HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

Cancer. 2021 April 01; 127(7): 1029–1038. doi:10.1002/cncr.33346.

TIMING, NUMBER, AND TYPE OF SEXUAL PARTNERS ASSOCIATED WITH RISK OF OROPHARYNGEAL CANCER

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Abstract

Background: Case-control studies from the early 2000s demonstrated that HPV-related oropharyngeal cancer (HPV-OPC) is a distinct entity associated with number of oral sex partners. Using contemporary data, we investigated novel risk factors (sexual debut behaviors, exposure intensity, and relationship dynamics) and serological markers on odds of HPV-OPC.

Methods: HPV-OPC patients and frequency-matched controls were enrolled in a multi-center study from 2013–2018. Participants completed a behavioral survey. Characteristics were compared using χ^2 for categorical and t-test for continuous variables. Adjusted odds ratios (aOR) were calculated using logistic regression.

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Conflicts of Interest: Dr. Waterboer serves on advisory boards for MSD (Merck Sharp & Dohme)

Results: 163 HPV-OPC cases and 345 controls were included. Lifetime number of oral sex partners was associated with significantly increased odds of HPV-OPC (>10 partners, odds ratio[OR]=4.3, 95% confidence interval[CI]=2.8–6.7). After adjustment for number of oral sex partners and smoking, younger age at first oral sex (<18 vs.>20 years, aOR=1.8, 95% CI=1.1–3.2) and oral sex intensity (>5 sex-years, aOR=2.8, 95% CI=1.1–7.5) remained associated with significantly increased odds of HPV-OPC. Type of sexual partner such as older partners when a case was younger (OR=1.7, 95% CI=1.1–2.6) or having a partner who had extramarital sex (OR=1.6, 95% CI=1.1–2.4) was associated with HPV-OPC. Seropositivity for antibodies to HPV16 E6 (OR=286, 95% CI=122–670) and any HPV16 E protein (*E1,E2,E6,E7*; OR=163, 95% CI=70–378) was associated with increased odds of HPV-OPC.

Conclusion: Number of oral sex partners remains a strong risk factor for HPV-OPC, however timing and intensity of oral sex are novel independent risk factors. These behaviors suggest additional nuances of how and why some individuals develop HPV-OPC.

Precis:

In this most comprehensive behavioral case-control study of HPV-related oropharyngeal cancer to date, ever performing oral sex and number of partners remain strong risk factors for HPV-related oropharyngeal cancer. Measures of oral sexual behavior including early age and intensity of exposure are independent risk factors, suggesting these behaviors may explain additional nuances of how and why some people develop HPV-related oropharyngeal cancer.

Keywords

Oropharyngeal neoplasms; sexual behavior; risk factors; papillomaviridae; head and neck cancer

Introduction

The epidemiology of head and neck cancer has changed dramatically in recent decades. Human papillomavirus (HPV) has driven an increase in incidence of oropharynx cancer (OPC) in the United States and other countries,[1,2] which is thought to be explained by trends in oral sexual behavior.[3] Case-control studies have demonstrated strong associations between sexual behaviors and odds of HPV-OPC.[4–9] However, these studies focused primarily on number of sexual partners without other contextual data about relationship dynamics, intensity of exposure, or order of acts at sexual debut.

It has been hypothesized, though not fully examined, that the sequence of specific sexual behaviors at debut may predispose to HPV infection.[10] Depending on site of initial mucosal exposure, serologic response may also differ.[11,12] For example, it has been posited that those whose initial exposure to HPV is through vaginal sex have a more robust immune response which decreases chances of subsequent acquisition when exposed to HPV orally. Conversely, exposure to oral HPV without the initial anogenital HPV exposure may increase the risk of oral HPV acquisition, persistence, and HPV-OPC. However, there is little such data to support these hypotheses.

Therefore, we performed a comprehensive contemporaneous examination of sexual and other novel risk factors for HPV-OPC. To better understand the role of other behavioral

factors in HPV-OPC risk, we explored differences in sexual behavior, relationship dynamics, and serologic response to HPV between cases of HPV-OPC and controls

Methods

Study Participants

Participants were enrolled in a previously described multicenter case-control study of squamous cell carcinomas called the Papillomavirus Role in Oral cancer Viral Etiology study (PROVE).[13] Briefly, cases with newly diagnosed OPC were enrolled between 2013 and 2018 at three National Comprehensive Cancer Network-designated cancer centers: the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital (JHH, Baltimore, MD), University of California San Francisco Helen Diller Family Comprehensive Cancer Center (UCSF, San Francisco, CA) and Tisch Cancer Institute at Icahn School of Medicine at Mount Sinai (MSHS, New York, NY). Cases had incident OPC and no prior history of malignancy (except skin cancer) or systemic chemotherapy. Controls were adult patients from otolaryngology clinics without a chief complaint related to cancer. Consent was obtained from all participants and the study was approved by the institutional review board at each site.

Data Collection

At enrollment, each participant completed a survey, provided a blood sample, and a tumor sample was obtained from cases. Medical record abstraction was performed. The behavioral risk survey was available in Mandarin, Spanish, and English and was administered through computer assisted self-interview (CASI) taken on either a tablet or computer. The survey included detailed questions on lifetime and recent sexual behaviors including number of partners, age of sexual initiation, type and order of sexual acts, partner dynamics, use of substances with sex, and extramarital sex. Data on demographics, substance use, and comorbidities were also collected.

Cases were centrally tested for p16 immunohistochemistry (MTM Laboratories, Heidelberg, Germany) and HPV16 E6/E7 RNA in situ hybridization (ISH; RNAscope®, Advanced Cell Diagnostics, Hayward, CA) at Johns Hopkins and interpreted by a head and neck pathologist (L.M.R.) to determine whether they were HPV-related.[12]

Specimen Testing

Serum was obtained before initiation of treatment and tested for antibodies to E6 and E7 for oncogenic HPV types 16, 18, 31, 33, 35, 45, 52, and 58 and E1, E2, E4 for HPV types 16 and 18 at the German Cancer Research Center (DKFZ, Heidelberg, Germany). In brief, multiplex serology, an antibody detection method based on glutathione S-transferase (GST) capture ELISA was used in combination with fluorescent bead-based technology.[14,15] Each antibody response was considered seropositive or seronegative based upon standardized cutoff values for median fluorescence intensity (MFI).[16]

Medical record abstraction was performed at the time of diagnosis for tumor site, tumor stage, and nodal stage using American Joint Committee on Cancer (AJCC) 7th edition,[17]

with additional abstraction later to record primary treatment modality. Data were stored using RedCap (Vanderbilt University, Nashville, TN).

Analysis

This analysis was restricted to HPV-positive cases who answered the "ever" oral sex survey question (97% included) and controls frequency-matched by age (decade of age), sex, race (White Non-Hispanic [NH], Black NH, Hispanic, Asian/Pacific Islander, Other/Multiracial), and study site. HPV-positivity was defined as being p16-positive and ISH-positive (RNA and/or DNA). For this analysis, all available matched controls who answered the survey question on whether they ever performed oral sex were included. Characteristics of cases and matched controls were compared using χ^2 for categorical and t-test for continuous variables. Odds ratios (OR) and 95% confidence intervals were calculated using conditional logistic regression. Multivariable models were performed adjusting for tobacco use (pack-years) and number of lifetime oral sex partners (categorical) to understand the independent effect of other sexual risk factors after these two known risk factors were controlled for, and adjusted OR (aOR) was reported. Similar adjusted models were run adjusting for lifetime number of vaginal sex partners instead of oral sex partners to understand the impact of oral sex specifically separate from general sexual exposure.

Variables were evaluated as both continuous and categorical variables, and alternative cutoffs were examined for categorical variables to explore dose response and ensure consistency of result regardless of selected cutoff (results not shown). Intensity of exposure was illustrated by sex-years, a novel metric defined as number of partners per ten years since sexual debut,[18] analogous to how pack-years describes tobacco history and drink-years characterizes alcohol use.[19] Never smoking was defined as <1 pack-year. Statistical significance was defined when the two-sided p-value was less than 0.05. The analysis was performed using STATA version 15.1 (College Station, TX).

Results

The study population consisted of 163 incident HPV-OPC cases and 345 matched controls with similar demographic characteristics (Table 1). The majority were male, 50–69 years of age, currently married or living with a partner, and identified as heterosexual. Cases were more likely to have a history of sexually transmitted infection than controls (p=0.003).

Sexual Behaviors

Differences in sexual behaviors between cases and controls are shown in Table 2. Oral sex timing, number, and intensity of partners were each associated with the diagnosis of HPV-OPC. HPV-related OPC cases were more likely than controls to have ever performed oral sex (98.8% vs. 90.4%, p<0.001) and to have performed oral sex at the time of sexual debut (Figure 1A; 33.3% in cases vs. 21.4% in controls, p=0.004; OR 1.8, 95% CI 1.2–2.8). Age of first performing oral sex was significantly younger among HPV-OPC cases than controls (Figure 1B; <18 years vs. >20 years, 37.4% vs. 22.6%, p<0.001; OR 3.1, 95% CI 2.0–5.0). Number of lifetime oral sex partners was higher among those with HPV-OPC (Figure 1C; >10 partners, 44.8% vs. 19.1%, p<0.001; OR 4.3, 95% CI 2.8–6.7). Intensity of oral sexual

exposure, measured by sex-years (number of partners per ten years) was significantly higher among cases than controls (Figure 1D; >5 sex-years, 30.8% vs. 11.1%, p<0.001, OR 5.6, 95% CI 3.3–9.6). After adjustment for lifetime number of oral sex partners and tobacco use (pack-years), ever performing oral sex (aOR 4.4, 95% CI 1.1–18.9), early age of first oral sex encounter (<18 years vs. >20 years, aOR 1.8, 95% CI 1.1–3.2) and oral sex intensity (>5 oral sex-years, aOR 2.8, 95% CI 1.1–7.5) each remained significantly associated with increased odds of HPV-OPC.

Other sexual behaviors were also associated with diagnosis of HPV-OPC. Odds of HPV-OPC increased with higher number of lifetime vaginal sex partners and deep kissing partners (each p<0.001, Table 2). Number of vaginal sex-years was also associated with HPV-OPC (p<0.001). Both number of vaginal sex partners and vaginal sex-years were associated with HPV-OPC after adjustment for smoking (pack-years) and number of lifetime oral sex partners. Models that adjusted for number of vaginal sex partners showed the associations with oral sexual behaviors all remained significant and were not explained by number of vaginal sex partners.

We examined odds of HPV-OPC in terms of relationship dynamics and characterized partner type. Increased number of casual sex partners was associated with odds of HPV-OPC (Figure 2A; >10 casual partners, 37.5% vs. 24.6%, p<0.001; OR 3.0, 95% CI 1.8–5.1). Extramarital sex (Figure 2B; 43.9% vs. 36.0%, p=0.002; OR 1.6, 95% CI 1.1–2.4) and suspicion that a partner had extramarital sex (10.8% vs. 4.2%, p=0.002; OR 3.4, 95% CI 1.6–7.5) were each associated with increased odds of HPV-OPC. Increased odds of HPV-OPC were also observed for those who had a sexual partner at least ten years older when the participant was younger than age 23 (Figure 2C; 30.0% vs. 20.0%, p=0.01; OR 1.7, 95% CI=1.1–2.6). Once number of lifetime oral sex partners and smoking were included in the model, only suspicion of extramarital sex remained associated with HPV-OPC. Associations were similar when explored only among men or only among women (Supplemental Table 3), although there was insufficient power to explore the associations among women due to limited numbers.

Substance Use

Substance use was also examined. There was no association between ever or current cigarette use, alcohol use, pack-years of smoking, or drink-years and odds of HPV-OPC (Table 3). Some types of drug use were associated with increased odds of HPV-OPC including ever marijuana use (p=0.001), ever cocaine use (p=0.01) and joint-years of smoking marijuana (p=0.01). However, after adjustment for oral sex behaviors, these associations did not remain significant.

Serum Biomarkers

HPV serum antibodies were compared among cases and controls (Table 4). Seropositivity for HPV16 E6 was extremely common among cases (93.6%) and rare among controls (6.4%). HPV16 E6 seropositivity (OR 286, 95% CI 122–670) and seropositivity for any HPV16 E protein (E1, E2, E6, or E7; OR 163, 95% CI 70–378) were associated with a 280-

fold and 160-fold increase in odds of HPV-OPC, respectively. HPV16 L1 antibodies were associated with a 34-fold increase in odds of HPV-OPC (OR 34, 95% CI 18–60).

Next, the number of HPV types individuals were seropositive to were considered for anti-E6, E7, and L1 (Table 4). In addition to the strong association of HPV16 E6 seropositivity, overall odds increased with E6 seropositivity to number of HPV types (1–2 vs. 0 types, OR 118, 95% CI 52–265) and had further increased odds of HPV-OPC in those with ≥3 vs. 0 types (OR 1020, 95% CI 123–8436). Similarly, odds of HPV-OPC increased with number of HPV types seropositive for anti-E7 (≥3 vs. 0 types, OR 712, 95% CI 95–5301) and anti-L1 antibodies (≥3 vs. 0 types, OR 14 95% CI 8–25).

HPV16 E6 Seropositive Controls

Of interest, there were 9 controls with HPV16 E6 seropositivity. Reflective of all the controls, a majority were male (n=7, 77.8%) and non-Hispanic white (n=7, 77.8%), with a median age of 59 years (IQR 54.6–65). They presented for otologic or laryngological evaluation and none had any known past or current medical history of any HPV-related cancer (anal, cervical, or penile). One reported a non-melanoma skin cancer. Compared to HPV16 E6 seronegative controls, these participants reported statistically similar sexual behaviors.

Discussion

HPV-related oropharyngeal cancer is now widely recognized as a distinct disease entity.[1,7,20,21] Since the time HPV was first suggested as having a causal role in OPC, several case-control studies have pointed to sexual behavior, specifically oral sexual behavior[10,22–24] as a risk factor for this malignancy. While lifetime number of oral sex partners, a surrogate for oral exposure[5] to HPV, is known to be associated with risk for HPV-OPC, this is the first study to demonstrate that other contextual factors such as the timing and intensity of oral sex are also associated with diagnosis of HPV-OPC. These findings underscore the importance of oral sex as a risk factor for HPV-OPC and that the association between oral sex and HPV-OPC is independent of general sexual exposure.

Younger age at oral sex debut is independently associated with increased odds of HPV-OPC. While early oral sex debut may be a surrogate for either riskier sexual behavior or higher lifetime potential exposure to HPV, it remained significant after adjusting for total number of both oral and vaginal sex partners, suggesting early oral sex may be capturing a different aspect of risk. Changing behavioral norms have shifted the population average toward an earlier age of sexual debut,[25] and younger generations are more likely to perform oral sex at sexual debut.[3] The finding that earlier age of oral sex may increase odds of HPV-OPC suggests this societal change in behavior could be one reason for the increasing incidence of HPV-OPC.[26]

The finding that timing of oral sexual behavior is associated with HPV-OPC led us to investigate other variables at sexual initiation, specifically order of acts at sexual debut. This is the first study to examine sequence of acts at sexual debut and association with risk of HPV-OPC. It has previously been speculated that order of sexual acts at debut might in part

explain increasing HPV-OPC rates,[10] but there has been no data to support this hypothesis. The rationale underlying this hypothesis is that first genital exposure to HPV results in a robust immune response, generating sufficient immunity when HPV is introduced orally. We found that cases were more likely to have performed oral sex at debut. Conversely, controls were more likely to have performed solely vaginal sex as first sexual act. Our behavioral data therefore support the theory that when first exposure to HPV is via oral mucosa without preceding genital exposure, a weaker immune response is produced and infection is more likely to persist.[10,11]

Another potential component of HPV-OPC risk described in this analysis is a novel measure of sexual intensity (measured by sex-years, a calculation of the number of oral sex partners per 10 years across different ages).[18] Similar to how pack-years describes tobacco history and drink-years characterizes alcohol use,[19] the new metric of sex-years characterizes cumulative sexual exposure over time as a surrogate for potential exposure to HPV. Our data suggest that higher concentration and intensity of partner exposure is an independent predictor of HPV-OPC risk, as evidenced by an association of increased sex-years with HPV-OPC even after adjusting for number of oral sex partners.

This paper also illustrates, to our knowledge for the first time, that partner behaviors and relationship dynamics may influence risk of HPV-OPC development. Cases of HPV-OPC were more likely to report history of casual partners and extramarital sex, similar to what has been reported in cervical cancer.[27,28] These findings also support the concept of sexual networks, which have been investigated in HIV and infectious disease epidemiological studies.[29] A sexual network is a collection of dyads linked by sexual contact who share a similar risk profile for social and behavioral norms.[30] Although this data may be colored by recall bias, it suggests that an individual's risk of HPV-OPC is impacted by not just their own practices, but by their partner's behaviors and exposures.

Age-disparate relationships have also been associated with risk of cervical cancer,[31] HIV infection,[32] and other sexually transmitted infections.[33] An increased risk of HPV-OPC was observed in those who had a significantly older sexual partner at a young age. This finding may reflect the hypothetically broader viral exposure burden which the older partner shares with the younger partner. It may also be a surrogate for power imbalance in a relationship or non-consensual sex, although the association was no longer significant after adjustment for number of vaginal sex partners.

Previous studies have found an independent association between marijuana and HPV-OPC.[8,20,34] In this analysis, marijuana use was associated with HPV-OPC in univariate analysis, but after adjustment this association was lost, consistent with other studies.[35–39] The inconsistent data concerning marijuana and its association with HPV-OPC highlights the potential confounding between drug use and sexual practices[34,40] and the evolving trends of casual marijuana use.[41–43]

Consistent with prior literature, seropositivity for antibodies to early HPV16 oncoproteins E6 and E7 was associated with diagnosis of HPV-OPC. E6 oncoprotein seroprevalence in this study was similar to other studies,[24,44,45] although some prospective cohort studies

reported lower seroprevalence.[16,46] While the presence of E1, E2, and E4 have been reported in a prospective cohort,[47] in this case-control analysis we evaluate the breadth of early oncoproteins. A combined biomarker consisting of anti-HPV16 E1, E2, E6 and E7 antibodies has been previously suggested as a marker for HPV-OPC risk,[47] and our findings would support this; almost all cases were positive for HPV16 E1, E2, E6, or E7. However, 10% of controls were seropositive to at least one E protein, suggesting low specificity for this combined biomarker.

Seropositivity for HPV16 E6 has high specificity for HPV-OPC, and seroprevalence is rare in individuals without cancer.[48,49] Prior studies have reported HPV16 E6/E7 seroprevalence rates from <1%[16,49] to 4%[5] in non-cancer controls. While HPV16 L1 seroconversion occurs soon after infection and denotes past exposure, development of E6/E7 antibodies occurs after initiation of carcinogenesis and therefore indicates conversion to a malignant state.[50] The HPV16 E6 seroprevalence observed in nine controls is therefore notable, and may herald later diagnosis with HPV-OPC or another HPV-driven malignancy (anal cancer).[49]

This report is the first to show that seropositivity for increasing number of distinct HPV types is associated with greater risk of HPV-OPC. We also examined the composition of HPV types in those who were seropositive for antibodies to more than one HPV E6 type. Seropositivity for HPV16 and HPV33 anti-E6 together was common, and antibodies to these two HPV types were identified together in 81.7% of cases. However, the antibody cross-reactivity of phylogenetically-related HPV types likely explains these findings[47,51,52] as it is rare that multiple infections cause HPV-OPC (<5%).[53] HPV16 drives 85–90% of HPV-OPC, [53–55] while HPV33 is responsible for 3–5% of cases.[56,57] The association we see with increasing number of HPV types and HPV-OPC diagnosis may rather reflect the antibody levels of the causative HPV type which thereby increases risk of cross-reactivity.

This study has strengths and limitations. This is a multi-institutional study with frequency-matched controls, centrally tested HPV tumor and blood biomarkers, and detailed behavioral data collected via a confidential computer assisted self interview (CASI). As with all self-reported behaviors, we cannot rule out the potential for recall bias or misreporting.

Even with this limitation, this data adds novel context and depth to our understanding of HPV-OPC. As HPV-OPC incidence in the United States continues to rise,[58] these findings have important public health implications and inform epidemiological understanding of head and neck cancer. While this detailed contextual understanding of HPV-OPC risk does not have direct implications for current disease detection or screening, we illustrate the complexity of the association between sexual practices and risk of oropharyngeal cancer, and these novel risk factors may contribute to identification of cohorts enriched for oral HPV.[59]

Conclusion

In conclusion, this study provides the most comprehensive behavioral picture of HPV-related oropharyngeal cancer to date. Ever performing oral sex and number of partners remain strong risk factors for HPV-OPC. Measures of sexual behavior including timing (age) of oral

sex and intensity of exposure (partners per 10 years) are independent risk factors for HPV-OPC, suggesting these behaviors may explain additional nuances of how and why some people develop HPV-OPC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

National Institute of Dental and Craniofacial Research (P50 DE019032) and the National Institute on Deafness and Other Communication Disorders (1K23DC014758)

References:

1. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol Off J Am Soc Clin Oncol. 2011;29(32):4294–4301. doi:10.1200/JCO.2011.36.4596
2. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(36):4550–4559. doi:10.1200/JCO.2013.50.3870
3. D'Souza G, Cullen K, Bowie J, Thorpe R, Fakhry C. Differences in oral sexual behaviors by gender, age, and race explain observed differences in prevalence of oral human papillomavirus infection. PloS One. 2014;9(1):e86023. doi:10.1371/journal.pone.0086023 [PubMed: 24475067]
4. Chen F, Yan L, Liu F, et al. Oral human papillomavirus infection, sexual behaviors and risk of oral squamous cell carcinoma in southeast of China: A case-control study. J Clin Virol. 2016;85:7–12. doi:10.1016/j.jcv.2016.10.011 [PubMed: 27788480]
5. D'Souza G, Kreimer AR, Viscidi R, et al. Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer. N Engl J Med. 2007;356(19):1944–1956. doi:10.1056/NEJMoa065497 [PubMed: 17494927]
6. Farsi NJ, El-Zein M, Gaied H, et al. Sexual behaviours and head and neck cancer: A systematic review and meta-analysis. Cancer Epidemiol. 2015;39(6):1036–1046. doi:10.1016/j.canep.2015.08.010 [PubMed: 26372414]
7. Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst. 2008;100(6):407–420. doi:10.1093/jnci/djn025 [PubMed: 18334711]
8. Heck JE, Berthiller J, Vaccarella S, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol. 2010;39(1):166–181. doi:10.1093/ije/dyp350 [PubMed: 20022926]
9. Laprise C, Madathil SA, Schlecht NF, et al. Increased risk of oropharyngeal cancers mediated by oral human papillomavirus infection: Results from a Canadian study. Head Neck. 2019;41(3):678–685. doi:10.1002/hed.25436 [PubMed: 30605251]
10. Rettig E, Kiess AP, Fakhry C. The role of sexual behavior in head and neck cancer: implications for prevention and therapy. Expert Rev Anticancer Ther. 2015;15(1):35–49. doi:10.1586/14737140.2015.957189 [PubMed: 25193346]
11. Lu B, Viscidi RP, Wu Y, et al. Seroprevalence of Human Papillomavirus (HPV) Type 6 and 16 Vary by Anatomic Site of HPV Infection in Men. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2012;21(9):1542–1546. doi:10.1158/1055-9965.EPI-12-0483
12. Windon MJ, Waterboer T, Hillel AT, et al. Sex differences in HPV immunity among adults without cancer. Hum Vaccines Immunother. 2019;15(7–8):1935–1941. doi:10.1080/21645515.2019.1568157

13. D'Souza G, Westra WH, Wang SJ, et al. Differences in the Prevalence of Human Papillomavirus (HPV) in Head and Neck Squamous Cell Cancers by Sex, Race, Anatomic Tumor Site, and HPV Detection Method. JAMA Oncol. 2017;3(2):169–177. doi:10.1001/jamaoncol.2016.3067 [PubMed: 27930766]
14. Holzinger D, Wichmann G, Baboci L, et al. Sensitivity and specificity of antibodies against HPV16 E6 and other early proteins for the detection of HPV16-driven oropharyngeal squamous cell carcinoma. Int J Cancer. 2017;140(12):2748–2757. doi:10.1002/ijc.30697 [PubMed: 28316084]
15. Waterboer T, Sehr P, Michael KM, et al. Multiplex human papillomavirus serology based on in situ-purified glutathione s-transferase fusion proteins. Clin Chem. 2005;51(10):1845–1853. doi:10.1373/clinchem.2005.052381 [PubMed: 16099939]
16. Kreimer AR, Johansson M, Waterboer T, et al. Evaluation of Human Papillomavirus Antibodies and Risk of Subsequent Head and Neck Cancer. J Clin Oncol. 2013;31(21):2708–2715. doi:10.1200/JCO.2012.47.2738 [PubMed: 23775966]
17. Fleming ID. AJCC Cancer Staging Manual. Fifth Edition. Lippincott-Raven; 1997. https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC5thEdCancerStagingManual.pdf
18. Fakhry C, Waterboer T, Westra WH, et al. Distinct biomarker and behavioral profiles of human papillomavirus-related oropharynx cancer patients by age. Oral Oncol. 2020;101:104522. doi:10.1016/j.oraloncology.2019.104522 [PubMed: 31881446]
19. Anantharaman D, Abedi-Ardekani B, Beachler DC, et al. Geographic heterogeneity in the prevalence of human papillomavirus in head and neck cancer. Int J Cancer. 2017;140(9):1968–1975. doi:10.1002/ijc.30608 [PubMed: 28108990]
20. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst. 2000;92(9):709–720. doi:10.1093/jnci/92.9.709 [PubMed: 10793107]
21. van Houten VMM, Snijders PJF, van den Brekel MWM, et al. Biological evidence that human papillomaviruses are etiologically involved in a subgroup of head and neck squamous cell carcinomas. Int J Cancer. 2001;93(2):232–235. doi:10.1002/ijc.1313 [PubMed: 11410871]
22. Chancellor JA, Ioannides SJ, Elwood JM. Oral and oropharyngeal cancer and the role of sexual behaviour: a systematic review. Community Dent Oral Epidemiol. 2017;45(1):20–34. doi:10.1111/cdoe.12255 [PubMed: 27642003]
23. Schnelle C, Whiteman DC, Porceddu SV, Panizza BJ, Antonsson A. Past sexual behaviors and risks of oropharyngeal squamous cell carcinoma: a case-case comparison. Int J Cancer. 2017;140(5):1027–1034. doi:10.1002/ijc.30519 [PubMed: 27859177]
24. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med. 2007;356(19):1944–1956. doi:10.1056/NEJMoa065497 [PubMed: 17494927]
25. Finer LB. Trends in premarital sex in the United States, 1954–2003. Public Health Rep Wash DC 1974. 2007;122(1):73–78. doi:10.1177/003335490712200110
26. Wittekindt C, Wagner S, Bushnak A, et al. Increasing Incidence rates of Oropharyngeal Squamous Cell Carcinoma in Germany and Significance of Disease Burden Attributed to Human Papillomavirus. Cancer Prev Res Phila Pa. 2019;12(6):375–382. doi:10.1158/1940-6207.CAPR-19-0098
27. Biswas LN, Manna B, Maiti PK, Sengupta S. Sexual risk factors for cervical cancer among rural Indian women: a case-control study. Int J Epidemiol. 1997;26(3):491–495. doi:10.1093/ije/26.3.491 [PubMed: 9222772]
28. Franceschi S, Plummer M, Clifford G, et al. Differences in the risk of cervical cancer and human papillomavirus infection by education level. Br J Cancer. 2009;101(5):865–870. doi:10.1038/sj.bjc.6605224 [PubMed: 19654578]
29. Hickson DA, Mena LA, Wilton L, et al. Sexual Networks, Dyadic Characteristics, and HIV Acquisition and Transmission Behaviors Among Black Men Who Have Sex With Men in 6 US Cities. Am J Epidemiol. 2017;185(9):786–800. doi:10.1093/aje/kww144 [PubMed: 28402405]

30. Amirkhanian YA. Social Networks, Sexual Networks and HIV Risk in Men Who Have Sex with Men. Curr HIV/AIDS Rep. 2014;11(1):81–92. doi:10.1007/s11904-013-0194-4 [PubMed: 24384832]

31. Baussano I, Diaz M, Tully S, et al. Effect of age-difference between heterosexual partners on risk of cervical cancer and human papillomavirus infection. Papillomavirus Res. 2017;3:98–104. doi:10.1016/j.pvr.2017.03.003 [PubMed: 28720465]

32. Gregson S, Nyamukapa CA, Garnett GP, et al. Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. Lancet Lond Engl. 2002;359(9321):1896–1903. doi:10.1016/S0140-6736(02)08780-9

33. Begley E, Crosby RA, DiClemente RJ, Wingood GM, Rose E. Older partners and STD prevalence among pregnant African American teens. Sex Transm Dis. 2003;30(3):211–213. doi:10.1097/00007435-200303000-00006 [PubMed: 12616137]

34. Marks MA, Chaturvedi AK, Kelsey K, et al. Association of marijuana smoking with oropharyngeal and oral tongue cancers: Pooled analysis from the INHANCE Consortium. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2014;23(1):160–171. doi:10.1158/1055-9965.EPI-13-0181

35. Berthiller J, Amy Lee Y, Boffetta P, et al. Marijuana smoking and the risk of head and neck cancer: pooled analysis in the INHANCE Consortium. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2009;18(5):1544–1551. doi:10.1158/1055-9965.EPI-08-0845

36. Hashibe M, Morgenstern H, Cui Y, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2006;15(10):1829–1834. doi:10.1158/1055-9965.EPI-06-0330

37. Llewellyn CD, Johnson NW, Warnakulasuriya KA. Risk factors for squamous cell carcinoma of the oral cavity in young people--a comprehensive literature review. Oral Oncol. 2001;37(5):401–418. doi:10.1016/s1368-8375(00)00135-4 [PubMed: 11377229]

38. Rosenblatt KA, Daling JR, Chen C, Sherman KJ, Schwartz SM. Marijuana use and risk of oral squamous cell carcinoma. Cancer Res. 2004;64(11):4049–4054. doi:10.1158/0008-5472.CAN-03-3425 [PubMed: 15173020]

39. Sidney S, Quesenberry CP, Friedman GD, Tekawa IS. Marijuana use and cancer incidence (California, United States). Cancer Causes Control CCC. 1997;8(5):722–728. doi:10.1023/a:1018427320658 [PubMed: 9328194]

40. Parks KA, Collins RL, Derrick JL. The influence of marijuana and alcohol use on condom use behavior: findings from a sample of young adult female bar drinkers. Psychol Addict Behav J Soc Psychol Addict Behav. 2012;26(4):888–894. doi:10.1037/a0028166

41. Grucza RA, Agrawal A, Krauss MJ, Cavazos-Rehg PA, Bierut LJ. Recent Trends in the Prevalence of Marijuana Use and Associated Disorders in the United States. JAMA Psychiatry. 2016;73(3):300–301. doi:10.1001/jamapsychiatry.2015.3111 [PubMed: 26864618]

42. Hasin DS. US Epidemiology of Cannabis Use and Associated Problems. Neuropsychopharmacology. 2018;43(1):195–212. doi:10.1038/npp.2017.198 [PubMed: 28853439]

43. Miech R, Koester S. Trends in U.S., Past-Year Marijuana Use from 1985–2009; An Age-Period-Cohort Analysis. Drug Alcohol Depend. 2012;124(3):259–267. doi:10.1016/j.drugalcdep.2012.01.020 [PubMed: 22361212]

44. Holzinger D, Wichmann G, Baboci L, et al. Sensitivity and specificity of antibodies against HPV16 E6 and other early proteins for the detection of HPV16-driven oropharyngeal squamous cell carcinoma. Int J Cancer. 2017;140(12):2748–2757. doi:10.1002/ijc.30697 [PubMed: 28316084]

45. Lang Kuhs KA, Kreimer AR, Trivedi S, et al. Human papillomavirus 16 E6 antibodies are sensitive for human papillomavirus-driven oropharyngeal cancer and are associated with recurrence. Cancer. 2017;123(22):4382–4390. doi:10.1002/cncr.30966 [PubMed: 28950407]

46. Kreimer AR, Johansson M, Yanik EL, et al. Kinetics of the Human Papillomavirus Type 16 E6 Antibody Response Prior to Oropharyngeal Cancer. J Natl Cancer Inst. 2017;109(8). doi:10.1093/jnci/djx005

47. Zhang Y, Waterboer T, Haddad RI, et al. Human papillomavirus (HPV) 16 antibodies at diagnosis of HPV-related oropharyngeal cancer and antibody trajectories after treatment. Oral Oncol. 2017;67:77–82. doi:10.1016/j.oraloncology.2017.02.004 [PubMed: 28351584]
48. Kreimer AR, Johansson M, Waterboer T, et al. Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(21):2708–2715. doi:10.1200/JCO.2012.47.2738
49. Lang Kuhs KA, Anantharaman D, Waterboer T, et al. Human Papillomavirus 16 E6 Antibodies in Individuals Without Diagnosed Cancer: A Pooled Analysis. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2015;24(4):683–689. doi:10.1158/1055-9965.EPI-14-1217
50. Kreimer AR, Brennan P, Lang Kuhs KA, et al. Human papillomavirus antibodies and future risk of anogenital cancer: a nested case-control study in the European prospective investigation into cancer and nutrition study. J Clin Oncol Off J Am Soc Clin Oncol. 2015;33(8):877–884. doi:10.1200/JCO.2014.57.8435
51. Michael KM, Waterboer T, Sehr P, et al. Seroprevalence of 34 Human Papillomavirus Types in the German General Population. PLoS Pathog. 2008;4(6). doi:10.1371/journal.ppat.1000091
52. Combes J-D, Pawlita M, Waterboer T, et al. Antibodies against high-risk human papillomavirus proteins as markers for invasive cervical cancer. Int J Cancer. 2014;135(10):2453–2461. doi:10.1002/ijc.28888 [PubMed: 24729277]
53. Ndiaye C, Mena M, Alemany L, et al. HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. Lancet Oncol. 2014;15(12):1319–1331. doi:10.1016/S1470-2045(14)70471-1 [PubMed: 25439690]
54. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 2017;141(4):664–670. doi:10.1002/ijc.30716 [PubMed: 28369882]
55. Walline HM, Komarck C, McHugh JB, et al. High-risk human papillomavirus detection in oropharyngeal, nasopharyngeal, and, oral cavity cancers: Comparison of multiple methods. JAMA Otolaryngol-- Head Neck Surg. 2013;139(12):1320–1327. doi:10.1001/jamaoto.2013.5460 [PubMed: 24177760]
56. Carlander A-LF, Larsen CG, Jensen DH, et al. Continuing rise in oropharyngeal cancer in a high HPV prevalence area: A Danish population-based study from 2011 to 2014. Eur J Cancer. 2017;70:75–82. doi:10.1016/j.ejca.2016.10.015 [PubMed: 27888679]
57. Schache AG, Powell NG, Cuschieri KS, et al. HPV-Related Oropharynx Cancer in the United Kingdom: An Evolution in the Understanding of Disease Etiology. Cancer Res. 2016;76(22):6598–6606. doi:10.1158/0008-5472.CAN-16-0633 [PubMed: 27569214]
58. Dyne EAV. Trends in Human Papillomavirus–Associated Cancers — United States, 1999–2015. MMWR Morb Mortal Wkly Rep. 2018;67. doi:10.15585/mmwr.mm6733a2
59. D'Souza G, McNeel TS, Fakhry C. Understanding personal risk of oropharyngeal cancer: risk-groups for oncogenic oral HPV infection and oropharyngeal cancer. Ann Oncol Off J Eur Soc Med Oncol. 2017;28(12):3065–3069. doi:10.1093/annonc/mdx535

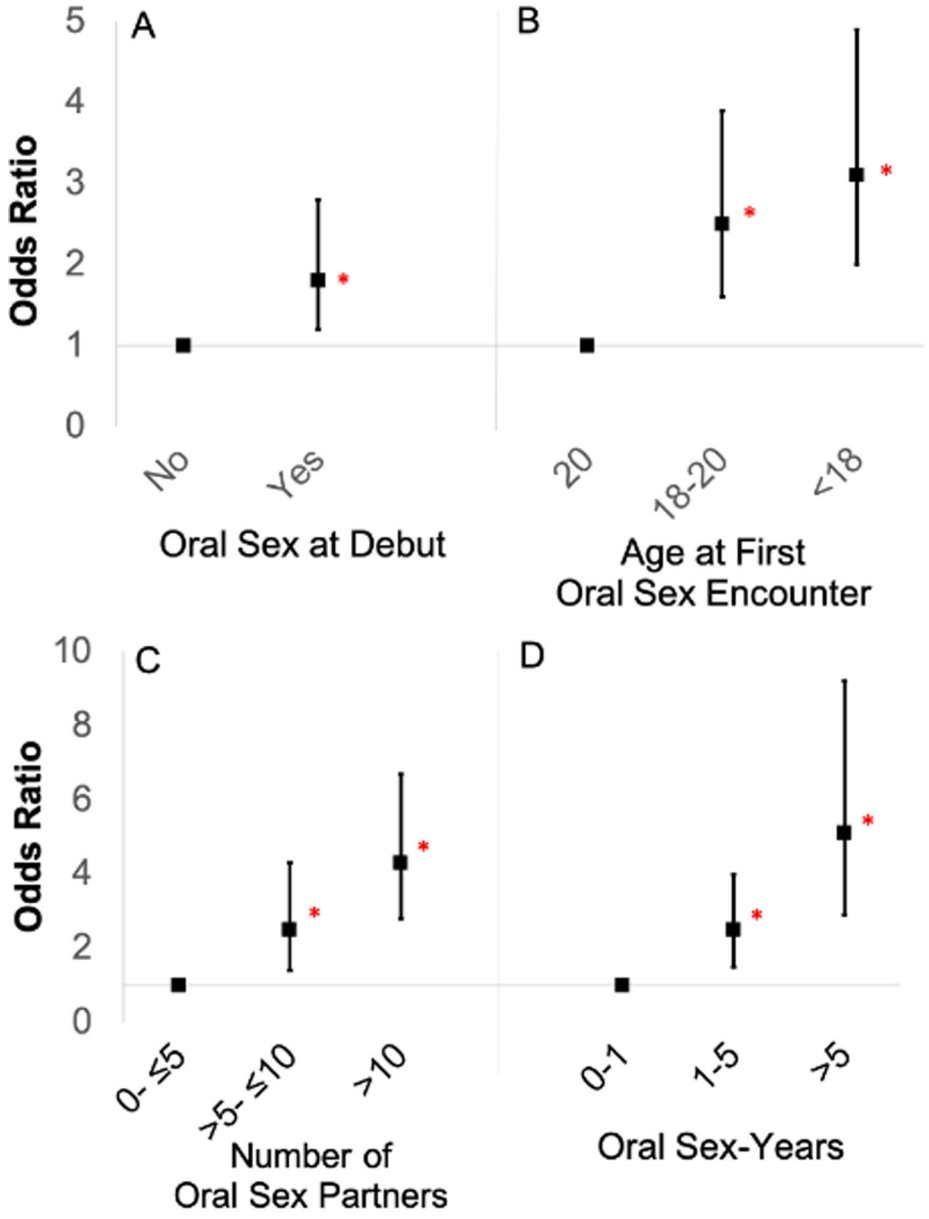

Figure 1:

Black squares represent unadjusted odds ratios of HPV-OPC for case subjects versus controls. Vertical lines represent 95% confidence intervals. Red asterisks represent statistical significance. Odds ratios and 95% confidence intervals were derived from conditional logistic regression analysis for case-control comparison. **A:** Odds of HPV-OPC if a participant reported performing oral sex at sexual debut. **B:** Dose-response relationship for age of first oral sex encounter. **C:** Dose-response relationship of number for people performed oral sex on in lifetime. **D:** Dose-response relationship for oral sex-years, a measure of intensity of oral sexual partners defined as number of partners performed oral sex on per ten years since sexual debut.

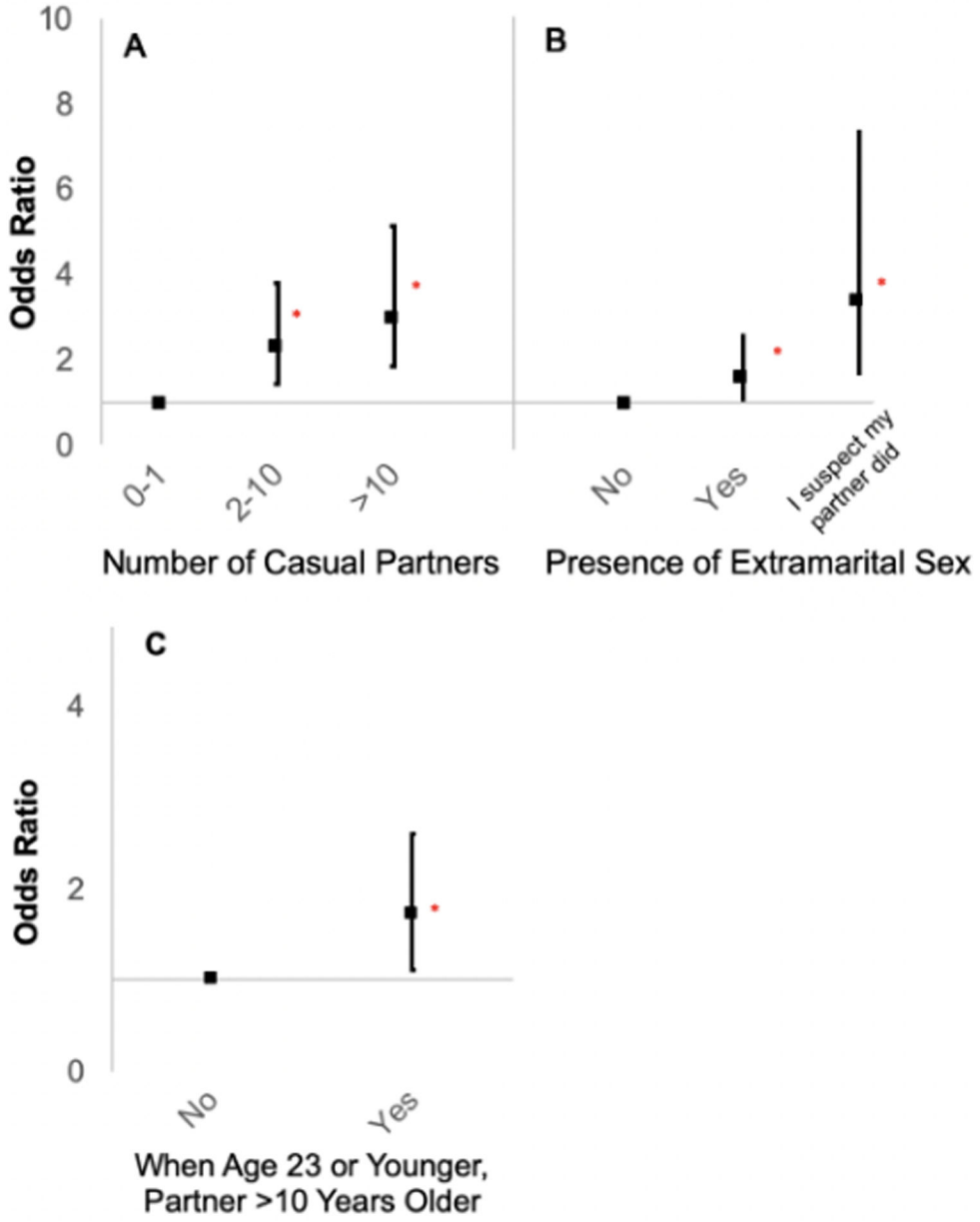

Figure 2:

Black squares represent unadjusted odds ratios of HPV-OPC for case subjects versus controls. Vertical lines represent 95% confidence intervals. Red asterisks represent statistical significance. Odds ratios and 95% confidence intervals were derived from conditional logistic regression analysis for case-control comparison. **A:** Dose-response relationship of number of casual sex partners and risk of HPV-OPC. **B:** Odds of HPV-OPC by presence or suspicion of extramarital sex **C:** Odds of HPV-OPC when a participant reported having a sexual partner greater than 10 years older when they were under 23 years old

Table 1:

Baseline demographics for HPV-OPC cases and controls

Characteristic	Cases	Controls	p-value
	n=163	n=345	
Sex			0.36
Male	85.3%	82.0%	
Female	14.7%	18.0%	
Age group			0.10
18–29	0.6%	0.3%	
30–39	1.8%	1.5%	
40–49	15.9%	10.1%	
50–59	38.7%	31.6%	
60–69	33.1%	39.4%	
70–79	7.4%	14.2%	
80–89	2.5%	2.9%	
Race			0.65
Non-Hispanic White	87.1%	85.5%	
Non-Hispanic Black	6.1%	8.4%	
Other	6.8%	6.1%	
Study site			0.14
JHU	68.0%	76.0%	
UCSF	16.0%	13.3%	
MSHS	16.0%	10.7%	
Currently married or living with a partner			0.57
No	22.7%	25.0%	
Yes	77.3%	75.0%	
Income			0.74
<$15,000	5.3%	2.9%	
$15,000–49,999	10.6%	12.2%	
$50,000–99,999	27.2%	28.0%	
$100,000–199,999	36.4%	37.6%	
>$200,000	20.5%	19.3%	
Highest degree			0.35
No High school	4.3%	2.3%	
High school	17.2%	15.1%	
Some college	19.0%	18.3%	
College	34.4%	31.1%	
Graduate	25.1%	33.2%	
Sexual orientation			0.34
Heterosexual	95.7%	93.6%	
Homosexual/Bisexual/Other/Not sure	4.3%	6.4%	
History of sexually transmitted infection			**0.003**

Characteristic	Cases	Controls	p-value
	n=163	**n=345**	
No	73.3%	84.5%	
Yes	26.7%	15.5%	

Abbreviations: JHU, Johns Hopkins University, UCSF, University of California; MSHS, Mount Sinai Health System

Bolding indicates statistical significance.

Table 2:

Sexual behavior of HPV-OPC cases vs. controls 1

Characteristic	Cases	Controls	p-value	OR (95%CI)	aOR (95% CI)*
Oral Sex Behaviors	**n=163**	**n=345**			
Ever performed oral sex			**<0.001**		
No	1.2%	9.6%		Ref	Ref
Yes	98.8%	90.4%		**8.5 (2.0–35.9)**	**4.4 (1.1–18.9)**
Oral sex at debut			**0.004**		
No	66.7%	78.6%		Ref	Ref
Yes	33.3%	21.4%		**1.8 (1.2–2.8)**	1.4 (0.9–2.2)
Age at first oral sex encounter (years)			**<0.001**		
>20	26.48%	50.1%		Ref	Ref
18–20	36.2%	27.3%		**2.5 (1.6–4.0)**	**2.1 (1.3–3.5)**
<18	37.4%	22.6%		**3.1 (2.0–5.0)**	**1.8 (1.1–3.2)**
Oral sex partners			**<0.001**		
0-≤5	36.2%	66.7%		Ref	N/A
>5-≤10	19.0%	14.2%		**2.5 (1.4–4.3)**	
>10	44.8%	19.1%		**4.3 (2.8–6.7)**	
Oral Sex-Years *(# partners/10 years since sexual debut)*			**<0.001**		
0–1	27.8%	56.1%		Ref	Ref
>1–5	41.4%	32.9%		**2.5 (1.6–4.0)**	1.7 (0.8–3.5)
>5	30.8%	11.1%		**5.6 (3.3–9.6)**	**2.8 (1.1–7.5)**
Other Sexual Behaviors					
Vaginal sex at debut			**0.003**		
No	34.6%	22.0%		Ref	Ref
Yes	65.4%	78.0%		**0.5 (0.4–0.8)**	0.7 (0.5–1.2)
Vaginal sex partners			**<0.001**		
0-≤5	17.2%	46.5%		Ref	Ref
>5-≤10	20.4%	20.4%		**2.7 (1.5–4.9)**	**2.7 (1.4–5.2)**
>10	62.4%	33.2%		**5.1 (3.1–8.3)**	**3.2 (1.7–6.0)**
Vaginal sex-years*(# partners/10 years since sexual debut)*			**<0.001**		
0–1	9.6%	36.1%		Ref	Ref
>1–5	46.5%	46.1%		**3.8 (2.1–7.0)**	**3.5 (1.8–6.8)**
>5	44.0%	17.8%		**9.3 (4.9–17.6)**	**5.7 (2.6–12.5)**
Deep kissing partners			**<0.001**		
0-≤5	9.3%	28.3%		Ref	Ref
>5-≤10	15.5%	25.7%		1.8 (0.9–3.7)	1.7 (0.8–3.5)
>10	75.2%	46.0%		**4.9 (2.7–9.0)**	**2.6 (1.3–5.3)**
Casual partners			**<0.001**		
0–1	19.4%	38.6%		Ref	Ref
2–10	43.1%	36.8%		**2.3 (1.4–3.8)**	1.6 (1.0–2.8)

Characteristic	Cases	Controls	p-value	OR (95%CI)	aOR (95% CI)*
Oral Sex Behaviors	**n=163**	**n=345**			
>10	37.5%	24.6%		**3.0 (1.8–5.1)**	1.2 (0.6–2.2)
Relationship Dynamics					
Extramarital sex by either partner			**0.002**		
No	45.3%	59.8%		Ref	Ref
Yes	43.9%	36.0%		**1.6 (1.1–2.4)**	1.0 (0.6–1.5)
I suspect my partner did	10.8%	4.2%		**3.4 (1.6–7.5)**	**3.6 (1.6–8.3)**
When <age 23, had partner >10 years older			**0.01**		
No	70.0%	80.0%		Ref	Ref
Yes	30%	20.0%		**1.7 (1.1–2.6)**	1.1 (0.7–1.8)

*Adjusted for number of lifetime oral sex partners and pack-years of smoking

Abbreviations: OR, odds ratio; aOR, adjusted odds ratio; Ref, reference group

Bolding indicates statistical significance with p<0.05.

Table 3:

Comparison of substance use among HPV-OPC cases and controls

	Prevalence				
Characteristic	**Cases**	**Controls**	**p-value**	**OR (95%CI)**	**aOR (95%CI)***
Ever Substance Use	**n=163**	**n=345**			
Cigarette Smoking			0.19		
Never	54.5%	60.7%		Ref	Ref
Ever	45.5%	39.3%		1.3 (0.8–1.9)	1.2 (0.8–1.8)
Current Smoking			0.77		
No	92.6%	93.3%		Ref	Ref
Yes	7.4%	6.7%		1.1 (0.5–2.4)	1.0 (0.4–6.7)
Alcohol Use			0.51		
Never	2.2%	3.3%		Ref	Ref
Ever	97.8%	96.7%		1.5 (0.4–5.6)	1.5 (0.4–5.7)
Marijuana Use			**0.001**		
Never	23.3%	37.5%		Ref	Ref
Ever	76.7%	62.5%		**2.0 (1.3–3.0)**	1.4 (0.9–2.2)
Cocaine Use			**0.01**		
Never	70.1%	79.9%		Ref	Ref
Ever	29.9%	20.1%		**1.7 (1.1–2.6)**	1.2 (0.8–2.0)
Intensity of Substance Use					
Pack-years of smokers			0.42		
0-<1	54.5%	60.7%		Ref	Ref
1-<10	14.1%	11.8%		1.3 (0.7–2.4)	1.2 (0.6–2.2)
10+	31.4%	27.5%		1.3 (0.8–2.0)	1.2 (0.8–1.9)
Drink-years			0.69		
0	2.6%	2.9%		Ref	Ref
>0-<10	8.0%	6.7%		1.9 (0.4–8.1)	1.8 (0.4–8.4)
10+	90.1%	90.4%		1.6 (0.4–5.8)	1.5 (0.4–6.0)
Joint-years of marijuana			**0.01**		
0	50.7%	69.7%		Ref	Ref
>0-<10	12.0%	8.7%		1.9 0.8–4.7)	1.2 (0.4–3.1)
10+	37.3%	21.6%		**2.4 (1.3–4.3)**	1.6 (0.8–3.1)

*Adjusted for number of lifetime oral sex partners

Abbreviations: OR, odds ratio; aOR, adjusted odds ratio; Ref, reference group

Bolding indicates statistical significance.

Table 4:

HPV seroprevalence and odds of HPV-OPC among cases and controls

Antibody Seroprevalence	Cases n=146	Controls n=304	p-value	OR (95% CI)
HPV16 E6			**<0.001**	
Negative	4.8%	95.2%		Ref
Positive	93.6%	6.4%		**286 (122–670**)
HPV16 E7			**<0.001**	
Negative	30.1%	93.1%		Ref
Positive	69.9%	6.9%		**31 (18–55)**
Any HPV 16 E protein (E1, E2, E6, E7)			**<0.001**	
Negative	4.8%	89.1%		Ref
Positive	95.2%	10.9%		**163 (70–378)**
HPV 16 L1			**<0.001**	
Negative	30.8%	93.8%		Ref
Positive	69.2%	6.3%		**34 (18–60)**
Number of HPV types seropositive for:				
Number seropositive for E6			**<0.001**	
0	5.5%	89.4%		Ref
1–2	74.0%	10.2%		**118 (52–265)**
≥3	20.6%	0.3%		**1020 (123–8436)**
Number seropositive for E7			**<0.001**	
0	21.2%	84.5%		Ref
1–2	19.9%	15.1%		**5.2 (2.8–9.5)**
≥3	58.9%	0.3%		**712 (95–5301)**
Number seropositive for L1			**<0.001**	
0	26.0%	74.3%		Ref
1–2	31.5%	17.1%		**5.3 (3.1–8.9)**
≥3	42.5%	8.6%		**14 (8–25)**

Abbreviations: OR, odds ratio; aOR, adjusted odds ratio; Ref, reference group; HPV, human papillomavirus

Bolding indicates statistical significance.