Epidemiology and Clinical Aspects of HPV in Head and Neck Cancers

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Abstract Human papillomavirus (HPV) infection is now established as a major etiologic factor for oropharyngeal cancers. Case–control studies conducted around the world show strong and consistent associations of markers of HPV exposure with risk of oropharyngeal cancers (range of odds ratios [OR] for oral oncogenic HPV infections = 3.6–230.0, ORs for HPV16 L1 antibodies = 2.3–182.0, and ORs for HPV16 E6/E7 antibodies = 9.2–231.0. HPV-positive oropharyngeal cancers are epidemiologically distinct from HPV-negative ones, and are characterized by younger age at onset, male predominance, and strong association with sexual behaviors. Importantly, HPV-positive oropharyngeal cancer patients have substantially improved outcomes (28–80 % reductions in the risk of death) than HPV-negative patients. Given the superior survival, younger age, and good performance status of HPV-positive oropharyngeal cancer patients, de-intensified therapies are currently being considered for this group of patients. Recent analyses of cancer registry data show dramatic increases in incidence of oropharyngeal cancers during the past 15–20 years in several parts of the world, highlighting the need for prevention strategies. If proven efficacious, currently available prophylactic HPV vaccines hold great promise for primary prevention of HPV-associated oropharyngeal cancers.

Keywords Human papillomavirus · HPV · Oropharyngeal cancer

Introduction

Head and neck squamous cell carcinomas (HNSCCs), which include cancers of the oral cavity, oropharynx, and larynx, are the sixth most common cancers worldwide with an estimated annual burden of 355,000 deaths and 633,000 incident cases [1]. Tobacco and alcohol use have traditionally been the major risk factors for all HNSCC subsites [2]. However, over the past 10–15 years, human papillomavirus (HPV) infection has been increasingly recognized as a major etiologic factor for a subset of HNSCCs—cancers arising from the oropharynx, including the base of tongue, tonsil, and other parts of the pharynx [2, 3]. This recognition of a subset of HNSCC as being virally-induced has key clinical and prevention implications. This manuscript shall review the epidemiologic association of HPV infection with oropharyngeal cancers, clinical features of HPV-positive oropharyngeal cancers, and the population-level burden and prevention potential of HPV-associated HNSCCs.

Epidemiologic Association of HPV with HNSCCs

Association of HPV with Oropharyngeal Cancers

Numerous case-series conducted in the late 1990s and 2000s have evaluated the prevalence of HPV infection in oropharyngeal cancers using molecular techniques such as PCR and in situ hybridization [4]. A systematic review of worldwide literature conducted by Kreimer et al. [5] in 2005 reported that HPV DNA was detected in 35.6 % of oropharyngeal cancers, with HPV type 16 accounting for a vast majority (87 %) of HPV-positive cases. In addition to investigating the presence of HPV DNA, several studies

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Table 1 HPV exposure measures utilized in case–control and cohort studies

Exposure measure	Limitations	Strengths
HPV DNA in oral specimens (Oral rinses or exfoliated cells)	Single time-point measure of HPV exposure	High assay sensitivity and specificity
HPV L1 antibodies in serum	Lack of anatomic site specificity Low sensitivity of assay	Indicative of cumulative lifetime exposure to HPV High specificity of the assay
HPV E6/E7 antibodies in serum	Low sensitivity of assay	Indicates the presence of HPV-associated cancer

Sensitivity and specificity for antibody assays are with reference to the ability of antibodies to detect non-site-specific HPV infection/exposure

have evaluated HPV functionality in oropharyngeal tumors [2]. These studies show specificity of HPV to tumor cell nuclei [6], integration of HPV DNA into the human genome [6, 7], high HPV viral copy numbers [8], and high-level expression of the HPV oncogenes (E6 and E7) in tumors [9], all of which underscore a causal association of HPV with oropharyngeal cancers.

Several analytic epidemiologic studies have evaluated the association of HPV with risk of oropharyngeal cancers,

predominantly through case–control study designs. These studies have utilized a variety of HPV exposure measures (Table 1) [2, 10]: presence of HPV DNA in oral specimens—a single time-point measure of HPV exposure, presence of antibodies to HPV’s major capsid L1 protein in serum—a measure of cumulative lifetime exposure to HPV at any anatomic site, and the presence of antibodies to HPV’s E6 and E7 oncoproteins—an indicator of the presence of HPV-associated cancer. Studies have also utilized sexual behaviors, such as the number of lifetime oral and vaginal sex partners, as surrogate measures for HPV exposure.

Case–control studies conducted around the world show strong and consistent associations of markers of HPV exposure with risk of oropharyngeal cancers, even after adjustment for important HNSCC risk factors such as age, gender, and tobacco and alcohol use. In studies utilizing the presence of oncogenic HPV DNA in the oral cavity, odds ratios (ORs) have ranged from 3.6 to 230.0, with a vast majority of studies reporting risk estimates higher than 10.0 [11–16] (Table 2). Similarly, studies utilizing type-specific HPV16 L1 antibodies have reported ORs in the range of 2.3–182.0 [11, 13–15, 17–22] (Table 2). Studies utilizing type-specific HPV16 E6/E7 antibodies have reported ORs in the range of 9.2–231.0 [11, 13, 15, 20, 22] (Table 2). Finally, studies utilizing sexual behaviors as surrogate markers for HPV exposure have reported ORs of 2.0–4.0 [2, 10, 23].

Table 2 Selected studies for the association of HPV infection with risk of oropharyngeal cancer

Study, year	Country	# Cases/# controls	Oral HPV DNA OR (95 % CI)	HPV16 L1 antibodies OR (95 % CI)	HPV16 E6/E7 antibodies OR (95 % CI)
Schwartz, 1998 [17]	USA	49/446	–	3.9 (2.0–7.8)	–
Mork, 2001 [18] ^a	Denmark, Finland, Sweden	26/1,568	–	14.4 (3.6–58.1)	–
Herrero, 2003 [11]	Multi-country	255/1,568	1.0 (0.4–2.5) ^b	3.5 (2.1–5.9)	9.2 (4.8–17.7)
Dahlstrom, 2003 [19]	USA	70/120	–	59.5 (57.0–620.2)	–
Smith, 2004 and 2007 [12, 20]	USA	71/326	3.6 (1.8–7.1) ^b	3/5 (1.9–6/5)	231.0 (62.0–859.0)
Hansson, 2005 [16]	Sweden	46/320	230.0 (44.0–1,200.0) ^b	–	–
D’Souza, 2007 [13]	USA	100/200	14.6 (6.3–36.6) ^c	32.2 (14.6–71.3)	58.4 (24.2–138.3)
Applebaum, 2007 [21]	USA	203/549	–	10.0 (6.6–15.3)	–
Pintos, 2008 [14]	Canada	72/128	19.3 (2.3–159.5) ^b	182.3 (7.0–4,753.0)	–
Tachezy, 2009 [15]	Czech Republic	86/104	41.9 (12.6–139.0) ^b	6.3 (2.9–13.9)	16.3 (5.9–4.5)
Ribeiro, 2011 [22]	Central Europe and Latin America	439/3,235	–	–	179.0 (35.8–899.0)

OR = odds ratio, CI = confidence intervals

– Not reported

^a The study by Mork et al. was the only study to prospectively evaluate risk of oropharyngeal cancer by HPV antibody status

^b Associations for any oncogenic/high-risk HPV infections

^c Associations for HPV16 infection

A potential limitation in prior case–control studies is the lack of temporal association between HPV infection and the occurrence of oropharyngeal cancer (i.e. evidence that HPV infection preceded the development of cancer). Only one study has addressed this question. In a nested case–control study conducted in Denmark, Finland, and Sweden, Mork et al. [18] reported that the presence of HPV16 L1 antibodies in pre-diagnostic serum samples was associated with a 14.4-fold increased risk of oropharyngeal cancer. Importantly, the presence of HPV16 antibodies preceded oropharyngeal cancers by more than 10 years, underscoring a temporal association.

Collectively, prior case–control studies show that HPV infection is strongly and consistently associated with increased risk of oropharyngeal cancers, with HPV16 infection accounting for an overwhelming majority of the HPV-associated cancers. The epidemiologic association of HPV infection in oropharyngeal cancers fulfills all of the criteria for causality [2, 10]: strength and consistency of associations across studies, specificity of the association to oropharyngeal cancers when compared to other head and neck cancer subsites (as noted below), temporality of the association, biologic gradient (albeit with limited evidence, given that only one study has reported that oropharyngeal cancer risk increases with increasing HPV antibody titer levels), and experimental evidence that expression of the HPV oncogenes is necessary for maintenance of the malignant phenotype, and biologic plausibility, analogy, and coherence (given the rich evidence for a causal association of HPV with other human cancers, such as cervical, anal, penile, vaginal, and vulvar cancer).

Association of HPV with Other Head and Neck Cancer Subsites

Several case-series have reported the presence of HPV DNA in oral cavity and laryngeal cancers. For example, the systematic review by Kreimer et al. [5] reported that 23.5 % of oral cavity cancers and 24 % of laryngeal cancers were HPV DNA positive. Similarly, a recent systematic review by Syrjänen et al. [24] reported that the prevalence of HPV DNA was fourfold higher among individuals with oral precancerous lesions (such as oral leukoplakia, lichen planus, and oral dysplasia) when compared to normal controls. However, supporting molecular evidence—specificity of HPV DNA to tumor cell nuclei, viral integration into the host genome, high HPV viral load, and expression of HPV oncogenes—has been lacking in the literature. Given the known susceptibility of PCR-based methods to contamination, in the absence of data on functionality of HPV in tumor cells, the etiologic role of HPV in oral cavity and laryngeal cancers remains unclear. Likewise, the etiologic role of HPV

infection in other head and neck cancers, such as sinonasal cancers and nasopharyngeal carcinomas currently remains unclear.

Prior case–control studies addressing the association of HPV with oral cavity and laryngeal cancers have reported weak and inconsistent associations with HPV exposures noted in Table 1, with ORs ranging from 2.0 to 4.0 [2]. Misclassification of the primary tumor site (e.g. misclassification of base of tongue cancers as oral tongue cancers) and confounding from positive correlations between tobacco use and sexual behaviors could potentially explain these modest associations.

In summary, additional molecular and epidemiologic studies are needed to further evaluate the association of HPV infection with oral cavity and laryngeal cancers. This question is particularly relevant given that the incidence of other head and neck subsites far exceeds that of oropharyngeal cancers in most parts of the world [25]. Therefore, even a small HPV-attributable proportion for oral cavity and laryngeal cancers would translate to a sizeable annual number of cancers worldwide.

Epidemiologic Features of HPV-Positive Oropharyngeal Cancers

Emerging epidemiologic evidence from case-series and case–control studies suggests that HPV-positive oropharyngeal cancers are distinct from HPV-negative cancers [3]. HPV-negative oropharyngeal cancers are characterized by older age at onset (typically in the 7th decade of life), male predominance (3:1 male: female ratio), strong associations with tobacco and alcohol use, and moderate associations with risk factors such as poor oral hygiene and a diet low in fruit and vegetable consumption [3]. In contrast, HPV-positive oropharyngeal cancers are characterized by a younger age at onset (3–5 years compared to HPV-negative oropharyngeal cancers), male predominance (3:1 male: female ratio), strong associations with sexual behaviors (consistent with the predominantly sexual acquisition of oral HPV infections), and inconsistent and weak associations with tobacco and alcohol use [3]. Gillison et al. [26] compared risk factor profiles for tumor HPV DNA-positive and tumor HPV DNA-negative oropharyngeal cancers with a common age and sex-matched control group. HPV-negative oropharyngeal cancers were significantly associated with tobacco and alcohol use and markers of poor oral hygiene. In contrast, HPV-positive oropharyngeal cancer risk was strongly associated with HPV exposure measures and marijuana use and was not associated with tobacco and alcohol use.

The reasons underlying the distinct epidemiologic profiles for HPV-positive and HPV-negative oropharyngeal cancers could be several-fold. For example, the younger

age at onset and male predominance for HPV-positive oropharyngeal cancers could arise from birth cohort effects of HPV exposure (discussed in the population-level burden section) and/or differences in sexual behaviors across age and gender. There is considerable debate regarding the association of tobacco and alcohol use with risk of HPV-positive oropharyngeal cancers as co-factors and the interaction between tobacco/alcohol and HPV infection. Current evidence regarding the role of tobacco/alcohol as co-factors for HPV-positive oropharyngeal cancers is equivocal, with some studies reporting a positive association [11, 12, 17, 22] and others reporting no association [13, 21]. Likewise, evidence is equivocal regarding effect modification between tobacco/alcohol and HPV infection, with studies reporting no interaction [13], super-additive interaction [12, 17], and sub-multiplicative interaction [11, 22]. The lack of strong association of tobacco/alcohol use with risk of HPV-positive oropharyngeal cancers is consistent with these risk factors targeting similar causal pathways (p53 and pRb pathways) with different mechanisms—genomic damage for tobacco/alcohol and functional disruption for HPV infection [4]. Despite the inconsistencies in the literature, it can be concluded that HPV-positive oropharyngeal cancers occur among both users and non-users of tobacco/alcohol. Additional studies, perhaps with larger sample sizes, are needed to precisely characterize the interplay of HPV infection with tobacco and alcohol use.

Epidemiology of Oral HPV Infection

Despite the recognition of HPV infection as a major etiologic factor for oropharyngeal cancers, systematic data on the epidemiology of oral HPV infections have only recently begun to emerge. In a systematic review of 18 published cross-sectional studies conducted among healthy individuals [27], prevalence of any detectable HPV type was 4.5 %, prevalence of high-risk HPV types was 3.5 %, and prevalence of HPV16 was 1.0 %. Modest sample sizes, heterogeneous HPV detection methods, and non-representative, convenience samples limit the interpretation of these results. More recently, Gillison et al. [28] conducted the first population-based evaluation of oral HPV prevalence among 5,500 US individuals aged 14–69 years as part of the nationally-representative National Health and Nutritional Examination Survey (NHANES 2009/2010). Overall prevalence of any of 37 detectable HPV types was 6.9 %, prevalence of high-risk HPV infections was 3.7 %, prevalence of low-risk HPV infection was 3.1 %, and prevalence of HPV16 infection was 1.0 %. In contrast to low oral HPV prevalence in the general population, prevalence rates are 3–4 times higher among individuals infected with human immunodeficiency virus (HIV) [29].

Consistent with the sexually transmitted nature of HPV infections, oral HPV prevalence is strongly associated with sexual behaviors, such as lifetime and recent number of any, oral, and vaginal sex partners [27, 28]. However, studies also show that non-sexual transmission of HPV infection to the oral cavity is plausible. For example, D'Souza et al. [30] reported that oral HPV prevalence increased with increased number of open-mouth kissing partners among college-aged men, suggesting the possibility of salivary transmission of oral HPV infection. Cigarette smoking is another risk factor consistently associated with oral HPV prevalence, with higher prevalence rates among current vs. never/former smokers [28, 31]. This association of smoking with increased HPV prevalence does not seem to be entirely explained by sexual behaviors, raising the possibility that smoking-induced immunosuppression could potentially play a role.

The association of age and sex with oral HPV infection has been inconsistent in the literature. Most studies evaluating oral HPV prevalence across ages have reported that prevalence either remains stable or significantly increases with age [27, 31]. In contrast to these prior reports, in the US NHANES, oral HPV prevalence showed a bimodal pattern, with peak prevalence at ages 30–34 years (7.3 %) and 60–64 years (11.4 %) [28]. Although the reasons are not currently clear, the bimodal pattern perhaps arises from a combination of differences in sexual behaviors across birth cohorts, increased oral HPV incidence at older ages, and re-activation of latent infections at older ages [28]. Prior studies have inconsistently reported higher oral HPV prevalence among men than women. For example, in the systematic review by Kreimer et al. [27] oral HPV prevalence was similar between sexes. In contrast, in the US NHANES study, oral HPV prevalence was significantly higher among men than women (10.1 % vs. 3.6 %) [28]. Although consistent with population-level incidence rates of HPV-positive oropharyngeal cancer [32], this threefold higher prevalence of oral HPV infection among men does not appear to be readily explained by differences in sexual behaviors, thus pointing to the possibility of biologic differences between men and women. Potential explanations for higher oral HPV prevalence among men could include higher transmissibility of HPV through oral sex among men and naturally-acquired protective immunity from genital HPV infections among women [28].

Very few prospective studies have evaluated the natural history of oral HPV infections. The limited data available in the literature suggests that oral HPV acquisition/incidence is rare (<1.7 per 100 person-months over a 6-month period) compared to cervical HPV infections (10.4 per 100 person-months) [33]. Despite lower incidence, the natural history in terms of persistence/clearance of oral HPV infections appears similar to cervical HPV infections [33].

Additional studies with adequate sample sizes are clearly needed to precisely estimate rates and predictors of incidence, persistence, and clearance of oral HPV infections.

Clinical Features of HPV-Positive Oropharyngeal Cancers

The clinical presentation of HPV-positive oropharyngeal cancers is distinct compared to HPV-negative cancers [3, 4, 34]. HPV-positive oropharyngeal cancers present at a more advanced clinical stage, often characterized by lower tumor size (T stage) and increased nodal involvement (N stage) compared to HPV-negative oropharyngeal cancers. HPV-positive oropharyngeal cancers are also characterized by distinct histologic features, such as moderate/poor tumor differentiation and nonkeratinizing or basaloid pathology [4].

Several retrospective case-series have shown that HPV-positive oropharyngeal cancer patients (identified using HPV PCR, HPV in situ hybridization, or p16 immunohistochemistry on tumor tissues) have significantly improved overall survival and disease-free survival compared to patients with HPV-negative oropharyngeal cancer patients [2, 3, 35]. The survival benefit for patients with HPV-positive oropharyngeal cancers has varied across studies from 20 to 80 % reductions in the risk of death [2]. A meta-analysis of published literature through 2007 showed that compared to HPV-negative oropharyngeal cancers, patients with HPV-positive oropharyngeal cancer had a 28 % reduction in the risk of death and a 49 % reduction in the risk of disease recurrence [36]. More recently, retrospective and prospective evaluations of tumor HPV status have been conducted within cooperative group clinical trials—ECOG 2399, RTOG 0129, TROG 2.02, TAX 324, and DHANCA 6 and 7 (Table 3) [34]. In these studies, HPV-positive oropharyngeal cancer patients had significantly better survival outcomes compared to HPV-negative oropharyngeal cancer patients, with 38–80 % reductions in the risk of death (Table 3) [37–41].

Of note, HPV-positive oropharyngeal cancer patients have significantly better survival compared to HPV-negative patients even after adjustment for differences in favorable prognostic factors often observed among HPV-positive patients—younger age, better performance status, fewer co-morbidities, and less exposure to tobacco smoking [38]. For example, Ang et al. [38] reported that these prognostic factors explained only 10 % of observed survival differences between HPV-positive and HPV-negative oropharyngeal cancers.

A few studies have evaluated epidemiologic and molecular modifiers of the survival benefit among HPV-positive oropharyngeal cancer patients. Cigarette smoking is the strongest modifier of prognosis among HPV-positive oropharyngeal cancer patients, with significantly better survival among HPV-positive never-smokers than HPV-positive smokers [38, 42]. Using recursive partitioning, Ang et al. [38] reported that cigarette smoking was the second most important predictor of survival following HPV infection. In this study, information on tumor HPV status, smoking, and TNM stage, could stratify oropharyngeal cancer patients into low, intermediate, and high-risk groups based on the risk of mortality. Molecular features, such as TP53 mutations and EGFR expression, have also been suggested as modifiers of prognosis among HPV-positive oropharyngeal cancer patients [43, 44]. However, these observations are based on sparse sample sizes. Larger studies are needed to evaluate the interaction of HPV infection with TP53 mutations and EGFR expression/copy number, particularly in view of negative correlations of these markers with tumor HPV status [43, 44].

The precise mechanisms for the favorable prognosis of HPV-positive patients are currently unclear. The superior survival is, in part, attributed to enhanced sensitivity of HPV-positive tumors to chemoradiation and induction chemotherapy [34, 37]. This enhanced therapeutic response is believed to arise from the absence of field carcinogenesis in HPV-induced tumors, and consequently, low rates of genomic damage. Compared to HPV-negative oropharyngeal tumors, HPV-positive tumors are known to harbor a

Table 3 Selected studies of the association of HPV infection with oropharyngeal cancer prognosis

Study	Author, year	Number of cases	HPV detection methods	Follow-up time (years)	Overall survival HR (95 % CI)
ECOG 2399	Fakhry, 2008	96	HPV16 DNA ISH	2	0.36 (0.15–0.85)
RTOG 0129	Ang, 2010	323	HPV16 DNA ISH	5	0.42 (0.27–0.66)
TROG 02.02	Rischin, 2010	185	p16 IHC	5	0.36 (0.17–0.74)
DHANCA 6 and 7	Lassen, 2011	794	p16 IHC	5	0.62 (0.49–0.78)
TAX 324	Posner, 2011	111	HPV16 DNA PCR	5	0.20 (0.10–0.38)

Abbreviations: ISH = in situ hybridization, IHC = immunohistochemistry, PCR = polymerase chain reaction, HR = hazard ratio, CI = confidence interval

Note: Adapted from Gillison et al., 2012 [10]

lower frequency of TP53 mutations [43, 45], lower loss of heterozygosity and lower microsatellite instability at key loci such as 3p, 9p, and 17p [9]. Indeed, recent studies using whole exome sequencing of oropharyngeal tumors show lower rates of genetic mutations in HPV-positive vs. HPV-negative tumors (4.8 vs. 20.6) [46]. Immune responses to HPV antigens (e.g. HPV E6/E7 proteins) have also been suggested as contributors to the superior survival among HPV-positive patients [47–49].

Given the superior survival, younger age, and good performance status of HPV-positive oropharyngeal cancer patients, de-intensified therapies are currently being considered for this group of patients [34]. Two clinical trials, a phase II ECOG trial and a phase III RTOG trial, are currently underway in the US to address this question [34].

Population-Level Burden and Prevention Potential

The proportion of oropharyngeal cancers caused by HPV infection has varied widely in the literature. For example, a case–control study conducted in Central Europe and Latin America during 1998–2003 reported very low HPV prevalence in oropharyngeal tumors (4.4 %) [22]. On the other hand, a molecular analysis of tonsil cancers that occurred during 2006–2007 in Sweden showed that 93 % of tonsil cancers were caused by HPV infection [50]. In the systematic review by Kreimer et al. [5], HPV prevalence in oropharyngeal cancers was 47 % in studies conducted in North America, 46 % in Asia, and 28 % in Europe. This heterogeneity at least in part could arise from geographic and temporal heterogeneity in sexual behaviors and tobacco exposures. Contemporary estimates based on multi-institutional studies conducted in the US show that 65–70 % of oropharyngeal cancers are caused by HPV infection [32, 37].

Recent analyses of cancer registry data show dramatic increases in incidence of oropharyngeal cancers during the past 15–20 years in several parts of the world (Table 4)—Australia [51], Canada [52], Denmark [53], Finland [54], Japan [55], The Netherlands [9], Norway [56], Scotland [57], Sweden [50, 58], UK [59], and USA [32, 60]. Notably, in most of these countries, incidence of other head and neck cancer sites, such as oral cavity cancers, declined significantly during the same calendar period (Table 4). The rising incidence of oropharyngeal cancers during an era of declining smoking has been attributed to HPV infection, a phenomenon characterized as a “virus-related epidemic. [3]” Indeed, molecular analyses of historically collected oropharyngeal tumors in Australia [51], Sweden [50], and the US [32] show dramatic increases in HPV prevalence over calendar time. For example, Chaturvedi et al. [32] recently reported that HPV prevalence in oropharyngeal tumors increased from 16 % during the late 1980s to 72 % during the early 2000s in the US. In this study, the incidence of HPV-positive oropharyngeal cancers increased by 225 % from the late 1980s to the early 2000s. These rapid increases in oropharyngeal cancer incidence are believed to arise from increased oral HPV exposure due to changes in sexual behaviors among recent birth cohorts. Indeed, data from Australia, Sweden, and the US show that markers of high-risk sexual behaviors, such as earlier ages of sexual debut, practice of premarital sex, average number of lifetime partners, and practice of oral sex, have all increased among recent birth cohorts [61].

In developed countries, given declining incidence of cervical cancers due to successful screening programs, HPV-associated oropharyngeal cancers could soon emerge as the dominant HPV-associated cancer. For example, should recent incidence trends continue in the US, the annual numbers of HPV-associated oropharyngeal cancers are projected to surpass that of cervical cancer by the year

Table 4 Selected studies of incidence trends for head and neck cancers

Country	Reference	Years	Incidence trends for oropharyngeal cancers		Incidence trends for other head and neck cancers	
			Men	Women	Men	Women
Australia	Hocking, 2011 [51]	1982–2005	Increase	Increase	Decrease	Stable
Canada	Auluck, 2010 [52]	1980–2006	Increase	Increase	Decrease	Stable
Denmark	Blomberg, 2011 [53]	1978–2007	Increase	Increase	Increase	Increase
England	Reddy, 2010 [59]	1985–2006	Increase	Increase	Increase	Increase
Japan	Ioka, 2005 [55]	1965–1999	Increase	Increase	Increase	Stable
The Netherlands	Braakhuis, 2009 [9]	1989–2006	Increase	Increase	Stable	Increase
Norway	Mork, 2010 [56]	1981–2005	Increase	Increase	Decrease	Stable/decrease
Sweden	Hammarstedt, 2006 [58]	1970–2002	Increase	Increase	NR	NR
USA	Chaturvedi, 2008 [60]	1973–2004	Increase	Decrease	Decrease	Decrease

Adapted from Gillison et al. 2012 [10]

2020 [32]. These observations highlight the need for prevention strategies for HPV-associated oropharyngeal cancers.

Cancers caused by HPV infection—anal, cervical, penile, vaginal, and vulvar—progress through a multi-step process of carcinogenesis through varying grades of cytologic and histologic precursor lesions (e.g. cervical intraepithelial neoplasia [CIN] grade I, CIN II, CIN III, carcinoma in situ, and invasive cervical cancer) [62]. The recognition of these precursor lesions, as well as the availability of screening and treatment methods, has greatly enabled secondary prevention strategies for HPV-associated cancers, such as cervical cancer [63]. In contrast, precursor lesions caused by HPV infection in the oropharyngeal region have not yet been identified. For example, Fakhry et al. [64] recently evaluated the feasibility of conducting a “pap smear equivalent” test through collection of tonsillar cytology samples for the detection of precancerous lesions in two populations at high risk of oropharyngeal cancer—patients with oropharyngeal abnormalities, 70 % of whom had invasive oropharyngeal cancer, and HIV-infected individuals. Among those with oropharyngeal abnormalities, both oral HPV16 infection and the presence of cytologic abnormalities were strongly associated with the presence of invasive oropharyngeal cancer. In contrast, cytologic abnormalities were rare and were not associated with oral HPV16 infection among HIV-infected individuals. This absence of detectable precancerous lesions among individuals without clinical disease perhaps arises from the difficulty in sampling the deep tonsillar crypts, the relevant anatomic location of HPV-induced cancers [62, 64]. In summary, the lack of an identifiable HPV-induced precursor lesion in the oropharyngeal region, the unavailability of screening modalities, and the lack of data on potential treatments for any precursor lesions in the oropharyngeal region all point to a lack of feasibility of secondary prevention of HPV-associated oropharyngeal cancers at this time [62].

Currently available prophylactic HPV vaccines (a bivalent vaccine against HPV types 16 and 18 and a quadrivalent vaccine against HPV types 16, 18, 6, and 11) hold great promise for primary prevention of HPV-associated oropharyngeal cancers [65]. Notably, both vaccines target HPV type 16, which accounts for over 90 % of HPV-associated oropharyngeal cancers. No study to date has evaluated the efficacy of HPV vaccines in preventing oral HPV infection. Nevertheless, the high efficacy for prevention of persistent HPV infections observed at other anatomic sites, such as anus, cervix, penis, vagina and vulva [66–70], points to the possibility of equivalent high efficacy of prophylactic vaccines in preventing persistent oral HPV infection. The burden of oral HPV infections and HPV-associated oropharyngeal cancers is higher among

men than women [32]. Therefore, the recent recommendation by the US Centers for Disease Control and Prevention for routine vaccination of boys and men aged 9–21 years [71], in addition to girls and women aged 9–26 years, augers well for primary prevention of HPV-associated oropharyngeal cancers among eligible birth cohort, provided vaccine coverage is adequately high.

Conclusions and Future Research Directions

Studies conducted over the past decade have led to an increased understanding regarding HPV-associated oropharyngeal cancers. However, several key questions remain. Molecular studies are needed to clarify HPV's role in the etiology of other HNSCCs, such as oral cavity and laryngeal cancers. Natural history studies of oral HPV infection are needed to characterize the routes of transmission, incidence, persistence, and clearance of oral HPV infections. Prospective studies are needed to estimate the absolute risk of HPV-associated oropharyngeal cancers among individuals with oral HPV infection. Clinical studies are needed to understand the reasons underlying the survival benefit of HPV-positive oropharyngeal cancers and to characterize optimal treatments for this patient population. Studies are also needed to investigate the feasibility of primary prevention through vaccination and secondary prevention through screening.

In conclusion, HPV infection is now recognized as a major etiologic factor for oropharyngeal cancers. HPV-positive oropharyngeal cancers represent a distinct epidemiologic entity compared to HPV-negative cancers. Importantly, HPV-positive oropharyngeal cancer patients have substantially improved outcomes compared to HPV-negative patients. The rapidly growing burden of HPV-associated oropharyngeal cancers in several regions of the world underscores the need for primary and secondary prevention strategies as well as for targeted treatments for patients with HPV-positive oropharyngeal cancers.

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