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Modifiable Risk Behaviors in Head and Neck Cancer Patients

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Abstract

Background—Use of tobacco products, excessive alcohol consumption, and high-risk sexual behaviors increase the risk of developing head and neck cancer and impacts treatment effectiveness after diagnosis. We examined smoking and engagement in other modifiable behavioral risk factors and human papillomavirus (HPV) status in head and neck cancer patients in order to facilitate identification and foster development of targeted interventions in high risk patients.

Methods—Participants were 102 head and neck cancer patients at a large urban cancer center who completed a self-report background and health questionnaire and provided a saliva sample for determination of the long-acting nicotine metabolite cotinine.

Results—Compared with former and never smokers, current smokers were less educated, less likely to be married or living with a partner and consumed more alcohol. Cotinine analysis indicated that four of sixteen (25%) patients who denied past-month cigarette use misrepresented their true smoking status. Of patients with oropharyngeal cancer, 74% were confirmed as HPV-positive, and compared with HPV-negative patients, they were younger, more likely to be married/partnered and of Caucasian race, and reported more past vaginal and oral sexual partners. Only one-third of HPV-positive patients were aware of their HPV disease status.

Conclusions—Cigarette smoking is associated with engagement in other modifiable risk factors in patients with head and neck cancer. Self-report measures of smoking may not accurately depict true smoking status. HPV-positive cancer patients were more likely to endorse a history of multiple sexual partners. Regular screening and targeted interventions for these distinct risk factors are warranted.

Keywords

head and neck cancer; tobacco use; smoking; alcohol drinking; sexual behavior; human papillomavirus (HPV)

Introduction

Head and neck cancers represent approximately 3% of all cancers in men and 1.5% of all cancers in women [1]. Use of tobacco products and excessive alcohol consumption increase the risk of developing head and neck cancers, with three-fourths of cases attributable to

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smoking and drinking. Furthermore, combined smoking and alcohol use affect the relative risk in a multiplicative fashion, with individuals who consume two or more packs of cigarettes and more than four alcoholic drinks per day having a 35-fold increase in risk for head and neck cancers [2]. However, smoking cessation can reduce the risk of head and neck cancers [3,4]. Individuals experience significantly reduced risk in as little as 1 to 4 years after quitting, with risk being reduced to that of a never-smoker after 20 years [5]. Research suggests that a sizeable portion of head and neck cancer patients continue to smoke after diagnosis and treatment, with prevalence estimates ranging from 21 to 35% [6,7]. In addition, about half of head and neck cancer patients are estimated to continue to consume alcohol after diagnosis [8]. Persistence in smoking and heavy drinking after head and neck cancer diagnosis is problematic and adversely impacts treatment effectiveness, complications, spread of disease, quality of life, and survival [9].

The majority of studies examining tobacco use in head and neck cancer patients have relied mainly on self-report measures, but there are discrepancies between self-report and objective biochemical measures due to some individuals underreporting exposure to nicotine [10–12]. Cotinine, a long-acting metabolite of nicotine with a half-life between 16–20 hours, is regarded as the best and most sensitive objective measure of smoking status [11,13]. Cotinine is detectable in blood and saliva for 3 to 4 days, and can reflect a cumulative nicotine intake of up to 7 days [14,15]. Studies utilizing cotinine measurement with head and neck cancer patients suggest that between 19–50% of self-reported ex-smokers may be actively smoking [6,16–18]. However, self-report remains the typical means physicians and researchers use to determine whether patients are actively smoking. Barriers to obtaining objective measures of smoking such as cotinine include time constraints, cost factors, and staffing needs to obtain and assay samples.

While the incidence of some primary sites of head and neck cancers in the US has fallen in recent years, those associated with human papillomavirus (HPV) has risen steadily, particularly in patients under age 50 with moderate to no history of alcohol or tobacco use [19,20]. HPV is associated with up to 20 to 25% of head and neck cancers, and the association varies based on the site of the tumor: HPV DNA is found in up to 67% of oropharyngeal cancer cases and less often in other locations such as the oral cavity (up to 18%) and larynx (up to 7%) [21]. Head and neck cancers related to HPV are thought to be biologically distinct and originate from different genetic alterations than those associated with alcohol and smoking behaviors [22]. Clinically, head and neck cancer from HPV is associated with better prognosis than are HPV-negative cancers [16]. HPV status, however, is not included in the clinical guidelines for head and neck cancer treatment, and thus data regarding HPV status may not be consistently documented and charted in the course of cancer diagnosis and treatment [20]. Furthermore, associations of modifiable risk factors for head and neck cancer, such as tobacco and alcohol use, sexual activity, and HPV related cancers are not well understood. Tobacco use increases risk of head and neck cancer for both HPV-positive and HPV-negative patients; however, HPV-positive smokers have a better cancer prognosis than HPV-negative smokers [23–25]. The extent to which engagement in modifiable risk factors differ between HPV-positive and HPV-negative head and neck cancer patients is unclear and more research is needed on the interaction of these factors.

The present study examined background characteristics, smoking, and engagement in other modifiable behavioral risk factors in head and neck cancer outpatients at a large urban medical center. Patients who were self-reported smokers in the past year were compared to former and never smokers on alcohol use behaviors, psychosocial factors, and sexual history. Self-reported smoking behaviors were objectively confirmed with a saliva sample for cotinine determination to examine the accuracy of self-report. Exploratory analyses

examined differences in background and modifiable risk behaviors between HPV-positive and HPV-negative head and neck cancer patients.

Methods

Participants

Patients with head and neck cancer were recruited at the University of Chicago. Eligible patients included those with newly diagnosed locally-advanced head and neck cancer. Patients were excluded if they were younger than 18 years or could not read or understand spoken English. Patients were also excluded if they were actively receiving or had recently completed (within the past 3 months) chemotherapy or radiation therapy or had recurrent or metastatic disease. The rationale for these exclusions was to avoid the interval surrounding acute treatment where side effects make smoking difficult and to control for physical barriers to smoking caused by the extremely poor health of late-stage cancer patients.

Procedures

The study was fully approved by the University of Chicago Institutional Review Board. Participants first provided informed consent and then completed a brief 15- minute self-report questionnaire concerning demographic characteristics, health background including knowledge of HPV status, and lifetime and current health risk behaviors including cigarette and alcohol use, and sexual behavior. Smoking status was defined using both self-report and objective measurement of cotinine levels. Patients who endorsed smoking 100 cigarettes or more in their lifetime were identified as ever smokers and those who endorsed less than 100 cigarettes lifetime were classified as never smokers [26]. Ever smokers were further sub-classified into either current smokers, defined as those who endorsed any cigarette smoking within the past year, or former smokers, i.e., those who had not smoked for one year or longer.

On completion of the questionnaire, patients were asked to provide a saliva sample for cotinine detection analyses. The sample was collected using a cotton Salivette® (Salimetrics LLC, State College, PA) tube, which each patient held in his or her mouth for 2 minutes until the cotton swab was saturated with saliva. Samples were then stored at -80 °C and analyzed using enzyme immunoassay. Cotinine detection sensitivity was 0.15 ng/mL. Values greater than 10 ng/mL were considered positive for biochemical confirmation of tobacco use [27]. HPV status was determined by p16 immunohistochemical staining as reported in patients' pathology reports or independent staining [28].

Statistical Analysis

Variable means, standard deviations and percentage values were calculated using frequency distribution and descriptive analyses. Comparisons across smoking status groups were conducted using univariate analyses of variance (ANOVA) or logistic regression analyses as appropriate. All statistical analyses were conducted with SPSS, v19.0 (IBM SPSS Statistics, Chicago, Illinois) or STATA v12.0 (StataCorp. 2011. College Station, TX).

Results

Sample

From June 2011 to March 2012, one hundred and twenty-six patients identified as meeting inclusion criteria were approached to participate in the study. Of these, 102 patients (81.0%) provided consent and completed the questionnaire, 21 patients declined to participate due to time constraints during their clinic visit, and three patients agreed to participate and signed the consent form, but did not complete and return the questionnaire (Figure 1).

Patient demographics, oncology and smoking history for the 102 patients enrolled in the study are provided in Table 1. Patients were primarily male, Caucasian, and married or living with a long-term partner. The mean age of the sample was 57 years and most had some college education. Over half were diagnosed with cancer of the oropharynx, stage IV. Approximately 64% of patients endorsed a lifetime history of cigarette use, with most reporting that they quit over one year ago. Among these ever-smokers, most endorsed smoking daily during their period of heaviest use with nearly half smoking at least one pack of cigarettes per day. About one-third of ever smokers reported that they attempted to quit smoking more than four times. The majority reported that they used “cold turkey” methods to quit smoking, but about one-third did report past use of nicotine replacement therapy (NRT).

Comparisons by smoking history

The three smoker status subgroups included current smokers (20%), former smokers (44%), and never smokers (36%). While former and never smokers did not differ significantly on any demographic or modifiable risk factors, current smokers differed from these groups on several factors (Table 2). First, compared to former and never smokers, current smokers were less educated and less likely to be married or living with a partner. Second, current smokers reported greater alcohol consumption and drank on average twice as much alcohol per occasion over the past year and their period of heaviest use compared with the other groups. There were no differences across groups in sexual history, i.e., as indexed by endorsement of 10 or more vaginal and 5 or more oral sex partners over their lifetimes.

Biochemical analysis of salivary cotinine

Biochemical analysis of salivary cotinine levels was conducted on 89 of 102 participants (87%), as samples from 13 patients had insufficient quantity for analysis. Of those assayed, sixteen (18%) patients were classified as cotinine-positive (> 10 ng/mL). Detailed characteristics of these patients are presented in Table 3. Cotinine values ranged from 40.67 ng/mL to 1000.28 ng/mL ($M=429.45$, $SD=296.54$). Of the 16 cotinine-positive patients, 15 (94%) were self-reported current (past year) smokers, and one was a self-reported former smoker, reporting his last cigarette was five years ago. Closer inspection of the data in self-reported current smokers revealed that four patients reported their last cigarette was smoked in a time whereby cotinine would no longer be positive: for one patient, the last cigarette was reported between 1–3 months ago, and for three patients, the last cigarette was reported between 3 months–1 year ago; however, one of these latter three patients endorsed use of NRT in the past week which may account for the cotinine positive result. Therefore, overall, there were four (25%) of 16 cotinine-positive patients who likely misrepresented their true smoking status as they self-reported past smoking but the time since their last reported cigarette did not match the cotinine positive status at the visit. Also of note were the cotinine levels in these patients, ranging from 63.41–699.77 ng/mL, indicating considerable variability in exposure but certainly significant underreporting of current/recent smoking of at least one pack of cigarettes daily for a few patients. Of interest, these four misrepresented smokers were all male and Caucasians and had stage IV cancer with chemotherapy and radiation treatment.

Comparisons by HPV status

Engagement in modifiable risk behaviors was also examined between patients with HPV-positive and HPV-negative head and neck cancers, restricted to patients with cancer of the oropharynx since this is most commonly associated with oral HPV diagnosis. Among the 43 patients diagnosed with oropharyngeal cancer, nearly three-fourths ($n=32$) were HPV-positive. Only one-third of these HPV-positive patients (12/32) were aware of their HPV status based on their self-report. Several differences between HPV groups were observed

(Table 4). Relative to patients who were HPV-negative, those who were HPV-positive had fewer years of smoking and endorsed less frequent drinking in the past. Differences in demographic characteristics and sexual risk behaviors were similar to previously reported findings.

Discussion

The present study sought to characterize patients seen in a large, NCI-designate Comprehensive Cancer Center renown for tertiary care and complex clinical presentations. In this study, patients with a lifetime history of cigarette smoking constituted a sizeable majority of those with advanced stage head and neck cancer. Furthermore, after diagnosis and treatment, approximately one in five patients self-reported continued smoking. These current smokers were found to be less educated, less likely to be married or living with a current partner, and were heavier drinkers relative to former and never smokers. Biochemical verification of smoking also revealed cotinine levels reflective of smoking in excess of one pack per day and high physical dependence in numerous cases (see Table 4) [29,30]. As in other studies, former (re: quit smoking > 1 year ago) and never smokers were found to be similar with regard to demographics and engagement in modifiable risk behaviors. Although efforts have long been underway to identify and educate smokers about the importance of quitting, increasing motivation to quit remains a challenge. Among cancer patients who smoke, 51% express interest in quitting and those who are younger or in the early stages of disease are more interested in participating in a smoking cessation program [6]. It is evident that there is a need for continued efforts to not only identify and educate smokers, but also to motivate and assist current smokers in quitting tobacco and alcohol use, particularly following diagnosis and treatment for advanced stage cancer.

Biochemical confirmation of cigarette use via salivary cotinine proved to be a useful tool in measuring accuracy of self-report data. One in four of those confirmed to be cotinine-positive denied recent smoking on self-report measures, thereby misrepresenting their continued smoking even in the context of a confidential clinical research survey. Cotinine levels obtained from these four patients reflected smoking patterns of at least a half-pack of cigarettes per day up to over one pack per day. All four patients were men with stage IV cancer, and all had received chemotherapy and radiation treatment, but not surgery. Research investigating the impact of treatment modality on continued smoking have found that those treated with chemotherapy and radiation are more likely to endorse ongoing smoking after treatment relative to those who receive surgery [7]. It has been suggested that surgical treatment may present barriers to continued smoking as a result of physical changes associated with the procedure as well as the psychological impact of having received such invasive treatment [7]. As treatment strategies for head and neck cancer become more technologically advanced, and less invasive and debilitating, it is possible that more patients in the future could return to harmful smoking and drinking. Therefore, smokers with advanced stage cancer that does not necessitate extensive surgical treatment may require targeted intervention to facilitate and maintain abstinence from smoking after cancer treatment.

Nearly three-quarters of patients with advanced stage oropharyngeal cancer were also HPV-positive. These individuals had less severe substance use histories and tended to have higher quit rates in smoking (i.e., percentage of former smokers) relative to HPV-negative oropharyngeal cancer patients. They also had demographic characteristics and sexual risk behavior patterns similar to what has been previously reported. [4,20,31]. These findings support conceptualization of HPV-positive cancer as distinct from HPV-negative cancer with differing risk factors which should be addressed in the course of cancer diagnosis and treatment. Cancer prevention methods, which often focus on minimizing engagement in risk

behaviors such as tobacco and alcohol use should also highlight the increased chances of developing head and neck cancer associated with risky sexual practices. Furthermore, it is unclear whether those with HPV-positive cancer continue to be infectious. While HPV-positive patients have an exceedingly low risk of second primary tumors, there are multiple reports of partners developing oropharyngeal cancer with the same HPV genotype. HPV transmission after cancer diagnosis and treatment is a relatively understudied area. Interestingly, nearly two-thirds of those who were HPV-positive were not aware of their disease status per self-report. Patients may benefit from being educated and informed about their HPV-positive status, as increased awareness may foster engagement in treatment and healthier living overall for themselves and their partners.

The strengths of the current study included providing well-described and simultaneous assessment of several different modifiable risk factors, use of both self-report and biochemical verification of smoking behavior and HPV disease status, and a high participation rate among clinic patients. Nonetheless, there are some limitations including the small sample size and preponderance of Caucasian male participants. While there was no recruitment bias per se as the characteristics of the sample are similar to those in the larger clinic, generalization of findings to women and minorities remain limited until larger studies with more diverse head and neck cancer samples are conducted. Moreover, the salivary cotinine measure was based on results from one sample collected on the day of the interview. Since participants were not aware of the study prior to being approached during their clinic visit, it is unlikely they modified their behavior in anticipation of participation; however, given that we included only a one-time measurement, it is possible there might have been an underestimation of current or sporadic smoking. The extent of the smoker misclassification found in this study (25%) may also be more modest or larger than that of the real population due to the small sample size and tumor site heterogeneity. Larger trials utilizing multiple random samples for cotinine determination may provide more detailed information about the prevalence of continued smoking among those with cancer [17].

In summary, it appears that cigarette smoking is indeed associated with engagement in other modifiable risk factors which may require focus as part of the overall treatment for advanced stage head and neck cancer. Education level, marital status, and alcohol use were main factors associated with smoking after diagnosis and treatment. Given that a quarter of smokers misrepresented true smoking behavior, it also appears that self-report measures of smoking may not accurately depict true smoking status. An objective measure such as salivary cotinine analysis in addition to self-report measures may better reflect actual smoking behavior in these patients. Furthermore, HPV-positive status was less often associated with risky behaviors such as cigarette and alcohol use, but more often involved a history of multiple sexual partners. Screening for engagement in high risk behaviors may therefore facilitate the identification of patients for whom targeted intervention is warranted.

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Figure 1.

Flow chart of participating patients. Current, former and never smokers from top to bottom according to self-report and biochemical verification of salivary cotinine.

Table 1

Patient Characteristics

Head and Neck Patients (N=102)	
	Number of patients (%)
<i>Demographics</i>	
Age (mean yrs; <i>SD</i>)	57 (9.47)
Sex (male)	86 (84%)
Race (Caucasian)	82 (80%)
Marital status (married/living with partner)	79 (77%)
Education (some college or higher)	70 (69%)
<i>Oncology history</i>	
<i>Tumor site</i>	
Oropharynx	48 (47%)
Oral cavity	22 (22%)
Other (nasopharynx, larynx, paranasal sinuses, etc.)	32 (31%)
<i>Stage</i>	
I & II	7 (7%)
III	13 (13%)
IV	80 (78%)
<i>Treatment</i>	
Chemotherapy & radiation	62 (61%)
Chemotherapy, radiation & surgery	27 (26%)
<i>Smoking history</i>	
<i>Lifetime tobacco use</i>	
Ever-smoker (lifetime use of >100 cigarettes)	65 (64%)
Years of cigarette use (mean, <i>SD</i>) ^a	28 (15.35)
Number of quit attempts (>4 times)	21 (34%)
<i>Period of heaviest smoking</i> ^a	
Frequency (daily)	43 (66%)
Quantity (> 21 cigarettes per day)	20 (43%)
<i>Methods used to quit smoking</i> ^b	
Cold turkey	40 (64%)
Nicotine replacement	19 (31%)
Bupropion, Varenicline	10 (16%)
Hypnosis, acupuncture, herbal, other	7 (11%)
Formal program or individual counseling	4 (6%)

^a Among ever-smokers (N=65)^b Percentage values may add to more than 100% due to use of multiple strategies by patient

Table 2

Comparisons between current, former and never smokers

	Current Smoker (n=20)	Former Smoker (n=45)	Never Smoker (n=37)	F (df)	OR (95% CI)	p
Demographics						
Mean age (SD)	58.00 (7.50)	58.78 (9.71)	54.65 (9.83)	2.08 (2, 99)	-	.13
Gender (male)	19 (95%)	36 (80%)	31 (84%)	-	1.44 (0.55–3.79)	.46
Race (Caucasian)	15 (75%)	34 (76%)	33 (89%)	-	0.50 (0.20–1.23)	.13
Education (some college or higher)	9 (45%) ^a	33 (73%) ^b	28 (76%) ^b	-	0.42 (0.19–0.96)	.04
Marital status (married/living with partner)	11 (55%) ^a	36 (80%) ^b	32 (86%) ^b	-	0.31 (0.12–0.78)	.01
Alcohol use history						
Age at first drink (SD)	19.47 (4.23)	18.70 (3.20)	18.71 (2.97)	0.38 (2, 84)	-	.68
Past year drinking						
> 3 days per week	4 (21%)	6 (14%)	4 (11%)	-	1.67 (0.57–4.87)	.34
Drinks per drinking day (SD)	6.00 (7.92) ^a	2.56 (1.76) ^b	2.58 (2.19) ^b	3.57 (2, 55)		.03
Period of heaviest drinking						
> 3 days per week	10 (67%)	16 (50%)	14 (50%)	-	1.31 (0.56–3.01)	.53
Drinks per drinking day (SD)	7.35 (5.36) ^a	3.87 (2.67) ^b	4.64 (3.58) ^b	3.99 (2, 62)	-	.02
Sexual history						
> 10 vaginal and 5 oral sex partners	2 (17%)	10 (25%)	19 (28%)	-	0.77 (0.28–2.09)	.60

Note. Data represent N(%). Means with different subscripts are significantly different at $p < .05$.

OR: Values represent odds of being a current smoker.

Sexual history: N, % of those responding. Current Smoker, n=12, former smoker, n=40, never smoker, n=32.

Table 3

Characteristics of cotinine-positive patients accuracy of self-reported tobacco use

Study ID	Sex	Self-reported smoking status	Last self-reported cigarette	Cotinine value (ng/mL)	NRT past week	Match?	Tumor site	Stage	Treatment
140	M	Current smoker	< 1 mo	150.29	N	Y	Oropharynx	IV	Chemo, RT
144	M	Current smoker	< 1 mo	204.20	N	Y	Oropharynx	III	Unknown
177	F	Current smoker	< 1 mo	869.24	N	Y	Oropharynx	IV	Chemo, RT, Surgery
193	M	Current smoker	< 1 mo	353.77	N	Y	Larynx	I	RT
194	M	Current smoker	< 1 mo	40.67	N	Y	Supraglottic larynx	IV	Chemo, RT, Surgery
197	M	Current smoker	< 1 mo	648.42	N	Y	Oral cavity	IV	Chemo, RT
200	M	Current smoker	< 1 mo	399.85	N	Y	Oropharynx	IV	Chemo, RT
205	M	Current smoker	< 1 mo	1000.28	N	Y	Oropharynx	IV	Chemo, RT
190	M	Current smoker	< 1 mo	442.83	Y	Y	Oropharynx	IV	Chemo, RT
195	M	Current smoker	< 1 mo	216.19	Y	Y	Oropharynx	IV	Surgery
204	M	Current smoker	< 1 mo	792.93	Y	Y	Oropharynx	IV	Chemo, RT
150	M	Current smoker	3 mo – 1 yr	158.74	Y	Y	Supraglottic larynx	IV	Chemo, RT
180	M	Current smoker	1 – 3 mo	63.41	N	N	Oral cavity	IV	Chemo, RT
149	M	Former smoker	> 5 yrs	356.44	N	N	Oropharynx	IV	Chemo, RT
182	M	Current smoker	3 mo – 1 yr	474.21	N	N	Unknown	IV	Chemo, RT
202	M	Current smoker	3 mo – 1 yr	699.77	N	N	Supraglottic larynx	IV	Chemo, RT

Note. M = Male, F = Female, Match=Match between self-reported and cotinine-verified tobacco use, Y= Yes, N= No match; NRT=Nicotine replacement therapy reported in the past week; Chemo=Chemotherapy, RT= Radiation therapy

Table 4

Comparisons between HPV-positive and HPV-negative patients with oropharyngeal cancer ($N=43$)

	HPV-positive (n=32)	HPV-negative (n=11)	F (df)	OR (95% CI)	p
Demographics					
Mean age (SD)	55.56 (8.18)	63.00 (9.44)	6.26 (1, 41)	-	.02
Gender (male)	30 (94%)	9 (82%)	-	3.22 (0.40–26.26)	.27
Race (Caucasian)	29 (91%)	7 (64%)	-	5.33 (0.96–29.51)	.05
Education (some college or higher)	22 (69%)	7 (64%)	-	1.20 (0.28–5.07)	.80
Marital status (married/living with partner)	28 (88%)	6 (54%)	-	7.78 (1.45–41.78)	.02
Smoking history^a					
Current smoker	4 (12%)	5 (46%)	-	0.15 (0.02–1.07)	.06
Former smoker	11 (34%)	2 (18%)	-		
Years of tobacco use	19.29 (14.97)	50.83 (9.17)	24.16 (1, 22)	-	.00
Period of heaviest smoking^a					
Frequency (> 3 days per week)	12 (92%)	5 (100%)	-	1.30 (0.10–17.73)	.84
Quantity (>20 cigarettes per day)	5 (38%)	2 (40%)	-	1.00 (0.13–7.45)	1.00
Alcohol use history					
Age at first drink (SD)	18.44 (2.71)	19.60 (4.35)	0.94 (1, 35)	-	.34
Past year drinking					
> 3 days per week	3 (10%)	5 (46%)	-	0.13 (0.02–0.72)	.02
Drinks per drinking day (SD)	4.30 (6.46)	3.94 (3.08)	0.02 (1, 26)	-	.88
Period of heaviest drinking					
> 3 days per week	10 (38%)	7 (78%)	-	0.16 (0.03–0.94)	.04
Drinks per drinking day (SD)	4.86 (2.99)	5.75 (6.39)	0.27 (1, 28)	-	.61
Sexual activity					
> 10 vaginal and 5 oral sex partners	12 (50%)	1 (11%)	-	9.00 (0.98–82.50)	.04

Note. Data represent $N(\%)$. HPV-positive patients are those verified in the medical record as diagnosed with HPV. OR: Values represent odds of being HPV-Positive.

^a Among ever-smokers ($N=22$).

Sexual history: N, % of those responding. HPV-positive, n=24, HPV-negative, n=9. Sexual activity analyzed by Fisher's Exact Test