Chapter 2
Behavioral Correlates of HPV-Associated Oropharyngeal Squamous Cell Carcinomas

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2.1 Introduction and Background

Since the recognition of a subset of head and neck squamous cell carcinomas (HNSCC) that present in an epidemiologically distinct manner, it is now understood that human papillomavirus (HPV) infection contributes to this difference. Furthermore, the HPV-related cancers were later found to have certain behavioral correlates that explained some of this distinction. The increasing incidence of HNSCC presenting without an association with alcohol and tobacco use has brought further attention to this disease (Antonsson et al. 2014). In the following chapter, the behavioral correlates to HPV infection, HPV-related HNSCC, and the differences compared to non-HPV-related HNSCC s will be discussed.

2.2 Behavioral Correlates to HPV Infections of the Oral Cavity

Overall prevalence of HPV in the oral cavity can vary between 2.3 and 20.0 % depending on the collection methods and the population studied (Antonsson et al. 2014; Colon-Lopez et al. 2014; Gillison et al. 2012). Certain behavioral correlates

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have been identified when investigating HPV oral DNA detection and persistence. There was some variability between studies about the behaviors that were associated with oral HPV infection. However, male gender and older age were demographic features most associated with oral HPV infection. Additionally, the most frequently reported associated behaviors were increased number of lifetime vaginal sex partners, increased number of lifetime oral sex partners, and current smoking. Table 2.1 summarizes the evidence from eight studies regarding the behavioral characteristics associated with HPV infection.

Cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) in 2009–2010 demonstrated that, regardless of specific sexual practice, oral HPV prevalence was eightfold higher in individuals who report ever having had sex as demonstrated in Fig. 2.1 (Gillison et al. 2012). This study also assessed ever having performed oral, anal, and vaginal sex. Prevalence of oral HPV detection was 7.8 % in women who reported engaging in oral sex, 9.5 % in women who reported anal sex, and 7.5 % in women who reported vaginal sex. The overall adjusted prevalence ratio (PR) for having greater than 21 lifetime sex partners was 10.65. The PR for men was greater than that for women (12.86 vs. 7.62, respectively). These characteristics are shown in Table 2.1. A smaller cohort in Australia noted that ever having sex was associated with an increased risk (OR of 1.75), but that this was not statistically significant. This study also found an increased odds ratio, (OR, 4.12) of detecting HPV in the oral cavity if one had given oral sex, but this characteristic was also not statistically significant. This study may have been limited by a relatively low overall HPV prevalence (2.3 %) and having only 307 participants (Antonsson et al. 2014).

The inconsistent effect of alcohol on oral HPV prevalence has been demonstrated in studies is likely due to the differences in the cutoffs used to determine the amount of alcohol consumed. Gillison et al. (2012) found a gradual increase in the HPV prevalence in the oral cavity as the number of alcoholic beverages consumed per week increased. The prevalence of HPV in the oral cavity was 12.3 % for study participants who consumed >14 drinks/week compared to a prevalence of 7.2 % in study participants who reported zero drinks/week. In contrast, a prospective cohort study showed that when adjusting for number of lifetime vaginal sex partners, reporting "ever drinking" alcohol was associated with oral HPV infection (Pickard et al. 2012). However, multiple studies have shown no association of alcohol with oral HPV infection (Antonsson et al. 2014; Beachler et al. 2012; Kreimer et al. 2013).

2.2.1 Behavioral Correlates of Oral HPV Infection in HIV-Infected Individuals

Several studies have examined behaviors associated with oral HPV infection in HIV positive compared to HIV negative individuals (Table 2.1). HIV negative individuals' risk factors include increasing age, being male, and HSV-2

Table 2.1 Risks factors HPV infection

Study	Study location	Recruitment years	Type of study	Ages studied	Risk factors for infection
Kreimer et al. (2004)	USA (Baltimore)	2001–2002	Cross-sectional	NR	*Tonsillar epithelium:*
					History of same-sex oral sex, >5 lifetime casual sex partners, STI history, current smoker
					Oral cavity:
					HIV positive—CD4 count <200 cells/mL, mucosal abnormality on exam, HSV-2 seropositivity, >1 oral sex partner in previous 12 months (13-fold increase), >1 casual sex partner
					HIV negative—increasing age, male gender, HSV-2 seropositivity
Smith et al. (2007)	USA (Iowa)	1998–2000	Prospective	Children and adolescents:	*Adolescent subset* (*aged 16–20 years*):
				2 weeks–20 years of age	Female gender ($p = 0.04$)
					Current smoking ($p = 0.01$)
					History of genital warts ($p < 0.01$)
					Higher frequency of HPV detection:
					Reporting sexual intercourse, earlier age at sexual debut, ≥3 lifetime sexual partners

(continued)

Table 2.1 (continued)

Study	Study location	Recruitment years	Type of study	Ages studied	Risk factors for infection
D'Souza et al. (2009)	USA (Baltimore)	2000–2006	Cross-sectional	Two populations:	*Outpatient adults*:
				≥18 years of age (outpatient adults)	Current smoker (OR 3.86, 95 % CI 1.17–12.7)
				>17 years of age (college aged men only)	>10 lifetime oral sex partners (OR 5.2, 95 % CI 1.13–24.7)
					>25 lifetime vaginal sex partners (OR 3.91, 95 % CI 1.05–14.6)
					College aged men:
					≥6 recent oral sex partners (OR 7.9, 95 % CI 1.09–59.0)
					≥6 recent open-mouthed kissing partners (OR 17.4, 95 % CI 1.5–198.0)
					Older age (p-trend = 0.02)
Beachler et al. (2012)	USA	2009–2010	Cross-sectional (nested within the Multicenter AIDS Cohort Study and the Women Interagency HIV Study)	NR	*HIV positive*:
					Current smoker
					Lower CD4 count
					Increased number of lifetime oral sex partners (p-trend 0.03)
					HIV negative:
					Older age
					Current smoker
					Increased number of recent oral sex partners (p-trend 0.003)
					Increased number of oral–anal sex partners (p-trend 0.002)

(continued)

Table 2.1 (continued)

Study	Study location	Recruitment years	Type of study	Ages studied	Risk factors for infection
Gillison et al. (2012)	USA	2009–2010	Cross-sectional	14–69 years of age	*Demographic factors*:
					Age (bimodal distribution—1st peak 30–34 years, 2nd peak 60–64 years), male gender, current smoker, increased number of drinks/week
					Sexual behaviors:
					Ever had sex (eightfold increase)
					Increased number of vaginal sex partners (p-trend <0.001)
					Increased number of oral sex partners (p-trend <0.001)
					Reported ever had anal sex (p-value 0.003)
Pickard et al. (2012)	USA (Ohio)	2009–2010	Prospective cohort	18–30 years of age	Older age
					Increased number of lifetime vaginal sex partners
					Increased number of lifetime oral sex partners
					Increased number of open-mouthed kissing partners
					Reporting marijuana use
Kreimer et al. (2013)	Multicenter (USA, Brazil, Mexico)	2007	Prospective cohort study (nested within the HPV Infection in Men cohort study)	Men 18–70 years of age	Marital status—single, divorced, separated, widowed
					Current or former smokers
					Bisexual men

(continued)

Table 2.1 (continued)

Study	Study location	Recruitment years	Type of study	Ages studied	Risk factors for infection
Antonsson et al. (2014)	Australia	NR	Prospective	University students:	Male gender ($p = 0.008$)
				18–35 years of age	Increased number of oral sex partners ($p = 0.0004$)
					Increased number of oral sex partners in the past year ($p = 0.008$)
					HIV positivity ($p = 0.023$)

NR not reported
CI Confidence Interval

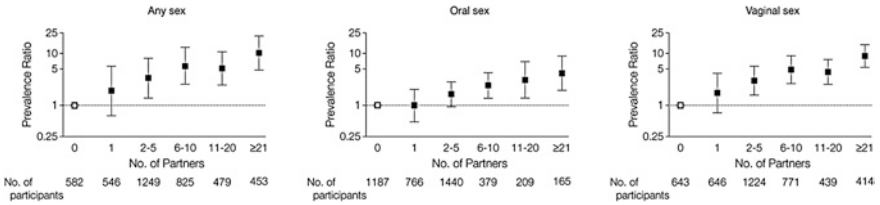

Fig. 2.1 Association of Number of Lifetime Sexual Partners With Prevalent Oral HPV Infection in the US Population Aged 14 to 59 **Years**. Human papillomavirus (HPV) prevalence ratio was adjusted for age (as a linear term), sex, race/ethnicity, marital status, and cigarette use. The analysis was restricted to individuals aged 14 to 59 years, for whom detailed sexual behavior data were available. Given high colinearity across sexual behaviors, each behavior was evaluated in separate models. $P < 0.001$ for trend in all three categories of sexual partner. Lifetime number of partners for performing oral sex included the sum of same- and opposite-sex partners; the reference category was 0 lifetime partners. Error bars indicate 95 % CIs. From: Gillison et al. (2012). doi:10.1001/jama.2012.101

seropositivity. HIV positive individuals' risk factors for oral HPV infection include CD4 cell count <200 cells/ml, HSV-2 seropositivity, and >1 oral sex partners in the preceding 12 months, which conferred a 13-fold increased risk (Kreimer et al. 2004). Interestingly in this study, increasing age did not seem to increase risk of oral HPV infection in HIV positive individuals, but did increase risk in HIV negative individuals. Another cross-sectional study nested within the Multicenter AIDS Cohort Study (MACS) and the Women Interagency HIV Study (WIHS) examined behaviors associated with oral HPV DNA detection. Increased number of oral sex partners, increased number of oral-anal sex partners, and increasing age were associated with increased risk for oral HPV infection in HIV negative individuals. HIV-infected individuals were significantly more likely to have a prevalent oral HPV infection than HIV-uninfected individuals (aOR = 2.1; 95 % CI, 1.6–2.8). The aOR of prevalent oncogenic and non-oncogenic HPV infections did not differ when these subjects were stratified by HIV status. In HIV positive individuals, risk was increased by increasing number of lifetime partners. However, this association was not observed in HIV-uninfected individuals. Smoking continued to be associated with increased risk for oral HPV infection in both HIV negative and HIV positive participants (Beachler et al. 2012).

Specific sexual behaviors in HIV-infected individuals have also been investigated. Beachler et al. found that the number of recent (defined as "within the last 6 months") oral sex partners was significantly associated with detection of prevalent HPV DNA in HIV negative individuals, but not HIV-infected individuals. Oral–anal contact was also significantly associated with oral HPV DNA detection in HIV-uninfected men who have sex with men (MSM), but not in HIV-infected MSM. Recent cigarette smoking was also associated with prevalent HPV DNA detection for both HIV-infected and uninfected individuals. Recent alcohol use was not associated, in this study, with prevalent HPV DNA detection in either group (Beachler et al. 2012).

2.2.2 *Prevalence of HPV at Other Sites and Its Effect on Oral HPV Prevalence*

Few studies have examined the effect of HPV prevalence at sites other than the oral cavity on the HPV prevalence in the oral cavity. Fakhry et al. (2006) performed a cross-sectional study, as part of the WIHS study, examining the prevalence's of oral and cervical HPV infections, as well as the relationship between oral and cervical infections in HIV positive and HIV negative women. Oral HPV infection was significantly less common than cervical HPV infection. In HIV positive women, oral HPV infection was found in 25.5 % compared to 76.9 % in the cervix. HIV negative women were less likely to have oral HPV infection (9 %), as well as cervical infection (44.9 %). Women with cervical infections were more likely to have HPV DNA also detected in their oral specimens. Fourteen women (6.3 %), all HIV positive, had type concordance between the two sites (Fakhry et al. 2006). Another cross-sectional study performed in Cambridge looked at HPV DNA detection across cervical, anal, and oropharyngeal sites in women with abnormal cervical cytology. When comparing HPV presence at multiple sites, comparing HPV detection in the cervix and the oropharynx, women with low-grade cervical lesions had HPV detected in both sites in 93.2 % of cases, and women with high-grade cervical lesions had HPV detected in both sites in 83.9 % of cases. When comparing HPV presence between the anus and the oropharynx, women with low-grade lesions had HPV detected in both sites in 95.1 % of cases, and women with high-grade cervical lesions had HPV detected in both sites in 76.9 % of cases. This study did not examine HPV type concordance between sites, the authors only examined presence of HPV at multiple sites (Crawford et al. 2011).

Steinau et al. (2014) examined the prevalence of HPV at the cervical and oral sites and associated behavioral correlates using data from NHANES, 2009–2010. There was an approximate fivefold increase in prevalence of HPV in the oral cavity (PR 4.9, 95 % CI 2.7–8.7) if women were positive for HPV DNA in the cervix, with only 43.2 % concordance for at least one HPV type between the sites. The prevalence of oral HPV infection in this study was also significantly associated with having $\geq$3 lifetime sexual partners with or without cervical HPV infection, but this factor did not meet statistical criteria for significance. Of note, the frequency of cervical HPV infections decreased with age, however, in oral HPV infections, this decline with age was not seen.

2.3 Behaviors Associated with Non-HPV-Associated Oropharyngeal Squamous Cell Carcinoma

Many studies of behaviors associated with HNSCC have been performed. It is well known that smoking and alcohol intake are associated with cancer risk. Tobacco is an independent risk factor for HNSCC, with increasing number of

cigarettes per day and duration of use increasing the risk for cancer (Gillison et al. 2008). Additionally, the risk associated with smoking increases with smoking nonfiltered cigarettes (Lissowska et al. 2003). The risk of cancer decreases with smoking cessation, generally after 10 years. Alcohol is also an independent risk factor of HNSCC. Risk increases with increasing number of drinks per week (specifically with greater than 21 drinks/week). However, HNSCC is not associated with age at initiation of alcohol consumption or duration of use. Depending on the study, concomitant tobacco and alcohol use increases risk on a multiplicative scale (Lissowska et al. 2003; Fernandez-Garrote et al. 2001). There is less consensus on data regarding dental condition and diet. However, poor overall mouth health, typically measured as less than daily tooth brushing and increasing number of teeth lost, have been associated with increased risk for HNSCC even after controlling for tobacco and alcohol use (Gillison et al. 2008; Talamini et al. 2000). Additionally, studies show a protective effect of increased intake of fresh fruits and vegetables (Fernandez-Garrote et al. 2001; Pavia et al. 2006).

2.4 Behavioral Correlates of HPV-Associated Head and Neck Cancers

HPV has been found in approximately 25 % of all HNSCC, and 30–70 % of oropharyngeal squamous cell carcinomas (Chaturvedi et al. 2011; Gillison et al. 2000; Giuliano et al. 2008). Approximately 90 % of HNSCC caused by HPV are caused by type 16 (Kreimer et al. 2005). The median age of diagnosis of HPV-associated HNSCC is 5 years younger than HNSCC associated with tobacco and alcohol. Individuals with HPV-associated HNSCC are less likely to use tobacco and alcohol, although these two cancer types are not mutually exclusive. Additionally, individuals are more likely to be Caucasian, be married, have a college education, and have a tumor in the oropharynx, lingual, or palatine tonsils (Gillison et al. 2008).

2.4.1 Sexual Behavioral Correlates

Table 2.2 summarizes the evidence from 13 studies (12 case-control, 1 case-to-case) regarding the association between HNSCC and sexual behavior. Four of these studies reported statistically significant associations of certain behaviors with HNSCC but did not specify an anatomic site, while four showed associations specifically with oropharyngeal sites and one showed association with oral cavity cancer. Four of these studies showed no association between HNSCC and sexual behavior. The most frequently reported sexual behaviors associated with risk for HNSCC include increasing numbers of lifetime vaginal and oral sex partners. Other factors that are more inconsistently associated with HNSCC risk include younger age at sexual debut, engaging in casual sex, oral–anal sex partners,

Table 2.2 Comparison of studies on HPV-associated head and neck cancers—sexual behaviors

Study	Study location	Recruitment years	Study design	Associations with HNSCC	Other factors (adjustment)
Maden et al. (1992)	USA (Washington)	January 1985–December 1989	Population-based case-control	In men—≥30 lifetime partners	Age, tobacco, alcohol, reference year
				Protective effect of ever having oral sex	
Schwartz et al. (1998)	USA (Washington)	1990–1995	Population-based case-control	In men—early age of sexual debut, increasing number of lifetime partners, history of genital warts	Age, tobacco, alcohol, race
Talamini et al. (2000)	Italy (Friuli-Venezia Giulia region)	July 1996–June 1999	Hospital-based case-control	No associations	Age, gender, fruit/vegetable intake, tobacco, alcohol
Fernandez-Garrote et al. (2001)	Cuba (Havana)	April 1996–July 1999	Hospital-based case-control	No associations	Age, gender, area of residence, education, tobacco, alcohol
Herrero et al. (2003)	Multicenter—Italy, Spain, Northern Ireland, Poland, India, Cuba, Canada, Australia, Sudan	April 1996–December 1999	Hospital-based case-control	No associations	Age, gender, country, tobacco, alcohol
Lissowska et al. (2003)	Poland (Warsaw)	March 1997–June 2000	Hospital-based case-control	No associations	
Rajkumar et al. (2003)	India (Bangalore, Madras, Trivandrum)	July 1996–May 1999	Hospital-based case-control	*Oral cavity cancer*:	Age, education, tobacco, alcohol, paan chewing
				In men—oral sex	
				In women—possibly >1 lifetime partner[b]	

(continued)

Table 2.2 (continued)

Study	Study location	Recruitment years	Study design	Associations with HNSCC	Other factors (adjustment)
Smith et al. (2004a)	USA (Iowa)	1994–1997	Hospital-based case-control	Sexual practices associated with HPV detection in cancers:	Age, tobacco, alcohol
				Higher mean number of sex partners, oral–anal sexual contact	
				In men—partners with abnormal PAP test	
D'Souza et al. (2007)	USA (Baltimore)	2000–2005	Hospital-based case-control	*Oropharyngeal SCC*:	Age, gender, tobacco, alcohol, oral hygiene, family history of HNSCC
				Higher number of lifetime vaginal or oral sex partners, engaging casual sex, early age at sexual debut, infrequent condom use	
Gillison et al. (2008)	USA (Baltimore)	May 2000–June 2006	Hospital-based case-control	*Oropharyngeal SCC*:	Race, tobacco, alcohol, marijuana use, oral hygiene
				Increasing number of lifetime vaginal or oral sex partners, ever engaging in casual sex, infrequent use of condoms (vaginal and oral sex), ever having a STI	
Tachezy et al. (2009)	Czech Republic (Prague)	2000–2004	Hospital-based case-control	Having engaged in oral–anal sexual contact	Age, tobacco, alcohol, HPV in exfoliated cells

(continued)

Table 2.2 (continued)

Study	Study location	Recruitment years	Study design	Associations with HNSCC	Other factors (adjustment)
Heck et al. (2010)	Multicenter (IARC INHANCE)		Population and hospital-based case-control	*Laryngeal cancer*: no associations	Age, gender, race/ethnicity, study site, education, tobacco, alcohol
				Oral cavity cancer: no associations	
				Oropharyngeal SCC:	
				≥6 lifetime sexual partners, ≥4 lifetime oral sex partners	
				Tonsillar cancer:	
				In men—oral sex (ever), younger age at sexual debut	
				≥4 oral sex partners	
				Base of the tongue cancer:	
				In women—oral sex (ever), 2 as compared to 1 sexual partner	
				In men—same-sex sexual partner	
Dahlstrom et al. (2011)[a]	USA (Texas)	May 1996–August 2006	Hospital-based case-to-case comparison study	*Oropharyngeal SCC*:	Age, gender, ethnicity, tobacco, income, lifetime number of sex partners
				Increased number of lifetime sex partners, increased number of oral sex partners	

[a]Case-to-case comparison of oropharyngeal squamous cell carcinoma to other head and neck squamous cell cancer sites
[b]Low number of women studied

history of STIs, inconsistent/infrequent condom usage, and same-sex sexual partners. Although not statistically significant, one study showed that men with HPV positive HNSCC were more likely to report partners with abnormal Pap smears or cervical dysplasia (Smith et al. 2004a).

Heck et al. (2010) performed a large epidemiologic study on sexual behaviors of 5642 HNSCC cases compared to sexual behaviors 6069 control subjects. This study was conducted by the International Head and Neck Cancer Epidemiology (INHANCE) consortium, which performed pooled analysis of four population-based, case-control studies and four hospital-based, case-control studies. In this analysis, risky behaviors varied based on cancer location within the head and neck. The authors did not find any association of sexual practices and increased risk for squamous cell carcinomas of the oral cavity or larynx. Oropharyngeal cancer was associated with history of six or more lifetime sexual partners [OR 1.25, 95 % CI 95 % 1.01–1.54] and four or more oral sex partners [OR 2.25, 95 % CI 1.42–3.58]. Tonsillar cancer was associated with four or more oral sex partners [OR 3.36, 95 % CI 1.32–8.53]. Additionally in men, tonsillar cancer was associated with ever reporting oral sex [OR 1.59, 95 % CI 1.09–2.33) and younger age of sexual debut [OR 2.36, 95 % CI 1.37–5.05]. Cancer at the base of the tongue was associated with ever reporting oral sex [OR 4.32, 95 % CI 1.06–17.59] in women and with reporting same-sex contact [OR 8.89, 95 % CI 2.14–36.8] in men. Additionally, the authors noted that there were no significant differences between the sexes for outcomes for oral sex, number of oral sex partners, and number of lifetime sex partners. Generally, there appears to be similar risks for sexual behaviors between men and women (Heck et al. 2010).

2.4.2 Tobacco and Alcohol Use

The literature regarding the association between tobacco and/or alcohol and increased risk of HPV positive HNSCC is inconsistent. Several studies have shown that tobacco and alcohol are cofactors in the development of HPV positive HNSCC, but are variable on whether there is effect modification or the degree of effect modification (Schwartz et al. 1998; Herrero et al. 2003; Riberio et al. 2011; Smith et al. 2004b, 2010). For example, a population-based, case-control study using HPV-16 L1 serology to measure HPV exposure found that an HPV seropositive individual who was currently smoking had an approximately eightfold increase for oral cancer compared to either a seronegative individual or an individual who was not currently smoking. This study found that the association was greater than expected and was considered to be synergistic. This synergistic association was not found for alcohol alone. When examining the combination of tobacco and alcohol, the authors found an association similar to tobacco alone (Schwartz et al. 1998). However, a hospital-based, case-control study also using HPV-16 L1 serology as a measure of HPV exposure, found that there were no synergistic effects between tobacco use and HPV seropositivity (Herrero et al. 2003).

Smith et al. (2010) performed a case-control study using HPV-16 L1 serology as the marker for HPV exposure which found no significant multiplicative effect modifications of HPV seropositivity and tobacco use, alcohol use, or combined tobacco and alcohol use.

However, other studies have shown that tobacco and alcohol are not cofactors of HPV in HPV positive HNSCC (D'Souza et al. 2007; Applebaum et al. 2007; Ji et al. 2008). D'Souza et al. (2007), using HPV-16 L1 serology and oral HPV DNA as markers of HPV exposure, found that there was no evidence of synergy with HPV and combined tobacco and alcohol use. Additionally, they found that HPV seropositivity and oral HPV DNA detection were associated with oropharyngeal cancer regardless of heavy tobacco and alcohol use. Studies performed by Applebaum et al. (2007) and Ji et al. (2008) found that the joint effects of HPV and tobacco were lower than expected. The risk for oropharyngeal cancers increased among heavy drinkers and smokers in the HPV seronegative population but not in the HPV seropositive population.

Additionally, site of the cancer may play a role in the effect that tobacco and alcohol have on HNSCC. Smith et al. (2012) performed a case control study examining the role of HPV seropositivity, tobacco, and alcohol on risk of oral cavity cancer compared to oropharyngeal cancer and controls. In oral cavity cancer, heavy tobacco or alcohol use increased cancer risk for HPV seropositive individuals compared to HPV seronegative individuals. In oropharyngeal cancer, heavy tobacco or alcohol use increased cancer risk for HPV seronegative individuals compared to HPV seropositive individuals.

These studies used different definitions for tobacco and alcohol use, used various measures for HPV exposure, and examined different sites of HNSCC, all of which likely contribute to the differences seen. It is unclear whether or not tobacco and/or alcohol are cofactors or effect modifiers for HPV positive HNSCC risk (Gillison et al. 2012). However, it has been shown that HPV infection can cause OPSCCs in individuals who use and do not use tobacco and alcohol (D'Souza et al. 2007).

2.4.3 Marijuana Use

Gillison et al. (2008) found that marijuana use was strongly associated with HPV-16 positive HNSCC. This association increased with increased intensity/frequency and duration of use. The odds ratios for HPV-16 positive HNSCC, measured by oral HPV DNA detection, decreased after cessation of use. These findings were not explained by confounding by tobacco or HPV exposure. This finding was much weaker in HNSCC not associated with HPV (Gillison et al. 2008). In contrast, Liang et al. (2009) performed a case-control study on marijuana's effects on HNSCC which, when stratified for HPV 16 seropositivity, showed no association with risk of HPV positive HNSCC.

2.4.4 Nutrition

A case-control study examining fruit consumption and risk for HPV positive HNSCC was performed between December 1999 and December 2003. HPV positivity was measured using HPV 16 antibodies. This study found that compared to HPV 16 seronegative individuals, those who were HPV 16 seropositive had an increased risk of HNSCC with increasing consumption of fruit. This same association was seen when limiting fruit consumption to citrus consumption. For the HPV 16 seronegative participants, increased fruit consumption, specifically citrus, was found to be protective of HNSCC. The authors did not find an association with vegetable intake (Meyer et al. 2008).

Another case-only, cross-sectional study examined the effect of micronutrients on risk of HPV positive tumors compared to HPV negative tumors. This study adjusted for age, sex, BMI, tumor site, energy intake (determined by adding the food intakes based on standard portion size, nutrient content, and consumption frequency), alcohol, and tobacco. The authors found that there was as significant association between HPV positive tumor status and increased intake of vitamin A, vitamin E, β-carotene, iron, and folate. There was not a significant association of HPV positive tumor status and vitamin C, vitamin D, calcium, zinc, copper, riboflavin, and vitamin B12 intake. The authors posited that these micronutrients may increase an individual's risk for HPV infection, which would put them at increased risk for HPV-associated HNSCC. There may be an association with these micronutrients and improved HNSCC prognosis, which needs to be examined further (Arthur et al. 2011).

2.4.5 Dental Health

There have been a couple of studies that have examined the effect of oral health on HPV-associated head and neck cancers. Gillison et al. (2008) examined oral hygiene as measured by frequency of tooth brushing and dental visits and number of missing teeth. This study did not find an association of poor oral health and HPV positive HNSCC. However, a case control study by Tezal et al. (2009) showed a significant association with higher mean alveolar bone loss (ABL) and prevalence of periodontitis with HPV positive head and neck cancers compared with HPV negative head and neck cancers. These associations remained strong after stratification for tobacco and alcohol use history. They found that for every millimeter of ABL, the risk for HPV-associated head and neck cancer increased fourfold. This study agreed with the study by Gillison et al. (2008) that number of missing teeth was not associated with HPV positive head and neck cancers.

2.5 Conclusion

In conclusion, there is a well-recognized subset of HNSCC that are associated with HPV infection. These cancers generally present in a younger population and are not specifically associated with tobacco and alcohol use. There are a variety of behaviors that are associated with increased risk of HNSCC caused by HPV. The most frequently reported sexual behaviors associated with increased cancer risk including increased number of lifetime vaginal or oral sex partners, younger age at sexual debut, oral–anal sex partners, history of other sexually transmitted infections, and same-sex sexual partners. The nonsexual behaviors (i.e., tobacco/alcohol, marijuana, nutrition, and dental health) data is less consistent in regards to the association with risk for HPV-associated HNSCC. Behavioral factors that contribute to oral HPV infection in HIV-infected individuals do not differ greatly from those in HIV-uninfected individuals. However, certain risk factors particular to HIV (such as decreasing CD4 count) impart an increased risk of oral HPV DNA detection. The understanding of the significant behavioral factors contributing to oral HPV DNA detection and the development of HPV-associated HNSCC has increased greatly over the years, but further studies are necessary to better delineate the main contributors in order to develop effective interventions.

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