.5%). Prevalence of HPV was consistently higher among men compared with women in all age categories and genotype categories. Among men, prevalence of all HPV genotypes was highest among those aged 51 to 60 years at 16.8% for any HPV type, 6.8% for HR type, and 2.1% for HPV-16. Among women, prevalence of any HPV genotype was also highest among those aged 51 to 60 years at 8.1%. High-risk-type prevalence was highest at ages 31 to 40 years (1.2%) and 51 to 60 years (1.4%), and HPV-16 remained below 1.0% for all age groups among women.

Table 1. Participant Characteristics (n = 3196)

Characteristic	No. (%)		
	Men (n = 1423)	Women (n = 1773)	Total (n = 3196)
Race, self-report (n = 2963)			
Asian	130 (9.7)	156 (9.6)	286 (9.7)
Black or African American	124 (9.3)	150 (9.3)	274 (9.2)
Native Hawaiian or Other Pacific Islander	7 (0.5)	3 (0.2)	10 (0.3)
White	970 (72.3)	1210 (74.6)	2180 (73.6)
>1 Race	110 (8.2)	103 (6.4)	213 (7.2)
Hispanic, self-report; yes	183 (13.4)	266 (16.0)	449 (14.8)
Age, mean (SD), y	39.3 (12.2)	39.9 (11.9)	39.6 (12.1)
18-30	406 (28.5)	472 (26.6)	878 (27.5)
31-40	352 (24.7)	428 (24.1)	780 (24.4)
41-50	325 (22.8)	430 (24.3)	755 (23.6)
51-60	340 (23.9)	443 (25.0)	783 (24.5)
Education level (n = 3032)			
<12th Grade	333 (24.3)	314 (18.9)	647 (21.3)
Some college	256 (18.7)	340 (20.5)	596 (19.7)
College graduate	781 (57.0)	1008 (60.6)	1789 (59.0)
Marital status (n = 3102)			
Single, divorced, separated, or widowed	566 (40.7)	676 (39.5)	1242 (40.0)
Married or cohabiting	825 (59.3)	1035 (60.5)	1860 (60.0)
Employment status (n = 3101)			
Employed full time	1137 (81.8)	1155 (67.5)	2292 (73.9)
Employed part time	108 (7.8)	270 (15.8)	378 (12.2)
Not employed	145 (10.4)	286 (16.7)	431 (13.9)
Locale (n = 3196)			
Urban (>50 000 inhabitants)	641 (45.0)	817 (47.0)	1458 (45.6)
Urban cluster (2500-49 000 inhabitants)	550 (38.7)	659 (36.6)	1209 (37.8)
Rural (<2500 inhabitants)	232 (16.3)	297 (16.5)	529 (16.6)
Weakened immune system, yes[a]	50 (3.7)	63 (3.8)	113 (3.7)
Smoking status (n = 3030)			
Never smoker	932 (68.3)	1293 (77.6)	2225 (73.4)
Ex-smoker	268 (19.6)	231 (13.9)	499 (16.5)
Current smoker	164 (12.0)	142 (8.5)	306 (10.1)
Cigarette pack-years (n = 3021), mean (SD)			7.6 (11.0)
Never smoker (0 pack-years)	945 (69.5)	1302 (78.3)	2247 (74.4)
Light (>0-20 pack-years)	359 (26.4)	330 (19.9)	689 (22.8)
Moderate (>20-40 pack-years)	39 (2.9)	25 (1.5)	64 (2.1)
Heavy (>40 pack-years)	16 (1.2)	5 (0.3)	21 (0.7)
Lifetime marijuana use, yes (n = 3015)	866 (63.8)	887 (53.5)	1753 (58.1)
Marijuana use in past 6 mo, yes (n = 3012)	353 (26.0)	325 (19.6)	678 (22.5)
Alcohol consumption in last 30 d, yes (n = 2598)			
None	436 (37.7)	572 (39.7)	1008 (38.8)
Low	620 (53.6)	779 (54.1)	1398 (53.8)
High	101 (8.7)	88 (6.1)	192 (7.4)
No. of missing teeth, mean (SD)[b]	3.4 (3.4)	3.4 (3.2)	3.4 (3.3)
Presence of gingivitis or periodontitis, yes[b]	389 (27.4)	357 (20.2)	746 (23.3)
Diagnosed with STI in past 6 mo, yes	66 (4.8)	62 (3.7)	128 (4.2)
Lifetime No. female sex partners (n = 2904)			
0	168 (13.1)	1378 (85.0)	1546 (53.2)
1-5	502 (39.2)	198 (12.2)	700 (24.1)
6-25	430 (33.5)	41 (2.5)	471 (16.2)
≥26	182 (14.2)	5 (0.3)	187 (6.4)

(continued)

Table 1. Participant Characteristics (n = 3196) (continued)

Characteristic	No. (%)		
	Men (n = 1423)	Women (n = 1773)	Total (n = 3196)
No. of new female sex partners in last 6 mo (n = 2901)			
0	1007 (78.5)	1589 (98.1)	2596 (89.5)
1	198 (15.4)	24 (1.5)	222 (7.7)
≥2	77 (6.0)	6 (0.4)	83 (2.9)
Lifetime No. of female oral sex partners (n = 2891)			
0	243 (19.1)	1462 (90.1)	1705 (59.0)
1-5	621 (48.9)	134 (8.3)	755 (26.1)
6-25	315 (24.8)	22 (1.4)	337 (11.7)
≥26	90 (7.1)	4 (0.2)	94 (3.3)
No. of new female oral sex partners in last 6 mo (n = 2917)			
0	1144 (88.3)	1606 (99.0)	2750 (94.3)
1	105 (8.1)	11 (0.7)	116 (4.0)
≥2	46 (3.6)	5 (0.3)	51 (1.7)
Lifetime No. of male sex partners (n = 2903)			
0	1175 (90.1)	175 (10.9)	1350 (46.5)
1-5	48 (3.7)	790 (49.4)	838 (28.9)
6-25	45 (3.5)	543 (34.0)	588 (20.3)
≥26	36 (2.8)	91 (5.7)	127 (4.4)
No. of new male sex partners in last 6 mo (n = 2903)			
0	1266 (96.6)	1289 (81.0)	2555 (88.0)
1	10 (0.8)	249 (15.6)	259 (8.9)
≥2	35 (2.7)	54 (3.4)	89 (3.1)
Lifetime No. of male oral sex partners (n = 1681)			
0	1216 (98.9)	249 (55.1)	1465 (87.2)
1-5	7 (0.6)	147 (32.5)	154 (9.2)
6-25	2 (0.2)	51 (11.3)	53 (3.2)
≥26	4 (0.3)	5 (1.1)	9 (0.5)
No. of new male oral sex partners in last 6 mo (n = 2858)			
0	1277 (97.0)	1373 (89.1)	2650 (92.7)
1	16 (1.2)	143 (9.3)	159 (5.6)
≥2	24 (1.8)	25 (1.6)	49 (1.7)
Sexual behavior (n = 2572)[c]			
Heterosexual	1010 (88.8)	1196 (83.4)	2206 (85.8)
Same sex	35 (3.1)	16 (1.1)	51 (2.0)
Bisexual	93 (8.2)	222 (15.5)	315 (12.2)
Self-reported HPV vaccination status (n = 3190; vaccinated)			
Vaccinated	25 (1.8)	66 (3.7)	91 (2.9)
Not vaccinated	1148 (80.7)	1269 (71.6)	2417 (75.6)
Unknown	250 (17.6)	438 (24.7)	688 (21.5)

Abbreviations: HPV, human papillomavirus; STI, sexually transmitted infection.

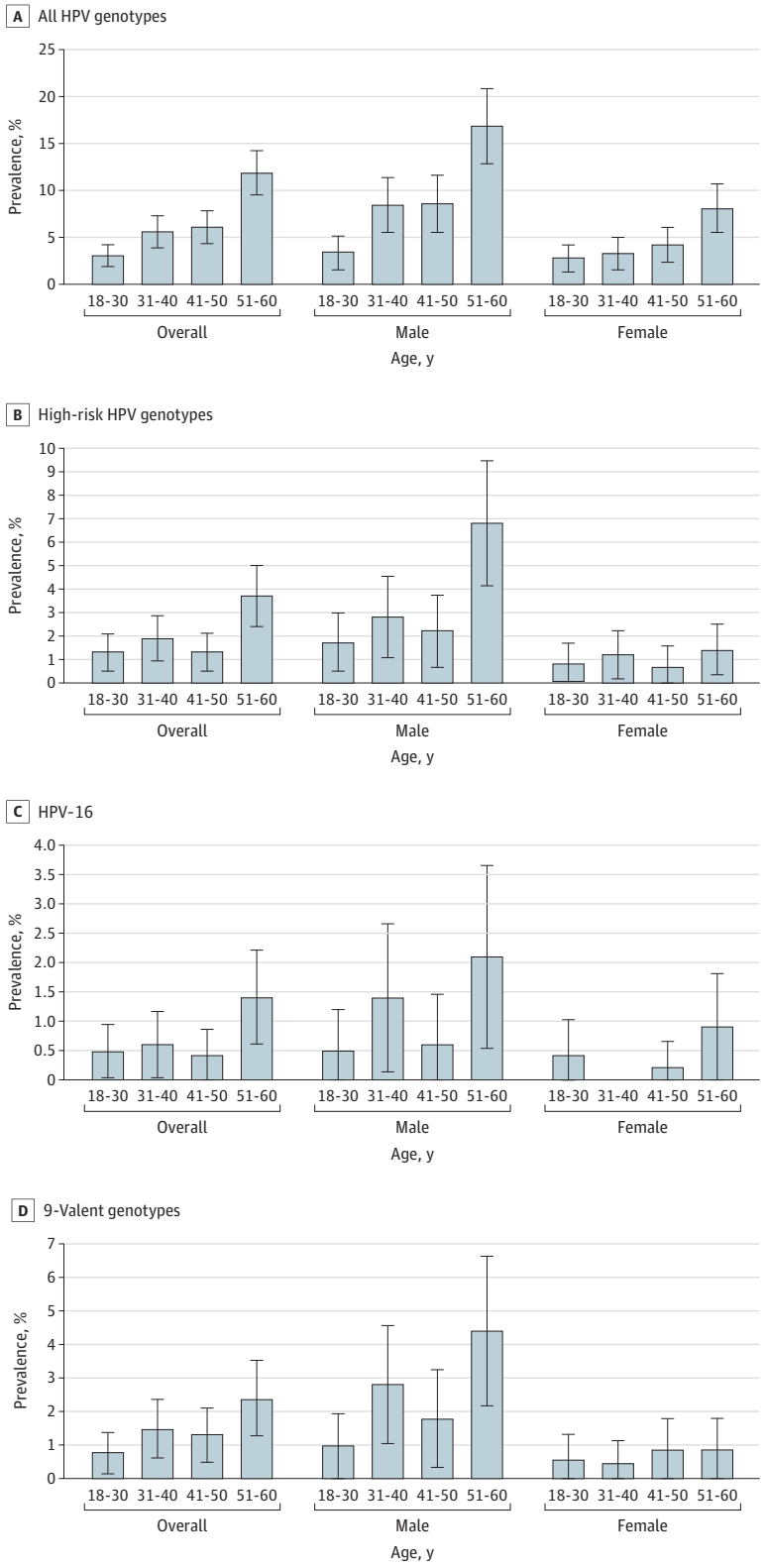
[a] If a participant reported having a blood disease, blood cancer, autoimmune disease, or HIV or if they are currently receiving corticosteroids, chemotherapy, biologic therapy, or other immunosuppressants.

[b] Data were reported by dentists after performing oral examination.

[c] Participants were classified as engaging in heterosexual behavior if they were men who reported sex with 1 or more female sex partners and 0 male sex partners in their lifetime, or if they were women who reported sex with 1 or more male sex partners and 0 female sex partners in their lifetime; participants were classified as engaging in same-sex behavior if they exclusively reported sex in their lifetime with 1 or more people of their same sex. Participants were classified as engaging in bisexual behavior if they reported sex in their lifetime with 1 or more males and 1 or more females.

Oral HPV prevalence by self-reported vaccination status is reported in eTable 1 in Supplement 1. Of the 210 prevalent infections, 5.5% (5 of 91) occurred among vaccinated participants, 7.2% (175 of 2417) among nonvaccinated participants, and 4.4% (30 of 688) among those with unknown status (difference between vaccinated and nonvaccinated, 1.8%; 95% CI, −5.0% to 5.1%). Of the 48 infections with HPV types that the 9-valent HPV vaccine is directed against, 1.1% (1 of 91) occurred among vaccinated participants, 1.6% (38 of 2417) among nonvaccinated participants, and 1.3% (9 of 688) among those with unknown status (difference between vaccinated and nonvaccinated, 0.47%; 95% CI, −0.44% to 1.6%). Of the 23

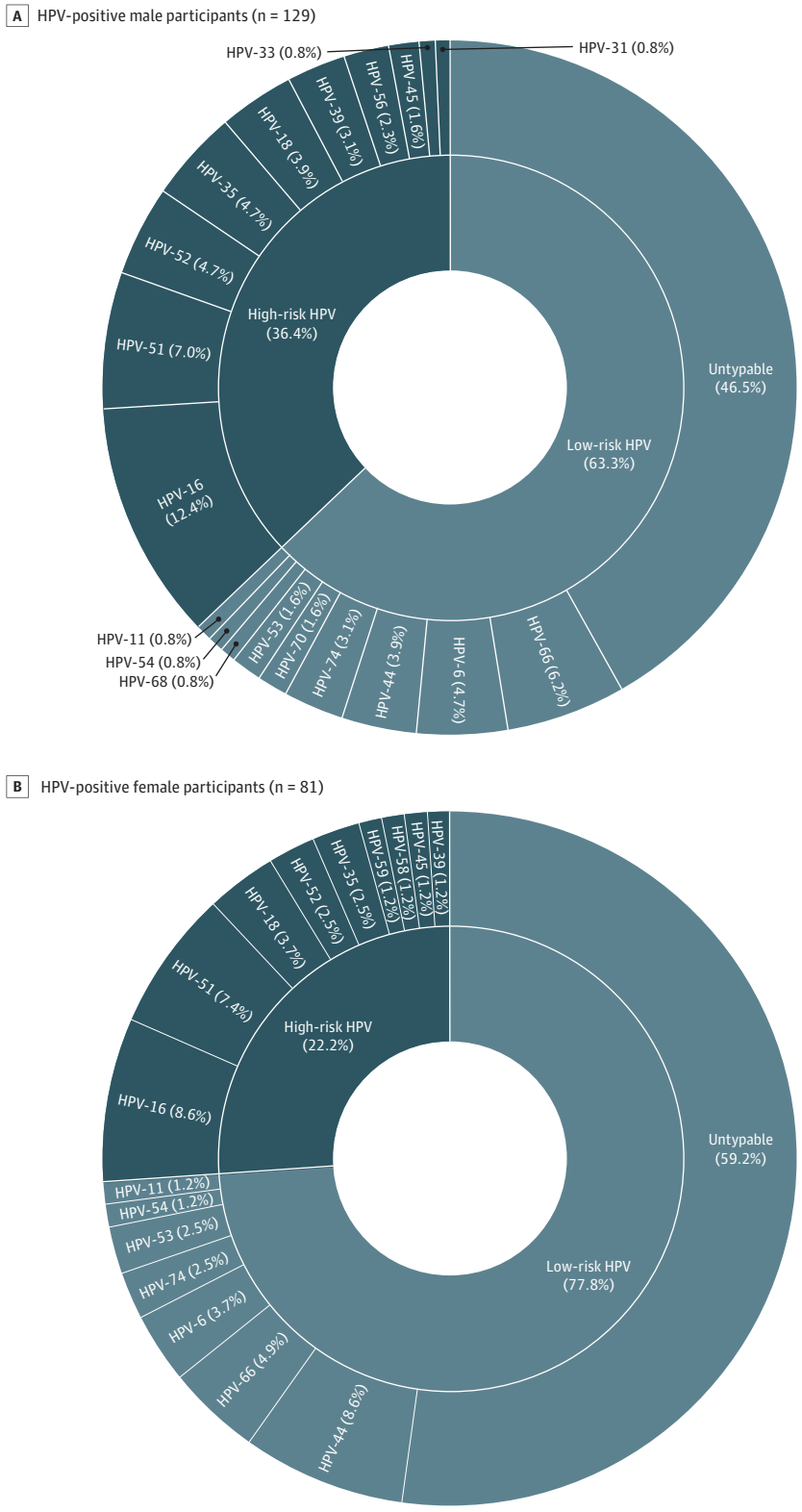
Figure 1. Prevalence of Oral Human Papillomavirus (HPV) Infection Stratified by Sex and Age



Error bars represent 95% CIs.

infections with HPV-16, 1.1% (1 of 91) occurred among vaccinated participants, 0.66% (16 of 2417) among nonvaccinated participants, and 0.87% (6 of 688) among those with unknown status.

Figure 2. Human Papillomavirus (HPV) Genotype Distribution Stratified by Sex



Oral HPV Genotype Distribution

Among men with detectable oral HPV (n = 129), HPV-16 was the most prevalent type (12.4%), followed by HPV-51 (7.0%), HPV-66 (6.2%), and HPV-52, 35, and 6 (all 4.7%; **Figure 2**). Among women with detectable oral HPV (n = 81), HPV-16 and 44 were the most prevalent types (both 8.6%), followed

by HPV-51 (7.4%), HPV-66 (4.9%), and HPV-6 and 18 (both 3.7%; Figure 2). Over one-third (36.4%) of male infections were HR, compared with 22.2% of infections among women.

Prevalence of HR and LR Oral HPV Infection by Sociodemographics, Medical History, and Risk Behaviors

Table 2 presents prevalence of HR infection by characteristic, stratified by sex. Prevalence of HR HPV in men was highest among those aged 51 to 60 years (7.5% vs 1.7%, 3.0%, and 2.3% among men aged 18-30, 31-40, and 41-50 years, respectively), heavy smokers (25.0% vs 3.1%, 3.0%, and 5.8% among never, light, and moderate pack-year smokers, respectively), those with 26 or more lifetime male sex partners (13.3% vs 2.9%, 4.5%, and 7.3% among those with 0, 1-5, and 6-25 partners, respectively), those with 26 or more lifetime female oral sex partners (5.9% vs 1.7%, 2.5%, and 5.4% among those with 0, 1-5, and 6-25 partners, respectively), and those who reported bisexual behavior (9.6% vs 3.3% and 3.1% of men reporting heterosexual sex and same-sex behavior, respectively). Prevalence of HR HPV among women was highest among those engaging in same-sex behavior (6.2% compared with 1.4% and 0.7% reporting bisexual and heterosexual sex, respectively). Prevalence did not vary substantially by other characteristics among women, which may be due to the small number of women with oral HR HPV detected.

Prevalence of LR HPV infection in men (eTable 2 in Supplement 1) was highest among those aged 51 to 60 years (10.7% vs 1.7%, 5.8%, and 6.6% among men aged 18-30, 31-40, and 41-50 years, respectively), heavy smokers (30.8% vs 5.0%, 7.4%, and 13.5% among never, light, and moderate smokers, respectively), those with present periodontitis/gingivitis (8.3% vs 5.0%), those with recent STI diagnosis (19.4% vs 5.2%), those with 26 or more lifetime male sex partners (18.8% vs 5.3%, 8.6%, and 9.5% among men with 0, 1-5, and 6-25 partners, respectively), and 1 or more male oral sex partners in the last 6 months (25.0% vs 4.5% and 5.8% among those with 0 or ≥2 partners, respectively). Prevalence of LR HPV infection in women was highest among those aged 51 to 60 years (6.8% vs 1.9%, 2.1%, and 3.5% among women aged 18-30, 31-40, and 41-50 years, respectively), heavy smokers (40.0% vs 3.4%, 3.0%, and 24.0% among never, light, and moderate smokers, respectively), those with a recent STI diagnosis (9.8% vs 3.3%), those with gingivitis/periodontitis (6.2% vs 2.9%), and those with 26 or more male sex partners (8.9% vs 2.9%, 2.9%, and 3.7% among women with 0, 1-5, and 6-25 partners, respectively).

In multivariable analyses, HR oral infection (**Table 3**) was associated with male sex (AOR, 3.1; 95% CI, 1.2-8.5), age 51 to 60 years (AOR, 3.3; 95% CI, 1.5-7.3), 26 or more lifetime male sex partners (AOR, 6.5; 95% CI, 2.3-18.7), and 6 to 25 female oral sex partners in the past 6 months (AOR, 3.4; 95% CI, 1.3-8.7). Low-risk oral infection was associated with male sex (AOR, 2.0; 95% CI, 1.1-4.7), ages 31 to 40, 41 to 50, and 51 to 60 years (AOR, 2.1; 95% CI, 1.1-4.1; AOR, 2.4; 95% CI, 1.3-4.7; AOR, 4.5; 95% CI, 2.5-8.3, respectively), moderate smoking (AOR, 2.3; 95% CI, 1.1-5.2), 26 or more lifetime male sex partners (AOR, 2.4; 95% CI, 1.1-5.2), and recent STI diagnosis (AOR, 2.9; 95% CI, 1.5-5.5).

Discussion

Among 3196 US adults attending dental clinics for routine care, 6.6% had a prevalent oral HPV infection, and 2.0% had a prevalent HR HPV infection. Oral HR HPV prevalence was 3-fold higher among men compared with women, and prevalence with types found in the 9-valent HPV vaccine was 3.5-fold higher among men compared with women. The most frequently detected genotype among both men and women was HPV-16, similar to other reports,[15] accounting for 12.4% of all infections among men and 8.6% of infections among women. The high oral HPV prevalence observed in this study among men, combined with increasing incidence of HPV-related OPC among men, highlights the need to increase HPV prevention efforts focused on men. Prophylactic HPV vaccination can protect against infection with vaccine-covered HPV types[16] and holds promise for reversing rising OPC incidence among men in the long term. In addition to the diagnosis and treatment of HPV-related OPC, otolaryngologists and HNC oncologists can play an important role in prevention through educating clinicians across all specialties regarding HPV and OPC and educating patients, families, and the public on prevention of HPV-associated OPC, including lifestyle modification, reducing high-risk sexual behavior, and consideration of vaccination.

Oral HPV prevalence increased with older age among men, with the highest prevalence observed among those aged 51 to 60 years for HR, LR, 9-valent-HPV vaccine types, and HPV-16. Participants aged 51 to 60 years had 3.5- and 5-times higher odds of HR and LR infection, respectively. Higher prevalence of oral HPV among older adults has been previously reported and may be due to increased HPV exposure, infection and/or persistence with age, potential loss of immune control, and/or reactivation of latent HPV infections.[9,17] Recent studies have also reported that median age at diagnosis for HPV-related OPC is increasing,[18,19] and that among patients 65 years and older, the proportion of HPV-related OPC increased from 41% during 1995 to 2000 to 75% during 2007 to 2013.[19] Reasons behind this trend are not fully understood, but it is therefore not surprising to observe an increased prevalence of oral HPV infection in middle-aged and older men, as HPV predates OPC occurrence. The survival benefit conferred by an HPV-positive tumor status appears to endure with increasing age at diagnosis, though attenuated compared with younger patients with HPV OPC.[19,20] Older men do not qualify for HPV vaccination. For this reason, studies will need to address OPC prevention, screening, and management of middle-aged and older patients, particularly men.

Measures of sexual activity were strongly associated with HR oral infection, as has been previously reported.[9] Participants with a high number of male sex partners and female oral sex partners had 6.5-fold and 3.2-fold increased odds of HR infection. We found previous STI diagnosis to be significantly associated with LR infection but not HR infection. Other studies have reported associations between STI and any oral HPV

Table 2. Prevalence of High-Risk (HR) Oral HPV Infection[a] by Demographics, Medical History, Smoking History, and Sexual Characteristics for Men and Women

Characteristic	Men			Women		
	HR HPV positive, No. (%)[b] (n = 47)	HPV negative, No. (%)[b] (n = 1294)	Effect size (95% CI)	HR HPV positive, No. (%)[b] (n = 18)	HPV negative, No. (%)[b] (n = 1692)	Effect size (95% CI)
Race						
Asian	1 (0.8)	125 (99.2)	0.34 (0.01 to 0.68)[c]	1 (0.6)	153 (99.4)	−0.14 (−0.63 to 0.34)[c]
Black or African American	4 (3.6)	107 (96.4)		1 (0.7)	142 (99.3)	
Native Hawaiian or Other Pacific Islander	0	7 (100)		0	3 (100)	
White	37 (4.1)	875 (95.9)		12 (1.0)	1153 (99.0)	
Other/more than 1 race	2 (1.9)	103 (98.1)		3 (3.0)	98 (97.0)	
Hispanic						
No	42 (3.8)	1073 (96.2)	0.15 (0.02 to 1.11)[d]	12 (0.9)	1334 (99.1)	0.46 (0.16 to 1.29)[d]
Yes	1 (0.6)	172 (99.4)		5 (1.9)	252 (98.1)	
Age, y						
18-30	7 (1.7)	392 (98.2)	0.12 (0.07 to 0.19)[e]	4 (0.8)	459 (99.1)	0.03 (0.01 to 0.09)[e]
31-40	10 (3.0)	322 (96.9)		5 (1.1)	414 (98.8)	
41-50	7 (2.3)	297 (97.6)		3 (0.7)	412 (99.2)	
51-60	23 (7.5)	283 (92.4)		6 (1.4)	407 (98.5)	
Education level						
<12th Grade	11 (3.5)	304 (96.5)	0.00 (0.01 to 0.08)[e]	1 (0.3)	297 (99.6)	0.06 (0.02 to 0.12)[e]
Some college	8 (3.3)	232 (96.7)		7 (2.1)	321 (97.8)	
College graduate	25 (3.4)	711 (96.6)		9 (0.9)	969 (99.1)	
Marital status						
Single, divorced, separated, widowed	20 (3.7)	518 (96.3)	1.20 (0.67 to 2.15)[d]	7 (1.0)	642 (98.9)	1.08 (0.99 to 1.01)[d]
Married or cohabiting	24 (3.1)	749 (96.9)		10 (0.9)	992 (99.0)	
Smoking status						
Nonsmoker	27 (3.0)	860 (96.9)	−0.16 (−0.44 to 0.12)[c]	12 (0.9)	1237 (99.0)	−0.06 (−0.58 to 0.46)[c]
Ex-smoker	8 (3.2)	240 (96.7)		3 (1.3)	223 (98.6)	
Current smoker	8 (5.4)	140 (94.6)		1 (0.7)	128 (99.2)	
Cigarette pack-years						
Never smoker (0 pack-years)	28 (3.1)	871 (96.8)	0.12 (0.03 to 0.26)[e]	12 (0.9)	1246 (99.0)	0.02 (NA)[e]
Light (>0-20 pack-years)	10 (3.0)	323 (96.9)		4 (1.2)	316 (98.7)	
Moderate (>20-40 pack- years)	2 (5.8)	32 (94.1)		0	19 (100)	
Heavy (>40 pack-years)	3 (25.0)	9 (75.0)		0	3 (100)	
Lifetime marijuana use						
No	10 (2.1)	461 (97.8)	1.93 (0.96 to 3.88)[d]	4 (0.5)	741 (99.4)	0.38 (0.12 to 1.18)[d]
Yes	33 (4.1)	772 (95.9)		12 (1.4)	840 (98.5)	
Alcohol consumption during the last 30 d						
None	10 (2.4)	393 (97.5)	0.04 (0.01 to 0.13)[e]	6 (1.0)	551 (98.9)	0.02 (0.01 to 0.09)[e]
Low	17 (2.8)	570 (97.1)		5 (0.6)	740 (99.3)	
High	5 (5.3)	89 (94.7)		1 (1.2)	82 (98.7)	
No. of missing teeth[f]						
<4	17 (3.0)	541 (96.9)	1.26 (0.70 to 2.26)[d]	8 (1.1)	661 (98.8)	1.00 (0.99 to 1.01)[d]
≥4	30 (3.8)	752 (96.2)		10 (0.9)	1026 (99.0)	
Presence of periodontitis or gingivitis[f]						
No	30 (3.0)	952 (96.9)	1.02 (0.99 to 1.04)[d]	12 (0.8)	1358 (99.1)	0.49 (0.18 to 1.29)[d]
Yes	17 (4.7)	341 (95.3)		6 (1.7)	329 (98.2)	
Diagnosed with STI in past 6 mo						
No	41 (3.2)	1204 (96.7)	0.44 (0.17 to 1.29)[d]	15 (0.9)	1565 (99.0)	0.53 (0.07 to 3.95)[d]
Yes	4 (7.4)	50 (92.6)		1 (1.7)	55 (98.2)	

(continued)

Table 2. Prevalence of High-Risk (HR) Oral HPV Infection[a] by Demographics, Medical History, Smoking History, and Sexual Characteristics for Men and Women (continued)

Characteristic	Men			Women		
	HR HPV positive, No. (%)[b] (n = 47)	HPV negative, No. (%)[b] (n = 1294)	Effect size (95% CI)	HR HPV positive, No. (%)[b] (n = 18)	HPV negative, No. (%)[b] (n = 1692)	Effect size (95% CI)
Lifetime No. of female sex partners						
0	2 (1.2)	159 (98.7)	0.09 (0.04 to 0.15)[e]	12 (0.9)	1314 (99.0)	0.03 (NA)[e]
1-5	12 (2.5)	464 (97.4)		3 (1.5)	190 (98.4)	
6-25	17 (4.2)	386 (95.7)		1 (2.5)	38 (97.4)	
≥26	11 (6.5)	157 (93.5)		0	5 (100)	
No. of new female sex partners last 6 mo						
0	29 (3.0)	915 (96.9)	0.09 (0.04 to 0.16)[e]	16 (1.0)	1517 (98.9)	0.01 (NA)[e]
1	13 (6.9)	174 (93.0)		0	23 (100)	
≥2	0	75 (100.0)		0	5 (100)	
Lifetime No. of female oral sex partners						
0	4 (1.7)	226 (98.2)	0.09 (0.04 to 0.16)[e]	14 (0.9)	1394 (99.0)	0.04 (NA)[e]
1-5	15 (2.5)	571 (97.4)		3 (2.2)	129 (97.7)	
6-25	16 (5.4)	278 (94.5)		0	20 (100)	
≥26	5 (5.9)	80 (94.1)		0	4 (100)	
No. of new female oral sex partners last 6 mo						
0	34 (3.1)	1042 (96.8)	0.05 (0.01 to 0.13)[e]	17 (1.0)	1532 (98.9)	0.01 (NA)[e]
1	5 (5.1)	93 (94.8)		0	11 (100)	
≥2	3 (6.7)	42 (93.3)		0	4 (100)	
Lifetime No. of male sex partners						
0	33 (2.9)	1081 (97)	0.10 (0.03 to 0.22)[e]	4 (2.4)	166 (97.6)	0.05 (0.02 to 0.13)[e]
1-5	2 (4.5)	42 (95.4)		6 (0.8)	761 (99.2)	
6-25	3 (7.3)	38 (92.6)		5 (0.9)	518 (99)	
≥26	4 (13.3)	26 (86.7)		2 (2.4)	81 (97.5)	
No. of new male sex partners last 6 mo						
0	40 (3.3)	1155 (96.7)	0.03 (0.01 to 0.11)[e]	16 (1.2)	1230 (98.7)	0.04 (0.02 to 0.06)[e]
1	0 (0.0)	8 (100.0)		1 (0.4)	238 (99.5)	
≥2	2 (6.3)	30 (93.8)		0	51 (100)	
Lifetime No. of male oral sex partners						
0	35 (3.0)	1117 (97.0)	0.02 (NA)[e]	4 (1.6)	240 (98.3)	0.09 (NA)[e]
1-5	0	7 (100)		0	141 (100)	
6-25	0	2 (100)		0	50 (100)	
≥26	0	4 (100)		0	5 (100)	
No. of new male oral sex partners last 6 mo						
0	39 (3.2)	1166 (96.7)	0.05 (0.02 to 0.15)[e]	16 (1.2)	1309 (98.7)	0.02 (0.01 to 0.04)[e]
1	0	12 (100)		1 (0.7)	138 (99.2)	
≥2	2 (8.7)	21 (91.3)		0	24 (100)	
Sexual behavior[g]						
Heterosexual	32 (3.3)	923 (96.6)	−0.42 (−0.73 to −0.12)[c]	9 (0.7)	1142 (99.2)	−0.34 (−0.82 to 0.14)[c]
Same sex	1 (3.1)	31 (96.8)		1 (6.2)	15 (93.7)	
Bisexual	8 (9.6)	75 (90.4)		3 (1.4)	213 (98.6)	

Abbreviations: HR, high-risk; NA, not applicable; STI, sexually transmitted infection.

[a] High-risk genotypes include genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.

[b] Percentage indicates the row percentage. Percentages may not sum to 100% because of rounding.

[c] Effect size measure is Goodman and Kruskal γ.

[d] Effect size measure is relative risk.

[e] Effect size measure is Cramer V; variables with NA CI are due to cell sizes less than 1.

[f] Data were reported by dentists after performing oral examination.

[g] Participants were classified as engaging in heterosexual behavior if they were men who reported sex with 1 or more female sex partners and 0 male sex partners in their lifetime, or if they were women who reported sex with 1 or more male sex partners and 0 female sex partners in their lifetime; participants were classified as engaging in same-sex behavior if they exclusively reported sex in their lifetime with 1 or more people of their same sex. Participants were classified as engaging in bisexual behavior if they reported sex in their lifetime with 1 or more males and 1 or more females.

infection[17,21]; more research is needed to explore if STI diagnosis is associated with HR infection in other populations. Additionally, women engaging in same-sex behavior had approximately 9 times the HR HPV prevalence compared with heterosexual women (6.2% vs 0.7%), and among men, those who had bisexual sex had the highest oral HR and LRHPV prevalence. Findings suggest that sexual minority populations may be at increased risk for oral HPV and represent a population at increased risk of developing OPC that should be prioritized in HPV prevention interventions. Despite this risk, there is a substantial literature gap related to how oral HPV risk may differ by sexual orientation and necessitates further research.

Our study uniquely identified associations between oral HPV infection and oral health indicators and found that LR infection was more prevalent among those with periodontitis, but the CI width prevents making definitive conclusions regarding the strength of the association. A key strength of our analysis was the use of oral health data obtained by dental examination. While the link between oral health and oral HPV has not been fully elucidated, possible explanations include that poor oral hygiene induces viral replication of HPV in the oral cavity[22] and that inflammatory periodontal tissue may increase the probability for exposed basal cells to become infected with HPV.[23] Associations between oral health and oral HPV infection are mixed in the literature, necessitating further research. This is particularly important in the US, where periodontitis is a common disorder affecting greater than 40% of US adults,[24] and periodontitis has been shown to be associated with increased risk of HNC.[25]

Higher prevalence of HR and LR HPV was found among tobacco smokers, which is consistent with other reports.[9] Notably, 25% of male heavy smokers had a prevalent HR infection, 30.8% had an LR infection, and 40% of female heavy smokers had an LR infection. Tobacco use was independently associated with LR but not HR oral infection; future research should investigate whether this trend exists in other populations. Although the biologic link responsible for increased prevalence of oral HPV in smokers has not been fully defined, the rationale lies in the local oral/oropharyngeal mucosal proinflammatory milieu and the immune suppression induced by tobacco use, which reduces capacity for the clearance of oncogenic HPV infection.[26]

Almost half of infections in men and 60% of infections detected in women were untypable, which reflect genotypes beyond the 25 detected by the SPF10 LiPA25 algorithm.[13] This proportion is higher than what has been reported in the anogenitals in other healthy populations.[27] Untypable infections most likely are LR,[14] but more research is needed to explore the relationship between untypable HPV infection and the risk of OPC and other HNCs.

Limitations

Findings must be interpreted considering limitations. While prevalence data were stratified by sex in bivariate analyses, it was not possible to create separate multivariable models by sex due to relatively small numbers of HR and LR infection detected (65 HR and 145 LR). Dentists collected self-reported HPV vaccination data, which were not verified by

Table 3. Sociodemographic and Behavioral Characteristics Associated With HR and LR Oral HPV Infection[a]

Characteristic	OR (95% CI)	AOR (95% CI)
HR oral HPV infection		
Sex		
Female	1 [Reference]	1 [Reference]
Male	3.4 (2.0-5.9)	3.1 (1.2-8.5)
Age, y		
18-30	1 [Reference]	1 [Reference]
31-40	1.6 (0.7-3.5)	1.4 (0.6-3.4)
41-50	1.1 (0.5-2.6)	0.9 (0.4-2.5)
51-60	3.3 (1.6-6.6)	3.3 (1.5-7.3)
Cigarette pack-years		
Never smoker (0 pack-years)	1 [Reference]	1 [Reference]
Light (>0-20 pack-years)	1.2 (0.6-2.2)	0.7 (0.4-1.4)
Moderate (>20-40 pack-years)	2.1 (0.5-8.8)	1.0 (0.2-4.7)
Heavy (>40 pack-years)	13.2 (3.6-48.7)	3.9 (0.9-16.3)
No. of male partners lifetime		
0	1 [Reference]	1 [Reference]
1-5	0.3 (0.2-0.7)	1.7 (0.6-5.0)
6-25	0.5 (0.2-1.1)	2.5 (0.9-7.3)
≥26	1.9 (0.8-4.6)	6.5 (2.3-18.7)
No. of lifetime female oral sex partners		
0	1 [Reference]	1 [Reference]
1-5	2.3 (1.2-4.5)	1.8 (0.7-4.3)
6-25	4.8 (2.4-9.6)	3.4 (1.3-8.7)
≥26	5.4 (1.9-14.8)	3.2 (0.9-11.3)
LR oral HPV infection		
Sex		
Female	1 [Reference]	1 [Reference]
Male	1.7 (1.2-2.4)	2.0 (1.1-4.7)
Age, y		
18-30	1 [Reference]	1 [Reference]
31-40	2.1 (1.1-3.9)	2.1 (1.1-4.1)
41-50	2.7 (1.5-4.9)	2.4 (1.3-4.7)
51-60	4.9 (2.8-8.6)	4.5 (2.5-8.3)
Cigarette pack-years		
Never smoker (0 pack-years)	1 [Reference]	1 [Reference]
Light (>0-20 pack-years)	1.3 (0.9-2.0)	0.9 (0.6-1.5)
Moderate (>20-40 pack-years)	5.1 (2.6-10.1)	2.3 (1.1-5.2)
Heavy (>40 pack-years)	11.8 (4.3-32.1)	2.7 (0.8-9.3)
Lifetime marijuana use		
No	1 [Reference]	1 [Reference]
Yes	1.6 (1.1-2.2)	1.5 (0.9-2.3)
Lifetime No. of male partners		
0	1 [Reference]	1 [Reference]
1-5	0.6 (0.4-1.0)	1.3 (0.7-2.6)
6-25	0.8 (0.5-1.3)	1.3 (0.6-2.8)
≥26	2.5 (1.3-4.6)	2.4 (1.1-5.2)
Diagnosed with STI in past 6 mo		
No	1 [Reference]	1 [Reference]
Yes	4.0 (2.3-6.7)	2.9 (1.5-5.5)
Presence of periodontal disease and/or gingivitis		
No	1 [Reference]	1 [Reference]
Yes	2.0 (1.4-2.8)	1.3 (0.9-1.9)

Abbreviations: AOR, adjusted odds ratio; HPV, human papillomavirus; HR, high-risk; LR, low-risk; OR, odds ratio; STI, sexually transmitted infection.

[a] High-risk genotypes include genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59; low-risk genotypes include genotypes 11, 34, 40, 42, 43, 44, 53, 54, 66, 68, 73, 70, 74, and untypable.

medical records. Given limitations of self-reported vaccination data, data must be interpreted with caution. The study's dental settings might introduce bias toward participants with higher socioeconomic levels because of their potential for better access to dental care.[28] Despite limitations, this study has several strengths. Our study collected data from a large sample of the US general population within 21 states spanning urban, urban cluster, and rural areas, increasing generalizability of the study. Sites used standardized protocols, and samples were analyzed at a central laboratory. We collected lifestyle and sexual behavior information from participants as well as oral health status that was ascertained and documented by dentists. Given these strengths, findings represent some of the most robust estimates of oral HPV prevalence and risk factors in the US. Findings from this study will serve as the baseline for a longitudinal study whereby participants will be followed for 24 months and tested for oral HPV at 6-month intervals to assess oral HPV incidence, clearance, and persistence.

Conclusions

In this cross-sectional study, 6.6% of participants had a prevalent oral infection of any HPV genotype, and 2.0% had a prevalent HR oral HPV infection. Findings demonstrate elevated HR oral HPV burden among older men, who may be at increased risk of developing OPC. Human papillomavirus prevention efforts are critical to prevent OPC among men in the long term. While to date the role of otolaryngologists and HNC oncologists has been primarily the treatment of HPV-related OPC, clinicians can potentially play an important role in HPV-related OPC prevention, such as through lifestyle modification, reducing high-risk sexual behavior, and consideration of vaccination.

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