

ORIGINAL ARTICLE

Understanding personal risk of oropharyngeal cancer: risk-groups for oncogenic oral HPV infection and oropharyngeal cancer

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Background: Incidence of human papillomavirus (HPV)-related oropharyngeal cancer is increasing. There is interest in identifying healthy individuals most at risk for development of oropharyngeal cancer to inform screening strategies.

Patients and methods: All data are from 2009 to 2014, including 13 089 people ages 20–69 in the National Health and Nutrition Examination Survey (NHANES), oropharyngeal cancer cases from the Surveillance, Epidemiology, and End Results (SEER 18) registries (representing ~28% of the US population), and oropharyngeal cancer mortality from National Center for Health Statistics (NCHS). Primary study outcomes are (i) prevalence of oncogenic HPV DNA in an oral rinse and gargle sample, and (ii) incident oropharyngeal squamous cell cancer.

Results: Oncogenic oral HPV DNA is detected in 3.5% of all adults age 20–69 years; however, the lifetime risk of oropharyngeal cancer is low (37 per 10 000). Among men 50–59 years old, 8.1% have an oncogenic oral HPV infection, 2.1% have an oral HPV16 infection, yet only 0.7% will 'ever' develop oropharyngeal cancer in their lifetime. Oncogenic oral HPV prevalence was higher in men than women, and increased with number of lifetime oral sexual partners and tobacco use. Men who currently smoked and had ≥5 lifetime oral sexual partners had 'elevated risk' (prevalence = 14.9%). Men with only one of these risk factors (i.e. either smoked and had 2–4 partners or did not smoke and had ≥5 partners) had 'medium risk' (7.3%). Regardless of what other risk factors participants had, oncogenic oral HPV prevalence was 'low' among those with only ≤1 lifetime oral sexual partner (women = 0.7% and men = 1.7%).

Conclusions: Screening based upon oncogenic oral HPV detection would be challenging. Most groups have low oncogenic oral HPV prevalence. In addition to the large numbers of individuals who would need to be screened to identify prevalent oncogenic oral HPV, the lifetime risk of developing oropharyngeal cancer among those with infection remains low.

Key words: oral HPV, oropharyngeal cancer, screening, risk triage, risk groups

Introduction

Human papillomavirus (HPV) is the most commonly sexually transmitted infection in the United States. HPV now causes ~70% of all oropharyngeal squamous cell cancer (OPC) in the United States [1] and the incidence of HPV-related OPC (HPV-OPC) among men has more than doubled over the past 20 years [2]. Indeed, OPC is projected to be more common than cervical cancer in the United States by 2020 [3]. Given the 'epidemic' of

HPV-OPC, there is interest in identifying specific groups that could benefit from screening, if effective tests were developed.

Sexual behaviors responsible for exposure to oral HPV infection are common (80% of the US population reports ever performing oral sex) [4]. Given the ubiquitous exposure to HPV infection and resulting anxiety [5], there is interest in identifying healthy individuals most at risk for development of OPC. As oncogenic oral HPV infection is the precursor to malignancy,

identification of individuals with oncogenic oral HPV infection may point to individuals with premalignant disease. Such risk triage could both inform screening approaches and assist the public in understanding personal risk. This analysis therefore aims to understand how common HPV16, oncogenic HPV and HPV-OPC are in groups of people with different risk factor profiles.

Methods

Study population

This study included 13 089 people ages 20–69 years old who participated in National Health and Nutrition Examination Survey (NHANES) between 2009 and 2014 and had oral HPV DNA testing. Analyses involving number of oral sex partners were limited to ages 20–59, with data for number of oral sex partners, resulting in a sample size of 9425. Incidence and incidence-based mortality data from SEER 18 registries between 2009 and 2014 [6] were used with NCHS mortality data for projections of OPC risk.

HPV measurement

As previously described [7, 8] oral HPV DNA was tested in exfoliated cells collected from an oral rinse and gargle sample using PCR amplification using PGMY 09/11 consensus primers and line blot for the detection of 37 specific HPV types. Oncogenic oral HPV was defined as detection of any of the following 12 types: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 [9].

Analytic methods

Analyses of NHANES oral HPV data were weighted by Mobile Examination Center (MEC) exam sampling weights, and conducted

using SUDAAN software (release 11.0.1, Research Triangle Institute) to account for survey sample design. Projected OPC risk was calculated using DevCan software [10].

To better understand subgroup risk, prevalence of oncogenic HPV and HPV16 were explored stratifying by multiple factors including sex, sexual behavior, age, and current smoking. Groups with similar prevalence were combined to create parsimonious risk stratification of people with similar prevalence.

Results

Oncogenic oral HPV and oral HPV16 infection are rare in the general US population. As expected, prevalence of infection is higher among men than women of every age group (oncogenic HPV; 6.0% versus 1.1%, $P < 0.001$; Table 1). Prevalence of oncogenic oral HPV is contrasted with risk of OPC in Table 1 by sex and age groups. While oncogenic oral HPV is detected in 3.5% of all adults age 20–69, the lifetime risk of OPC is low (37 per 10 000). For example, among men 50–59 years old, 8.1% have an oncogenic oral HPV infection, 2.1% have an oral HPV16 infection, yet 0.7% will ‘ever’ develop OPC in their lifetime; and risk of developing OPC in the next 10 (0.2%) or 20 (0.4%) years is even lower (Table 1).

While prevalence of oncogenic oral HPV infection is low, the distribution of infections is not representative of the population (supplementary Table S1, available at *Annals of Oncology* online). Indeed 84% of oncogenic oral HPV infections in 20- to 69-year olds were among men. To elucidate why oncogenic oral HPV was more concentrated among certain groups, behavioral characteristics were considered. Performing oral sex and smoking are each strongly associated with detection of oncogenic oral HPV

Table 1. Oral HPV prevalence by sex and age, compared with the risk of developing oropharyngeal cancer (OPC) in each group

Sex	Age	Risk spectrum: infection to cancer				
		NHANES ^a (prevalence)		SEER ^b (OPC risk: cases/100 people)		
		Oncogenic Oral HPV (%)	Oral HPV16 (%)	Lifetime (%)	Next 20 years (%)	Next 10 years (%)
Men	20–29	4.8	1.1	0.7	0.01	<0.01
	30–39	4.7	1.5	0.7	0.07	0.01
	40–49	6.2	2.3	0.7	0.3	0.06
	50–59	8.1	2.1	0.7	0.4	0.2
	60–69	6.1	2.4	0.5	0.4	0.3
	Total	6.0	1.9	0.7	–	–
Women	20–29	1.4	0.3	0.2	<0.01	<0.01
	30–39	1.0	0.3	0.2	0.01	<0.01
	40–49	0.8	0.1	0.2	0.05	0.01
	50–59	1.6	0.5	0.2	0.08	0.03
	60–69	0.7	0.1	0.1	0.10	0.05
	Total	1.1	0.3	0.2	–	–
Men and women	All	3.5	1.1	0.4	–	–

^aWeighted prevalence accounting for NHANES study design weights to reflect the general US population.

^bEstimates of OPC risk combine data on cancer occurrence from SEER with population data. OPC is shown as risk per 100 people to contrast with HPV prevalence. For reference in interpretation, 0.6% risk represent that 0.6 people out of the 100 (or 6 out of 1000, or 600 out of 100 000) would develop OPC.

Table 2. Oncogenic oral HPV prevalence by participant characteristics and behaviors

Characteristics (among those 20–69 years old)	No. of people	Oncogenic oral HPV prevalence ^a (%)			P-value ^b
		Men N = 6420	Women N = 6669	All N = 13 089	
Sex					
Women	6669	–	1.1	1.1	<0.0001
Men	6420	6.0	–	6.0	
Currently smoke					
No	10 041	4.5	0.9	2.6	<0.0001
Yes	3044	10.5	2.1	6.7	
Age, in years					
20–29	2738	4.8	1.4	3.1	0.13
30–39	2668	4.7	1.0	2.8	
40–49	2699	6.2	0.8	3.4	
50–59	2494	8.1	1.6	4.8	
60–69	2490	6.1	0.7	3.3	
Race/ethnicity					
White non-Hispanic	5135	6.3	1.1	3.7	0.008
Black non-Hispanic	2931	7.5	1.4	4.2	
Any race Hispanic	3347	4.5	1.3	2.9	
Other	1676	3.7	0.7	2.1	
Ever oral sex (or man or woman)					
No	2453	2.3	0.2	1.1	<0.0001
Yes	9272	6.5	1.4	4.0	
Ever oral sex on a woman					
No	6660	3.6	1.0	1.4	<0.0001
Yes	5095	6.4	3.5	6.2	
Ever oral sex on a man					
No	7054	5.8	0.2	4.9	<0.0001
Yes	4693	10.2	1.4	1.8	
Number of partners performed oral sex on in lifetime ^c					
0	1661	2.4	0.2	1.2	<0.0001
1	1877	1.2	1.0	1.1	
2–4	3165	4.8	0.7	2.5	
5–9	1363	3.9	2.5	3.3	
10+	1359	14.4	3.0	11.1	

^aWeighted prevalence accounting for NHANES study design weights to reflect the civilian non-institutionalized US population.

^bWald *F* test (based on transforming the Wald χ^2) for independence of row variable and oral HPV16, not accounting for sex (except where sex is the row variable).

^cData on number of lifetime oral sex partners was not collected consistently in those 60 and older so is only presented among those 20–59 years old.

(Table 2) and HPV16 (supplementary Table S2, available at *Annals of Oncology* online). Oncogenic oral HPV prevalence is low (<2.5%) among both men and women who never performed oral sex. Prevalence of oncogenic oral HPV increased with number of lifetime oral sexual partners, up to 14.4% in men age 20–59 years old with ≥ 10 lifetime oral sexual partners (Table 2).

Oncogenic oral HPV prevalence was explored by sex, sexual behavior, and tobacco use to better understand groups that have higher and lower prevalence (Figure 1). Regardless of what other risk factors participants had, oncogenic oral HPV prevalence was low among those with only ≤ 1 lifetime oral sexual partner (women = 0.7% and men = 1.7%). Oncogenic oral HPV prevalence doubled among women with ≥ 2 versus 0–1 lifetime oral sexual partners (1.5% versus 0.7%, $P = 0.02$), but remained low among women with higher number lifetime oral sexual partners

(Table 2). Oncogenic oral HPV prevalence was highest among men who currently smoked and had ≥ 5 lifetime oral sexual partners (14.9%, 95% CI = 11.4–19.1). Men with only one of these risk factors (i.e. either smoked and had two to four partners or did not smoke and had ≥ 5 partners) had ‘medium risk’, with 7.3% (95% CI = 5.8–9.1) oncogenic oral HPV prevalence (Figure 1). Findings were similar when considering oral HPV16 infection specifically.

Discussion

This analysis highlights that the yield of oncologic oral HPV screening would be limited in most groups in the United States. With the increasing incidence of OPC, there is a need to

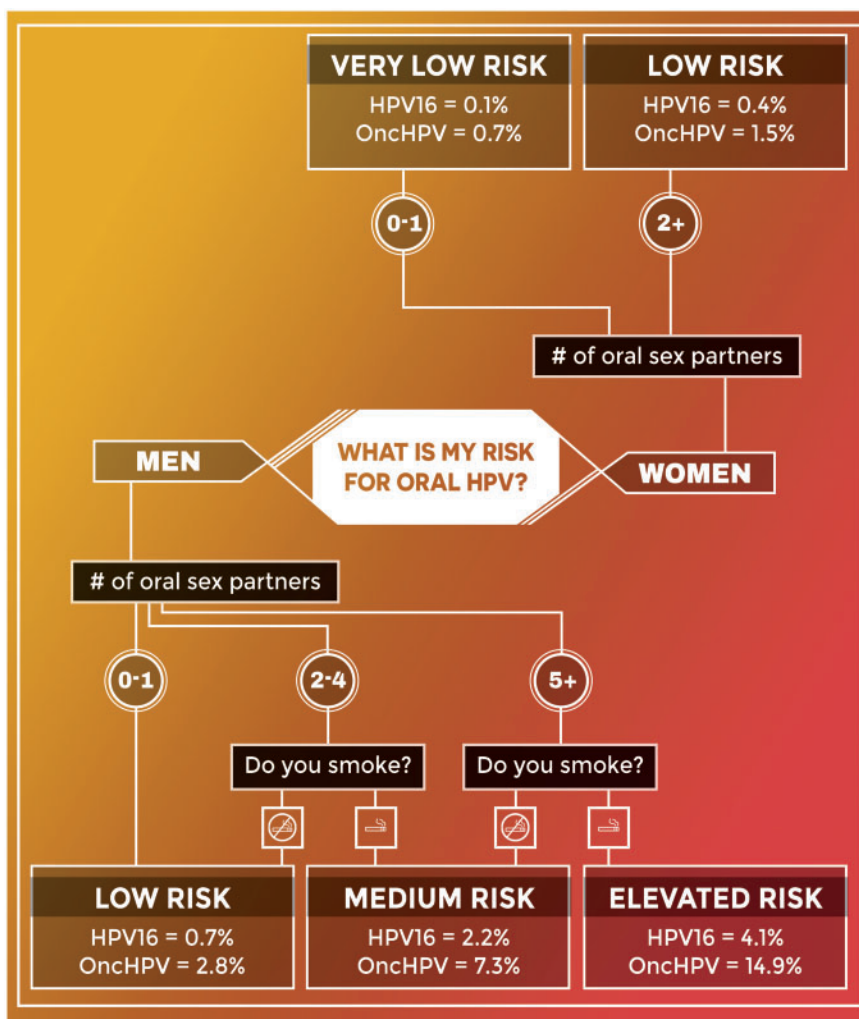


Figure 1. What is my risk of oral HPV? Prevalence of oral HPV16 and any oncogenic oral HPV infection by risk group. In the ‘very low-risk’ group (among women with 0–1 lifetime oral sexual partners), oncogenic oral HPV was similar among smokers and nonsmokers (1.8% versus 0.5%, $P = 0.26$). In the ‘low-risk’ group of women, oncogenic oral HPV prevalence was 1.5% among women with two or more lifetime oral sexual partners. In the ‘low-risk’ group of men, oncogenic oral HPV prevalence was 1.7% among men with 0–1 lifetime oral sexual partners and was higher among men who did not smoke and had 2–4 lifetime oral sexual partners (4.1%, $P = 0.0042$). In the ‘medium risk’ group, oral HPV16 prevalence was 7.1% among men who smoke and had 2–4 partners and 7.4% among men who do not smoke and had 5+ partners ($P = 0.87$).

understand how to identify individuals at risk of OPC. Oncogenic oral HPV detection is attractive as it samples the relevant epithelium in a non-invasive method, has relatively low cost and serves as a biomarker for HPV-OPC. However, for screening to succeed, a high prevalence population is needed to limit false positives, and balance the psychologic and physical harms of screening with the benefits.

From this analysis, it is clear that screening based upon oncogenic oral HPV detection would be challenging. Women across all categories have low prevalence of infection and low risk of OPC and therefore benefits of screening are unlikely to outweigh harms in this group. The higher prevalence of oncogenic oral HPV in men than women is thought to be due to both a higher per partner risk of acquisition when performing oral sex [11, 12], and decreased clearance among men than women [11, 13]. While there are specific risk groups of men enriched for oncogenic oral HPV, most men have low prevalence of infection. Even among

the elevated risk group, the majority of men do not have a prevalent oncogenic oral HPV. In addition to the large numbers of individuals who would need to be screened to identify prevalent oncogenic oral HPV, the lifetime risk of developing OPC among those with infection remains low [11, 14].

These characteristics suggest that other tests will need to be combined or supplant present methods to accurately identify those with the greatest risk of OPC in the population. Serum HPV oncoprotein antibody tests are specific [15], but are even rarer than oral HPV16 infection [16], so may be impractical to use in most groups. An additional challenge for screening is that precursor lesions for HPV-OPC have not been found and the ability to detect lesions early in an ‘elevated-risk’ group is unknown.

With growing appreciation of the relationship between oral sex, infection, and cancer, some individuals have questions about their risk of having oncogenic oral HPV infection. To address

concerns about infection among individuals with high number of oral sex partners or others concerned about their cancer risk, the infographic can be used to reassure that oncogenic oral HPV prevalence is low among most groups. This analysis has several limitations. Data on oral HPV infection were cross-sectional, with no information linking HPV and SEER data used for cancer risk. Comparing oncogenic oral HPV prevalence and OPC risk in this way informs potential future screening studies, and personal risk assessment. In summary, this analysis shows that screening based upon oncogenic oral HPV infection will not be useful and presents data to communicate to the layperson the low risk of infection and cancer.

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Disclosure

The authors have declared no conflicts of interest.

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