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Human papillomavirus-related Diseases: Oropharynx Cancers and Potential Implications for Adolescent HPV Vaccination

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Abstract

Molecular and epidemiological data now support an etiologic role for oncogenic human papillomavirus (HPV) in oral cancers in women and men. Recent studies have demonstrated an increase in the incidence of HPV-associated oral cancers in the United States (US). Moreover, the incidence rates for these cancers are higher in men than women. Oral HPV infections acquired through oral sex appear to be the principal risk factor for HPV-associated oral cancers. Despite reports in the popular press that the prevalence of oral sexual behaviors is increasing in the adolescent population, trends in these behaviors over time are largely unavailable. However, data indicate that oral-genital contact is frequently practiced among adolescents; adolescents do not typically consider this a risky behavior. The majority of oral cancers (approximately 90%) caused by HPV are identified as HPV 16 positive. Therefore, HPV-associated oral cancers could be prevented by a prophylactic vaccine if the vaccine were demonstrated to be capable of preventing oral HPV 16 infection. These findings have created new potential opportunities for the primary prevention of oral cancers.

HPV-associated oral cancer

Human papillomavirus (HPV) infection is necessary for the development of cervical cancer and a subset of anogenital cancers (e.g., anal, penile, vulvar, and vaginal carcinomas). There are now sufficient molecular and epidemiological data to support a causal role for HPV in a non-anogenital cancer, specifically squamous cell carcinoma of the oropharynx. A role for HPV in the pathogenesis of head and neck squamous cell carcinomas (HNSCCs) was first suggested in 1983 when histopathological features, consistent with HPV infection, were identified in oral cancers [1]. Viral DNA from oncogenic (“high-risk”) HPV 16 was detected in an oral carcinoma by Southern blot hybridization two years later [2]. Subsequently, viral DNA of unclear etiologic significance was identified by different laboratory methods in a variable proportion of all HNSCCs [3]. A strong and consistent association of HPV with carcinomas of the lingual and palatine tonsils within the oropharynx began to emerge in the early 1990s, with the specific identification of viral DNA [4] and viral oncogene expression in tonsillar carcinomas [5]. In 2000, investigators in the United States (US) utilized a number of laboratory techniques to demonstrate that oncogenic HPV 16 was present in high copy number, frequently integrated into host chromosomal DNA, and specific to the tumor cell nuclei of a distinct clinical subset of oropharyngeal cancers [6].

Although oncogenic HPV-DNA can be detected by polymerase chain reaction (PCR) in a variety of head and neck cancers, more robust molecular data currently indicate a role for oncogenic HPV in the pathogenesis of oropharyngeal cancers. For these tumors, both viral load (indicating the presence of one or more viral copies per tumor cell) [7–11] and viral integration into the host cell genome have been demonstrated [5,6,12–14]. However, some investigators have predominantly found episomal virus in tonsillar carcinomas [10]. Expression of HPV E6/E7 oncogenes, the current gold standard for establishing a causal role for oncogenic HPV in human tumors, has been demonstrated in HPV 16 DNA-positive oropharyngeal cancer specimens by RNA *in situ* hybridization [5,15], Northern blot analysis [13], and reverse transcription-PCR [5,11,14,16–19]

HPV-positive head and neck cancers appear distinct from HPV-negative cancers with regard to clinical characteristics [6,12,14,16,20–22]. The majority of HPV-positive tumors in head and neck cancers predominantly arise from the lingual and palatine tonsils and tend to have a poorly differentiated and frequently basaloid histopathology [23]. Additionally, patients with HPV-positive HNSCC tend to be younger (under approximately 60 years of age) when compared with HPV-negative HNSCC patients (over approximately 60 years of age) [24–28]. In a meta-analysis of HPV-positive versus HPV-negative HNSCC, patients with HPV-positive oropharyngeal tumors also appeared to have an improved prognosis when compared with patients with HPV-negative tumors [29,30].

In a recent worldwide meta-analysis of head and neck cancers, overall HPV-DNA prevalence by PCR-based detection was 25.9%(95% CI, 24.7–27.2) [31]. A separate review of the literature found a similar prevalence of HPV-DNA (22%) in head and neck cancers [32]. HPV prevalence was highest for oropharyngeal cancers (approximately 36%) [31] and, in particular, for tonsillar cancers (approximately 51%) [33]. In these literature summaries, high-risk HPV 16 was present in 84% of HPV-positive tumors. For HPV-positive oropharyngeal cancers, high-risk HPV 16 was present in 93% of cases, HPV 18 in 3%, HPV 33 in 3%, and HPV 35, 45, or 59 in 0.6% [31]. In an international case-control study of oral cavity and oropharynx cancers conducted by the International Agency for Research on Cancer (IARC), HPV 16-DNA was found in 95% of HPV-DNA-positive cancers [34]. In a recent monograph summarizing evidence for HPV as a human carcinogen, the IARC concluded that there is sufficient evidence for a causal role of HPV 16 in the pathogenesis of oropharyngeal cancers, and perhaps for a smaller subset of oral cavity carcinomas [35]. These findings have created new opportunities for the primary prevention of some head and neck cancers [36].

Risk factors for HPV-associated oral cancers

Sexually acquired oral HPV infection appears to be the principal risk factor for HPV-associated oral cancer, a finding of critical importance in potentially preventing HPV-associated oral cancer through vaccination. Case-control studies have consistently demonstrated strong associations between serologic evidence of HPV exposure and risk for head and neck cancers (Table 1). Consistent with the HPV-DNA type distribution reported in molecular studies, risk is strongly and consistently associated with exposure to HPV 16, but not with exposure to HPV 18, 31, or 33 [37,38]. Although significant associations between exposure and risk of all head and neck cancers are reported, after stratification by anatomic site, associations are preserved primarily for oropharyngeal cancers [20,37–40], but observed for oral cavity carcinomas in some studies [41]. In a recently reported case-control study, after adjustment for age, gender, alcohol, tobacco, oral hygiene, and family history of head and neck cancers, individuals seropositive for HPV 16 had a 32-fold increase in risk for oropharyngeal cancer when compared with seronegative individuals [42].

A limitation of case-control studies is that they do not provide evidence for a temporal association between exposure and disease. However, the findings from the case-control studies noted above are consistent with estimates of risk in a nested case-control study in Scandinavia [22]. In this study, sera were drawn approximately nine years before cancer developed. HPV 16 seropositive individuals had more than a 14-fold increase in the risk of oropharyngeal cancer when compared with seronegative individuals after adjustments for age, gender, and serum cotinine levels. Seropositivity to HPV 18, 33, and 73 was not associated with increased risk. This study is the only study to date that has provided evidence that exposure to HPV 16 precedes oropharyngeal cancer development.

Although strong associations between serologic evidence of HPV exposure and oropharyngeal cancer have been reported, detection of HPV serum antibodies does not provide information regarding the site of infection [43]. In addition, only 50% of women generate an immune response to natural HPV infection [44,45]. Therefore, it is important to note that several case-control studies have established oral oncogenic HPV infection to be strongly associated with head and neck cancers, especially oropharyngeal cancer (Table 2) [38,46–48]. These studies defined oral HPV infection by the detection of HPV-DNA in either oral rinse samples or exfoliated buccal cells. In studies that included multiple anatomic sites, the strongest associations were consistently observed between infection with HPV 16 and oropharyngeal cancers (Table 2). Risk is particularly high for oral HPV 16 infection. In a recent study, oral HPV 16 infection was estimated to confer a 15-fold increase in risk for oropharyngeal cancer [42].

Timing of administration prior to potential exposure to HPV is of critical importance to the success of a prophylactic vaccine. It is clear from numerous epidemiological studies that anogenital HPV infection is sexually acquired [49] and, therefore, vaccination should occur prior to sexual debut. For oral HPV infection, studies have clearly demonstrated that peripartum transmission occurs [50] and is strongly associated with a risk of respiratory papillomatosis [51]. However, the majority of studies indicate that peripartum transmission of oral HPV infection is relatively rare (<2.0%) [52,53], controversy notwithstanding [54,55]. A bimodal age distribution for oral HPV infection was recently reported among children aged 2 weeks to 20 years, consistent with peripartum transmission followed by gradual acquisition later in childhood. Among 16 to 20 year-olds, oral HPV infection prevalence was approximately 3% and was associated with female gender, genital warts, and current smoking status [56]. Estimates of oral, high-risk HPV infection prevalence in adult populations range from 1.5% to 14% [20,41,42,57–60]. Current factors associated with elevated odds of oral HPV infection in adults include increasing age, male gender, human immunodeficiency virus (HIV) infection, immunosuppressive medical therapy, the presence of a cervical HPV infection, history of a sexually transmitted disease (STD), and number of oral sex partners [57,59,61–63]. The influence of sexual orientation of oral HPV infection prevalence is currently unknown. These studies indicate that oral HPV infection is likely acquired through sexual behavior. However, transmission by other means, such as via mouth-to-mouth contact, cannot be excluded, and prospective cohort studies designed to evaluate risk factors for incident oral HPV infection have yet to be reported. Further analysis is clearly needed.

Consistent with the data for oral HPV infection, sexual behavior has recently been associated with head and neck cancers in some but not all studies. Lifetime number of sexual partners as well as a history of oral-genital and oral-anal sex have been independently associated with HPV-positive head and neck cancers when compared with patients with HPV-negative cancers [37,64,65]. Lifetime number of sexual partners, a history of genital warts, and young age at first intercourse each increased the odds of developing oral cancer among men in a population-based case-control study in Seattle, Washington [20]. However,

other case-control studies of head and neck cancers in the US [37,47] and an international study of oral cancers reported no such associations [41]. In a recent case-control study limited to oropharyngeal cancers, number of lifetime sexual partners, number of oral sexual partners, young age at first intercourse, and a history of STDs were all associated with oropharynx cancer [42]. These associations were no longer significant after adjustment for HPV 16 exposure as measured by serology, indicating that sexual behaviors are a surrogate for HPV 16 exposure.

In summary, current data indicate that oral HPV 16 infection is primarily sexually acquired and is a strong risk factor for oropharyngeal cancer. Therefore, HPV-associated head and neck cancers could likely be prevented by a prophylactic vaccine capable of preventing oral HPV 16 infection. However, in order for vaccination against oncogenic HPV infection to have the greatest benefit, administration should occur prior to the onset of sexual behavior.

The potential to prevent HPV-associated HNSCC with HPV vaccines

A detailed discussion on the development of vaccines targeted against oncogenic HPV, as well as the ongoing clinical trials, is available elsewhere in this supplement. All vaccine trials reported to date have been designed to investigate the ability of the vaccines to generate protection against the consequences of anogenital HPV infection in women. However, there is reason to be optimistic that the existing vaccines may be protective against oral HPV infection, and therefore effective in preventing vaccine-type HPV-associated head and neck cancers in both men and women. For example, in a canine model of oral papillomavirus infection, dogs vaccinated with L1 canine oral papillomavirus (COPV) virus-like particles (VLPs) were completely protected against oral papillomas when subsequently challenged with COPV. Passive transfer of serum to unvaccinated dogs was protective [66], indicating that serum neutralizing IgG antibodies were important in the mechanism of protection against oral infection. Moreover, the majority of oral IgG is derived from oral mucosal transudate from the serum [67]. In several studies, HPV-specific IgG antibodies have been detected in oral mucosal transudate and correlate with seropositivity among HIV-positive individuals [68], women with cervical HPV infection [69] or dysplasia [70,71], and in dental clinic attendees [72]. The immune response elicited by VLPs in human subjects has conferred protection against oncogenic HPV infection in women [73,74]. Additionally, immunogenicity studies have demonstrated that the vaccines elicit a robust humoral immune response in males as well as females [75], an important finding given the majority of HPV-associated head and neck cancers occur in men.

Clinical trials to evaluate the efficacy of the quadrivalent HPV vaccine in protecting against oral HPV infection are currently in development. However, clinical trials to assess the potential for HPV vaccines in preventing penile HPV infection and anogenital warts in men are underway, with preliminary results anticipated in 2009. Current generation HPV 16 and 18 L1 VLP vaccines hold potential promise for the prevention of a greater majority of HPV-positive oral cancers than for cervical cancer. This is due to the narrow HPV type distribution for oral cancers. Worldwide, HPV 16 consistently accounts for 86% to 95% of HPV-DNA positive head and neck cancers [31], and the remainder of these cancers are positive for HPV-DNA from phylogenetically-related members of the A9 clade. With regard to worldwide cervical cancer cases, however, HPV 16 and 18 are responsible for approximately 70% these cancers [76,77]. Thus, it is possible that an HPV vaccine could have benefits beyond the current target population.

It is difficult to estimate the number of head and neck cancers worldwide that could be prevented by an effective prophylactic or therapeutic vaccine for oral HPV infection. HPV prevalence in tumors is highly dependent on the laboratory method used for classification

and may differ significantly by the geographic region sampled and by calendar time. Based on HPV-DNA detection results from an international case-control study conducted by the IARC from 1996 to 1999 [41], Parkin and colleagues estimated that 3% of oral cavity and 12% of oropharynx cancers worldwide are attributable to HPV, accounting for 14,500 cases in 2002 [78]. Using HPV-DNA prevalence estimates from a worldwide review conducted by the IARC [31], this number would increase to 82,962 cases for 2002. Initial studies indicate that the proportion of cancers that are HPV-positive may differ substantially by geographic region [79], but further studies are clearly needed.

The Centers for Disease Control and Prevention (CDC) completed an analysis of cancer incidence data to estimate the burden of HPV-associated cancers in the US during the pre-vaccine era (1998–2003) [80]. In this analysis, anatomic site of the tumor was used as a surrogate for HPV-associated head and neck cancers. Based on data from 38 cancer registries representing 83% of the US population, the average annual incidence for HPV-associated head and neck cancers was estimated to be 5,658 cases among men and 1,702 among women. Age-adjusted incidence rates were estimated to be 5.2 and 1.3 per 100,000 among men and women, respectively. Thus, the disease burden for HPV-associated oral cancers was second among all HPV-associated cancers only to cervical cancers, with 10,966 cases per year and an incidence rate estimated to be 9.0 per 100,000 women.

The aforementioned CDC values likely underestimate the current and future burden of HPV-positive head and neck cancers in the US. Several recent analyses of population-based cancer registries have demonstrated significant increases in the incidence of oropharyngeal cancers in the US since 1973 [81–84]. While incidence rates for most cancer sites in the oral cavity declined or remained constant, those for tonsillar and base-of-tongue carcinomas increased significantly, predominantly for Caucasian men under the age of 65 years [81,83]. Similarly, tonsillar cancer incidence increased in Sweden from 1960 through 2003, with an annual percent increase of 1.1% in women and 2.6% in men [85]. The HPV prevalence in tumors increased from 28% in the 1970s to 68% in 2000 to 2002, consistent with a role for HPV in driving these trends. Although trends in incidence rates for oral cancers have mainly been attributed to population fluctuations in use of alcohol and tobacco [3], the use of alcohol and tobacco in the US has largely declined since 1964 and thus cannot explain the recent increase in cancer incidence[86]. It is likely that declining tobacco use and tonsillectomy rates have influenced trends in tonsillar cancer incidence. However, cigarette smoking has been shown to independently elevate the odds for persistent anogenital HPV infection, but analogous data for oral infection is not available [87]. It is also possible that reported changes in sexual behaviors [88,89] may have also contributed to the increase in oral cancer incidence.

Oral sexual behavior in the US and implications for vaccination

Data in support of an association between oral sexual behavior or acquisition of oral HPV infection and risk of oral cancer are sparse. Nevertheless, existing data support a reasonable hypothesis that oral HPV infection, like other viral and non-viral STDs [90,91], can be acquired via oral sex. Transmission by other means, such as oral-to-oral, remains possible and is an active area of investigation.

The risk of HPV exposure at both oral and anogenital sites may need to be factored into the age consideration for administration of currently available HPV vaccines. Most surveys of adolescent sexual behavior indicate that a significant proportion of adolescents engage in oral sex prior to vaginal intercourse, and perceive oral sex as less risky [92]. Adolescents may also report having more oral than vaginal sex partners [93]. Based on data from the 2002 National Survey of Family Growth, 38.8% of males and 43.6% of females aged 15 to

19 years in the US have performed oral sex. Additionally, approximately 12% of males and 10% of females in this age group have had oral sex but not vaginal intercourse [94]. Similarly, a 2004 survey among students in the United Kingdom (UK) reported that 22% of virgins aged 16 to 21 years have had oral sex, and 70% of non-virgins reported a history of oral sex prior to vaginal intercourse [95]. Based upon these behavioral data, a higher proportion of adolescents may be at risk at a slightly younger age for oral, as opposed to anogenital, HPV infection. However, US population-based sexual behavior surveys among adolescents have not evaluated differences between age at first oral sex versus age at first vaginal sex.

According to Young Risk Behavior Surveys, the proportion of US high school students who had vaginal intercourse or multiple sexual partners declined by 13% and 24%, respectively, from 1991 to 2005 [96]. In contrast to perceptions in the lay press, there are little data in support of significant changes over time with regard to age at onset or proportion of adolescents participating in oral sex in the US. This is due largely to the paucity of such measures from surveys on sexual behavior. The proportion of men and women aged 18 to 44 years who reported performing oral sex did not change from 1991 to 2002, according to four national US surveys of sexual behavior [94]. Limited data from the UK and Australia suggest that age at onset of oral sexual behavior has declined while the prevalence has increased over time. In the UK, a clinic-based survey reported that the proportion of women who had performed oral sex increased significantly from 70% to 82% from 1982 to 1992 [88]. A population-based survey performed in Australia from 2001 to 2002 indicated that the age at which oral sex is being initiated was younger in cohorts born from 1981 to 1986 when compared with those born from 1941 to 1950 [97]. Analogous trends have not been reported in the US.

Because HPV-positive head and neck cancers occur in both men and women, gender as well as racial and social influences on oral sexual behavior may be important. A meta-analysis of sexual behavior studies indicated that males initiate most sexual behaviors earlier than females [98]. In most studies, both young age of oral sex initiation and prevalence of oral sex among Caucasians are higher than among African Americans [99]. Social cofactors, such as history of sexual abuse, marijuana use, and same-gender sex, have been associated with earlier onset of oral sex [99]. These findings are important because orally acquired HPV might also, in theory, be transmissible to the genital tract. Because risk of acquisition of oral HPV infection may precede risk for anogenital infection for a substantial proportion of adolescents, oral sexual behavior may warrant consideration in future policy for HPV vaccination, provided the vaccine is effective in preventing oral HPV infection.

Conclusion

It is now apparent that HPV is a causal factor for a distinct group of oral cancers that occur more frequently in men than women. Sexual behavior is associated with risk for this cancer. HPV 16 is found in the majority of HPV-positive oral cancers. The increasing incidence of HPV-associated oral cancer (oropharyngeal cancer) in the US underscores the potential importance of cancer prevention via HPV prophylactic vaccination of both women and men. Currently, vaccines targeted against oncogenic HPV infection have been indicated for use in women only. Vaccinating males against oncogenic HPV infection may be a particularly important approach for the prevention of oral cancer, given the incidence is higher in men. Clinical trials are in progress to determine the efficacy of such vaccines in preventing genital oncogenic HPV infection in men. Clinical trials to evaluate the potential for vaccines to prevent oral HPV 16 infection are in the developmental stages. In the absence of such clinical trial data, vaccine effectiveness may only be evaluable via surveillance of cancer incidence rates in vaccinated populations over the next several decades.

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Table 1

Odds ratios for HNSCC associated with HPV 16 L1 seropositivity in case-control studies

				Seroprevalence %		
Author	**Period of enrollment**	**Location**	**Tumor site**	**Cases (N)**	**Controls (N)**	**Adj OR (95% CI)**
Schwartz	1990–1995	US	Oral cavity	51.4 (259)	35.0 (446)	2.3 (1.6–3.3)[1]
			Oropharynx			
Herrero	1996–1999	International	Oral cavity	8.9 (1,319)	6.0 (1,527)	1.5 (1.1–2.1)[2]
			Oropharynx	13.4 (238)	6.0 (1,527)	3.5 (2.1–5.9)[2]
Smith	2000–2004	US	Oral cavity	26.8 (142)	22.4 (326)	1.2 (0.7–2.0)[3]
			Oropharynx	50.0 (62)	22.4 (326)	3.5 (1.9–6.5)[3]
Furniss	1999–2003	US	Oral cavity	14.7 (190)	10.7 (550)	1.4 (0.9–2.4)[4]
			Tongue, tonsil, pharynx	40.3 (228)	10.7 (550)	6.0 (4.1–8.7)
Pintos	1997–2001	Canada	Oral cavity	6.9 (72)	3.9 (129)	3.9 (0.9–17.5)[5]
			Base of tongue and tonsil	12.5 (72)	3.9 (129)	182.3 (7–4,753)[5]
Sitas	1995–2000	South Africa	Oral cavity and pharynx	36.3 (102)	30.8 (2,055)	1.5 (0.89–2.51)[6]
			Oropharynx	13.4 (238)	6.0 (1,527)	3.5 (2.1–5.9)[6]
D'souza	2000–2005	US	Oropharynx	57.0 (100)	7.0 (200)	32.2 (14.6–71.3)[7]
			All			
Gillison	2000–2006	US	HPV16-positive tumor	59 (92)	9 (184)	18.3 (6.8–49)[8]
			HPV16-negative tumor	8 (148)	8 (296)	0.9 (0.4–2.2)[8]

[1] Adjusted for age, gender, smoking, alcohol

[2] Adjusted for age, gender, country, smoking, alcohol, paan chewing

[3] Adjusted for age, alcohol, tobacco

[4] Adjusted for age, race, gender, smoking, drinking

[5] Adjusted for age, gender, tobacco, alcohol

[6] Adjusted for age, gender, education, residence, alcohol, tobacco

[7] Adjusted for age, gender, tobacco, alcohol, oral hygiene, family history of HNSCC

[8] Adjusted for race, tobacco, alcohol, marijuana, dental hygiene, number of oral sex partners. Matched on age and gender

Table 2

Odds ratios for HNSCC associated with oral HPV infection from case-control studies

Study	Enrollment	Location	Tumor site	Matching	Sampling	PCR detection	HPV type Specification	HPV Types	Prevalence % (N) Cases	Prevalence % (N) Controls	Adj OR (95% CI)
Schwartz	1990–1995	US	Oral cavity	Age, Gender	Tap water rinse and cytobrush	MY09/11 PCR	Southern blot	16,	5.9 (237)	4.1 (435)	1.3 (0.6–2.9)[4]
								18,			
								31,			
								33,			
								35			
			Oropharynx					6 or 11	2.5 (237)	4.4 (435)	0.5 (0.6–2.9)[4]
Herrero	1996–1999	International	Oral cavity	Age, gender, center	Saline oral rinse and cytobrush	GP5+/6+	EIA, Southern blot	High and Low Risk	Oral Cavity, 4.7 (511)	6.9 (613)	NS
			Oropharynx						Oropharynx, 8.9 (90)	6.9 (613)	NS
Smith	1994–1997	US	All sites	Age, gender	Saline oral rinse	MY09/11 PCR	Sequencing	High-risk	22.9 (210)	10.8 (333)	2.6 (1.5–4.2)[3]
								Low-risk	5.5 (210)	7.5 (333)	0.8 (0.4–1.7)[3]
Hansson	NR	Sweden	Oral cavity	Age, gender, residence	Saline oral rinse	MY09/11-GP5+/6+ Nested PCR	Sequencing	High-risk	25.2 (131)	0.6 (320)	63 (14–280)[1]
			Oropharynx					Low-risk	4.6 (131)	3.8 (320)	1.4 (0.5–4.3)[1]

Study	Enrollment	Location	Tumor site	Matching	Sampling	PCR detection	HPV type Specification	HPV Types	Prevalence % (N) Cases	Prevalence % (N) Controls	Adj OR (95% CI)
Pintos	1997–2001	Canada	Oral cavity	Age, gender, hospital	Saline oral rinse and cytobrush	PGMY09/11 PCR	Line blot	High-risk	18.1 (72)	3.1 (129)	4.8 (1.2–19.4)[2]
			Oropharynx								
D'souza	2000–2005	US	Oropharynx	Age, gender	Saline oral rinse and cytobrush	PGMY09/11	Line blot	High- and low-risk	37.0 (100)	6.0 (200)	12.3 (5.4–26.4)[5]
						HPV 16 RTPCRHPV 16 RT-PCR	Internal probe				
								16	32.0 (100)	4.0 (200)	14.6 (6.3–36.6)[5]
Gillison	2000–2006	US	All HPV16^{+} tumor	Age, gender	Saline oral rinse and cytobrush	HPV 16 RT-PCR	Internal probe				
			HPV16^{-} tumor					16	33.0 (92)	3 (184)	53 (8.5–333)
								16	4.0 (148)	3 (296)	1.1 (0.2–4.8)

[1] Adjusted for alcohol, tobacco

[2] Adjusted for age, gender, schooling, race, religion, language, tobacco, alcohol

[3] Adjusted for age, tobacco pack years, number of alcoholic drinks per week

[4] Adjusted for age, gender, cigarette smoking, drinks per week

[5] Adjusted for age, gender, tobacco pack years, alcohol drink-years, oral hygeine, family history of HNSCC

[6] Adjusted for age, gender, race, tobacco pack years, alcohol drink-years, oral hygeine, family history of HNSCC, number of oral sex partners.