

## Role of human papillomavirus in oropharyngeal squamous cell carcinoma: A review

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### Abstract

Human papillomavirus (HPV) has been implicated in the pathogenesis of a subset of oropharyngeal squamous cell carcinoma. As a result, traditional paradigms in relation to the management of head and neck squamous cell carcinoma have been changing. Research into HPV-related oropharyngeal squamous cell carcinoma is rapidly expanding, however many molecular pathological and clinical aspects of the role of HPV remain uncertain and are the subject of ongoing investigation. A detailed search of the literature pertaining to HPV-related oropharyngeal squamous cell carcinoma was performed and information on the topic was gathered. In this article, we present an extensive review of the current literature on the role of HPV in oropharyngeal squamous cell carcinoma, particularly in relation to epidemiology, risk factors, carcinogenesis, biomarkers and clinical

implications. HPV has been established as a causative agent in oropharyngeal squamous cell carcinoma and biologically active HPV can act as a prognosticator with better overall survival than HPV-negative tumours. A distinct group of younger patients with limited tobacco and alcohol exposure have emerged as characteristic of this HPV-related subset of squamous cell carcinoma of the head and neck. However, the exact molecular mechanisms of carcinogenesis are not completely understood and further studies are needed to assist development of optimal prevention and treatment modalities.

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**Key words:** Human papillomavirus; Human papillomavirus; Oropharynx; Oropharyngeal; Squamous cell carcinoma; Head and neck; Oncology

**Core tip:** Human papillomavirus has been accepted as a causative agent in a subset of head and neck squamous cell carcinoma (SCC), particularly of the tonsils and base of tongue. Importantly, there is an increasing incidence of this subset of patients, who demonstrate improved prognosis and may respond more favourably to treatment. Similarities and differences are evident between cervical and oropharyngeal human papillomavirus-related SCCs and the comparison between these tumours warrants further investigation to better understand the disease process.

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### INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is

Epidemiology	Increasing incidence of HPV-related oropharyngeal SCC Most cases attributable to HPV-16
Risk factors	HPV-related SCCs associated with younger age at presentation, sexual behaviours, oral HPV infection immunodeficiency, male gender and higher socio-economic status
Carcinogenesis	Distinct molecular genetic alterations mediated by E6 and E7 oncoproteins, similar to cervical SCC Affected downstream pathways similar to non HPV-related SCC
Biomarkers	Controversy over the use of p16 as a surrogate biomarker Findings in many of the studies on biomarkers have been inconsistent or contradictory
Clinical implications	HPV-related oropharyngeal SCCs represent a different clinical entity with potential for de-escalation of therapy The effects of prophylactic HPV vaccination on oropharyngeal SCC remain unclear

**Figure 1 Summary of key points.** HPV: Human papillomavirus; SCC: Squamous cell carcinoma.

the sixth most common type of cancer worldwide with approximately 633000 new cases diagnosed and 355000 deaths annually<sup>[1]</sup>. Over the past 10-15 years, the traditional paradigms of HNSCC have been changing significantly. It has emerged as a heterogeneous group of diseases, with distinct molecular genetic changes<sup>[2,3]</sup>.

Human papillomavirus (HPV) has been linked to the pathogenesis of squamous cell carcinoma (SCC) since the 1970s<sup>[4]</sup> and, in 1995, it was recognised by the International Agency for Research on Cancer (IARC) that high risk HPV types 16 and 18 were carcinogenic in humans<sup>[5]</sup>. The role of HPV in cervical cancer is well described<sup>[6]</sup>, however high risk HPV types are also linked with other ano-genital tumours and with SCCs of the head and neck<sup>[7,8]</sup>, as well as potentially playing a role in cutaneous SCCs<sup>[9]</sup>. HPV accounts for roughly 4.8%-5.2% of the total global cancer burden, making it the highest among all viruses<sup>[10,11]</sup>.

Since it was first suggested in 1983<sup>[12]</sup> and first identified in 1985<sup>[13]</sup>, HPV infection has been increasingly recognized as a major aetiologic factor for HNSCCs, particularly a subset that arise from the oropharynx, mostly the base of tongue and palatine tonsils<sup>[14-16]</sup>. This subset is seen as a distinct clinicopathological entity in comparison to the traditional smoking and alcohol related HNSCCs<sup>[16-20]</sup>. Specific genetic changes induced through HPV E6 and E7 protein expression define this subset<sup>[21-23]</sup>. In contrast, tobacco associated HNSCCs are usually more genetically diverse<sup>[24]</sup>. HPV-related tumours of the oropharynx display specificity of HPV to the tumour cell nuclei<sup>[16]</sup>, integration of HPV DNA into the host cell<sup>[16,25]</sup> and high viral copy numbers<sup>[26]</sup>, giving evidence for the functional role of HPV in the pathogenesis of these tumours.

HPV-related SCC tends to display unique histology characterized by poorly differentiated, non-keratinising morphology with a basaloid appearance<sup>[17,27]</sup>. Nevertheless, even some true basaloid squamous cell carcinomas

of the oropharynx have demonstrated HPV-positivity<sup>[28]</sup>, and other variants such as papillary SCC, adenosquamous carcinoma, lymphoepithelial carcinoma-like tumours and small cell carcinoma have been associated with HPV infection<sup>[29-34]</sup>.

It is estimated that the probability of a cancer of the oropharynx being attributable to HPV is five times higher than the oral cavity, larynx or hypopharynx<sup>[35]</sup>, with HPV-related oropharyngeal SCC being described as an epidemic<sup>[36-40]</sup>. Current data from studies that assessed in situ hybridization or HPV E6/E7 mRNA suggest that HPV-related HNSCC is rare in the oral cavity, larynx, hypopharynx and other HNSCC sites<sup>[35]</sup>, however the role of HPV in non-oropharyngeal sites remains unclear<sup>[41]</sup> and a causative relationship at these sites has not been established<sup>[42]</sup>.

We review the current literature regarding HPV-related oropharyngeal tumours with regard to epidemiology, risk factors, carcinogenesis, biomarkers and clinical implications. A summary is shown in Figure 1.

## HUMAN PAPILLOMAVIRIDIAE

HPV is an epitheliotropic, non-enveloped DNA virus measuring approximately 55 nm in diameter, and carries a single molecule of circular double-stranded DNA, consisting of approximately 8000 base pairs<sup>[43]</sup>. The genome is broken down into three regions which consist of a long control region (LCR), an early (E) region and a late (L) region. There are eight genes in the E region and two in the L region. These genes in E and L encode viral proteins while LCR is an upstream non-coding regulatory region containing the origin of viral DNA replication and transcriptional regulatory elements.

At present, over 200 different genotypes of papillomaviridae, characterized by at least 10% nucleotide divergence in capsid gene (*L1*)<sup>[44]</sup>, have been identified by various techniques<sup>[45]</sup>. These can be classified according to similarities in their DNA sequences. They have also been grouped into mucosal (mostly of the alpha genus) or cutaneous (mostly of the beta genus) types based on their tropism for specific epithelia and they can be classified into low and high risk types based on their capacity to promote malignant transformation in host cells. Of these, HPV 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73 and 82 are examples of those classified as high risk viruses, detectable in high grade squamous intraepithelial lesions in the cervix or in invasive cancer; while HPV 6, 11, 40, 42, 43, 44, 54, 61, 72, 81, and 89 can be considered as viruses with low oncogenic risk and can be isolated from low grade epithelial lesions of the cervix. There remain a number of HPV types that are potentially high risk with an unknown oncogenic potential. There exists some degree of intratypic variation<sup>[46,47]</sup>, which may also relate to pathogenesis<sup>[48-50]</sup>, as well as geographic variation in genotype prevalence<sup>[46,51]</sup>.

HPV is one of the most powerful human carcinogens. The E6 and E7 genes produce E6 and E7 oncoproteins,

which confer the virus with oncogenic potential through their inhibitory effects on p53 and retinoblastoma (Rb) proteins, more of which is discussed later.

## EPIDEMIOLOGY

HNSCC includes tumours from a number of subsites, of which the oropharynx accounts for approximately 10%<sup>[52]</sup>. Worldwide, there were an estimated 85000 new cases of oropharyngeal SCC in 2008, of which 25.6% (22000) were estimated to be HPV-related<sup>[53]</sup>. Of the HPV-related cases, more than three quarters (17000) were estimated to be male.

Genotypes of oncogenic HPV found in cervical cancer in order of prevalence are 16, 18, 58, 33, 45, 31, 52, 35, 59, 39, 51 and 56<sup>[54]</sup>. However, the distribution of HPV types differs somewhat in oropharyngeal when compared to cervical cancers<sup>[55]</sup>. A systematic review found that HPV-16 was present in 95.7% of HPV-related oropharyngeal SCC, but only 73.9% of HPV-positive non-oropharyngeal HNSCCs<sup>[56]</sup>, while only approximately 61% of cervical cancer display HPV-16<sup>[57]</sup>. While a significant number of other oncogenic HPV types are found in cervical cancer, only a small proportion of oropharyngeal cancers may be caused by additional HPV types such as 18, 31, 33, 35, 52 and 58<sup>[58,59]</sup>. HPV-16 is the commonest genotype found in oral cavity infection<sup>[60]</sup>, while it constitutes over 90% of the genotype distribution in tonsil cancers<sup>[61]</sup>.

Prevalence of oral high risk HPV infection in the general population is reported at 3.5%-3.7%<sup>[62,63]</sup>, with higher rates for those also infected with HIV<sup>[64]</sup>. A systematic review of the literature in 2005 reported detection of HPV DNA in 35.6% of oropharyngeal tumours<sup>[65]</sup>. However, there exists a wide geographic variation, with a reported prevalence as high as 72%<sup>[59]</sup> in North America compared to 17% in southern Europe<sup>[53]</sup>, 12.6% in Taiwan<sup>[66]</sup> and even as low as 4.4% reported in central Europe and Latin America<sup>[67]</sup>. Some of these figures are based on the assumption that detection of high-risk HPV DNA in tumour tissue signifies cancer attributable to HPV, however this does not delineate from the effects of tobacco exposure and alcohol in these cases. It has been recorded that HPV accounts for approximately 7.7% and 2.2% of all cancer cases in developing and developed countries, respectively<sup>[10]</sup>. The variations could partly be explained by geographic and temporal heterogeneity in sexual behaviours and tobacco exposure<sup>[41]</sup>. A more recent systematic review in 2012 reported a prevalence of HPV in oropharyngeal SCC of 59.9% in the United States, compared to 39.7% in Europe and 32.5% in the rest of the world<sup>[56]</sup>. There are limited data from less developed regions, but the incidence appears much lower.

Despite the variation in prevalence, 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<sup>[41]</sup>.

While incidence of other HNSCCs has decreased over the past two decades, correlating with decreased tobacco use, the age-adjusted incidence of oropharyngeal SCC has been increasing in this same period<sup>[68,69]</sup>, particularly of the base of tongue and tonsil region<sup>[70]</sup>. Meanwhile the population-level incidence of HPV positive oropharyngeal SCC increased by 225% between 1988 and 2004, with a concomitant decline by 50% for HPV-negative oropharyngeal SCC<sup>[59]</sup>. A particularly steep rise of over 70% has been reported for prevalence of HPV-related oropharyngeal SCC in the past decade, with prevalence in Europe increasing at a faster rate than North America<sup>[56]</sup>. This rise further emphasises the predilection of HPV for the oropharynx and suggests that it plays a less significant role in other HNSCCs.

With the rise in HPV-related oropharyngeal SCC coupled with the decline of HPV-related cervical SCC, it has been suggested that the annual numbers of HPV-related oropharyngeal cases could soon surpass that of cervical cancer<sup>[41]</sup>.

## RISK FACTORS

HNSCCs, including those of the oropharynx, have traditionally been strongly associated with patients who have a long history of heavy smoking and alcohol consumption, with previous studies clearly showing a dose-response relationship with the frequency and duration of tobacco and alcohol exposure<sup>[71]</sup>. Age of onset is generally in an older age group (usually seventh decade) in these traditional HPV-negative oropharyngeal SCCs. Other risk factor associations with these tumours include poor oral hygiene<sup>[72,73]</sup>, a diet low in fruit and vegetable consumption<sup>[74,75]</sup> and chronic inflammatory disease in the oral cavity<sup>[76-78]</sup>.

### Age

The distinct subset of HPV-positive oropharyngeal SCCs generally present at a younger age, averaging a few years lower than HPV-negative tumours<sup>[39]</sup>. Although phenotypically similar to those in older patients, HNSCCs developing in younger patients are undoubtedly different at a genetic level with both germline and somatic differences seen<sup>[3,79-82]</sup>. One study showed that patients under 55 had a 3.4-fold higher risk of infection with carcinogenic HPV<sup>[83]</sup>, while a strong association has been demonstrated with HPV-16 infection and tonsillar cancer in males under 40 years old<sup>[84]</sup>. Increasing incidence of oropharyngeal SCC is seen in those aged under 60<sup>[85]</sup>, with a particularly steep rise seen between the ages of 50-59<sup>[86]</sup>, although it is possible this may be due to other risk factor exposures in this birth cohort.

### Sexual behaviours

HPV-related oropharyngeal SCCs also show strong associations with sexual behaviours, correlating with disease<sup>[87]</sup>. In a large number of studies, both HPV-positive

HNSCCs and oropharyngeal SCCs have been strongly associated in comparison to other HNSCCs with number of lifetime sexual partners, number of vaginal, oral and anal sexual partners, young age at first intercourse/earlier sexual contact and history of sexually transmitted diseases, including genital warts<sup>[27,83,87-93]</sup>. After adjusting for HPV-16 serology, the associations in a case-control series were no longer significant, suggesting that sexual behaviours can be seen as a surrogate for HPV-16 exposure<sup>[27]</sup>.

Data from a number of developed countries show that markers of high-risk sexual behaviours, 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<sup>[94]</sup>.

### Oral HPV infection

Oral HPV is predominantly acquired *via* sexual transmission and oral HPV prevalence has been associated with some of the above sexual behaviours. Studies have demonstrated increased HPV acquisition around sexual debut with oral HPV prevalence of 1.5% in 12-15 year olds, 3.3% in 16-20 year olds and 4.5%-6.9% in healthy adults<sup>[62,63,89,95]</sup>. Higher oral HPV prevalence has been reported in women with cervical HPV infection<sup>[96,97]</sup>, and people infected with Human Immunodeficiency Virus (HIV)<sup>[96,98]</sup>. Several studies and some case reports have described concordant oral HPV infection between couples<sup>[99-102]</sup>, however preliminary results from the HPV oral transmission study in partners over time (HOTSPOT) have not backed up these findings.

It has even been suggested that non-sexual HPV transmission through kissing may be possible<sup>[95,103]</sup>, as well as intrapartum transmission<sup>[104]</sup> and transmission during laser surgery<sup>[105]</sup>. In itself, oral HPV-16 infection is a strong risk factor for oropharyngeal cancer, while the relationship is not necessarily clear for oral SCCs<sup>[106,107]</sup>. However, oral HPV prevalence is lower than cervical, perhaps explained by a lower proportion in oral-genital than genital-genital partners<sup>[55]</sup>, but the natural history of HPV infection in the oral cavity appears similar to cervical infections<sup>[108]</sup>. Although type-specific concordance is low, HPV infection of the cervix and oral cavity are not independent<sup>[109]</sup> and so cervical HPV infection could be considered a risk factor for oral cavity HPV infection. Although the full natural history of HPV infection in the oral cavity and oropharynx is not entirely understood, there is an estimated incidence of 4.4% per year with most infections being cleared within one year<sup>[110]</sup>. However, changing sexual practices are potentially leading to higher rates of infection that could become recalcitrant to immune responses.

### Tobacco and alcohol exposure

Evidence of a role for tobacco exposure and alcohol use in HPV-related oropharyngeal SCCs and in oral HPV infection is equivocal, with some studies reporting positive association and suggesting smoking-induced immunosuppression or potentiation of carcinogenesis could play a role, while others report no association<sup>[41]</sup>. A role for

tobacco smoking in cervical cancer, however, has been demonstrated, although this association becomes weak after adjustment for sexual and reproductive factors<sup>[111]</sup>. In comparison to traditional HNSCCs, these patients are less likely to have excessive tobacco exposure and alcohol use<sup>[16,88,112]</sup>, however HPV-related oropharyngeal SCCs do occur in both in those with tobacco exposure and alcohol use and in those without. It is highly plausible that tobacco exposure potentiates the effects of HPV carcinogenesis<sup>[113]</sup> but a role in the causation of HPV-related oropharyngeal SCCs has not been definitively determined from available evidence<sup>[55]</sup>. Marijuana use has also been associated with oropharyngeal SCCs<sup>[87,114]</sup>, however after adjustment for sexual behaviour variables in one study, this disappeared<sup>[62]</sup>.

### Gender

Both HPV-related and non HPV-related HNSCC exhibit male predominance at a ratio of approximately 3:1. In tobacco and alcohol related HNSCC, this difference has decreased particularly as trends in smoking have changed, with 43% of men and 30% of women smoking in 1974 compared to 26% of men and 21% of women in 2000<sup>[115]</sup>. Nonetheless, the difference still remains for HPV-related HNSCC and the reason for this is uncertain. The male predominance exhibited cannot be fully explained by difference in sexual behaviours, which suggests potential biologic differences between men and women<sup>[41,116]</sup>, or that some male characteristic preferentially predisposes to cancer of the oropharynx<sup>[117]</sup>. It has been suggested that hormonal differences<sup>[55,118]</sup> or the potential protective immunity from seroconversion in response to cervical HPV infections among women<sup>[119,120]</sup> may play a role. Although not all studies agree<sup>[63]</sup>, the majority of studies report that oral HPV infection is more common in men than women<sup>[62,121,122]</sup>. It has also been suggested that transmissibility of oral HPV may be higher for men performing oral sex on women, possibly due to a higher HPV copy number in the vagina/cervix<sup>[94]</sup>.

### Immunodeficiency

Immunodeficiency is a risk factor for a large number of tumours and HPV-related oropharyngeal SCC is included in that. For example, it is reported that patients infected with human immunodeficiency virus (HIV) have a 2-6 times increased risk of HPV-related HNSCC<sup>[123,124]</sup>, although they are at greater risk of ano-genital SCCs than oropharyngeal<sup>[125]</sup>. It has been demonstrated in cervical cancer patients that immunosuppression leads to HPV persistence and disease progression<sup>[126-128]</sup>. The association of a deficient immune system with increased HPV-related HNSCC may partly explain any potential association with tobacco exposure due to the immunosuppressive effects of smoking<sup>[129]</sup>, with one paper demonstrating a reduced antibody response in smokers<sup>[130]</sup>.

### Socio-economic status

HNSCCs have been associated with patients from a low socio-economic group for many years<sup>[131]</sup>. However, HPV-

related oropharyngeal SCCs are associated with patients who are from a higher socio-economic group and who have a better performance status<sup>[132,133]</sup>, although this has been refuted in one study<sup>[116]</sup>. Nonetheless, white males seem to be particularly at risk, with a rise in incidence reported in this group alone<sup>[59,85,116]</sup>. HPV positivity in oropharyngeal cancer is lower in African Americans than in other racial groups, with poorer survival in this racial group from oropharyngeal SCC, because a higher proportion is related to tobacco and alcohol exposure<sup>[134,135]</sup>.

### HPV serology

There is a strong association between serologic evidence of HPV infection and HNSCC risk, even after adjustment for other HNSCC risk factors<sup>[106]</sup>. One study has even shown a temporal association, with pre-diagnostic serum samples from ten years prior that were positive for HPV-16 capsid antibodies conferring an increased risk of oropharyngeal SCC of 14.4<sup>[136]</sup>, while patients with pre-diagnostic E6 seropositivity had a significantly higher risk of oropharyngeal cancer in another study<sup>[137]</sup>.

It is evident that a number of factors can facilitate or increase the risk of HPV-related oropharyngeal SCCs. This includes oral HPV infection, male gender, younger age, white race, immunosuppression and a variety of sexual behaviours. Differences in sexual behaviours across age and gender and consequent HPV exposure risk could account for the rapidly increasing incidence of HPV-related oropharyngeal SCCs among younger patients. Interestingly a separate specific subgroup of younger females with non HPV-related oral cavity SCCs has also been identified<sup>[138]</sup>.

## CARCINOGENESIS

The model for development of SCC involves exposure to carcinogens over time leading to progressive genetic and epigenetic changes that accumulate and lead to premalignant and eventually malignant lesions. However, HNSCC is a heterogeneous disease with a number of subtypes described, based on histological appearance, and supported by different gene expression profiles<sup>[139,140]</sup>. Squamous cell carcinomas from different sites in the body share a number of molecular characteristics but recent whole-exome sequencing<sup>[141-144]</sup> has helped to characterise the specific molecular pathogenesis of HNSCC with roles identified for tumour suppressor pathways including p53, Rb/INK4/ARF and NOTCH<sup>[145]</sup>. A role for cancer stem cells in HNSCC is likely, based on recent evidence<sup>[146-149]</sup>, and further study of these progenitor cells will help to elucidate mechanisms of carcinogenesis.

Recent deep-sequencing studies on the HNSCC on-genome have demonstrated a vast number of diverse genetic alterations, however most of these converge on four targetable molecular pathways<sup>[150]</sup>; mitogenic signalling and in particular amplification or up-regulation of epidermal growth factor receptor (EGFR) and the downstream pathway of phosphoinositide 3-kinase (PI3K)/mTOR as well as PTEN inactivation, each leading to

pathways involving proliferation, DNA repair, survival and spread; defective differentiation involving NOTCH signalling alterations; cell cycle de-regulation involving inactivation of CDKN2A (encoding p16 INK4A) tumour suppressor gene and CCND1 (encoding CYCLIN D1) amplification; genomic instability involving loss of TP53, which occurs in a large percentage of non HPV-related HNSCC and is the single most common mutational event, and other genes related to DNA damage recognition and repair. It is possible that smoking and alcohol affect distinct genes<sup>[151]</sup>, giving further evidence for a synergistic effect of tobacco and alcohol exposure in relation to HNSCC carcinogenesis.

HNSCC usually displays field cancerisation, a term first coined in 1953<sup>[152]</sup>, whereby specific genetic alterations can be widely distributed throughout the mucosa lining the aerodigestive tract even in the absence of overt histopathologic changes of malignancy<sup>[25]</sup>. Only a minority of precancerous fields in the oral cavity are recognised as leukoplakia or erythroplakia<sup>[153]</sup> and only 6%-36% of patients with leukoplakia or erythroplakia go on to develop oral SCC<sup>[154]</sup>, particularly those demonstrating aneuploidy<sup>[155,156]</sup>. The accumulation of further genetic changes in precancerous fields leads to the development of SCC, with presence of field change leading to a higher risk of multiple synchronous or metachronous primary tumours. Exposure to carcinogens bring about these field changes, however evidence for a field effect is lacking for HPV-related SCC<sup>[157]</sup> and the risk of second primary malignancy in oropharyngeal SCC has markedly decreased over time<sup>[158]</sup>, with the mutation rate of HPV-positive tumours only approximately half of that found in HPV-negative HNSCC<sup>[141,142]</sup>.

Specific differences in chromosomal alteration and gene transcription have been identified between HPV and non HPV-related HNSCCs<sup>[21,22,159,160]</sup>. TP53 mutations, loss of 9p21, hypermethylation of 14-3-3 $\sigma$  and RASS-F1A promoters and overexpression of cyclin D are all common in non HPV-related oropharyngeal SCCs, while pRb levels are normal and p16 is often decreased<sup>[161,162]</sup>.

In the cervix, after initial infection at the transformation zone, viral genomes are maintained as episomes in the basal layer, with viral gene expression being tightly controlled as the infected cells move toward the epithelial surface<sup>[163]</sup>. Subsequent high-grade neoplasia represents an abortive infection in which viral gene expression becomes deregulated and the normal life cycle of the virus cannot be completed. The squamous epithelium in the cervix and the head and neck derive embryologically from endoderm and are susceptible to metaplasia<sup>[164]</sup>. In the head and neck, there is a predilection for HPV-positive tumours to occur in the reticular crypt epithelium of palatine and lingual tonsils and head and neck sites with mucosa associated lymphoid tissue<sup>[25,165,166]</sup>. It is possible that this occurs due to the particular microanatomy of the crypts, where there are breaks in the non-keratinising squamous epithelium that could allow viral entry, while a microabrasion theory of entry to basal cells at other head and neck sites has been proposed. Entry may be facilitat-

ed by M-cells lining the crypt epithelium<sup>[167]</sup>, as with other viruses<sup>[168,169]</sup>. Another theory postulated is an influence on HPV carcinogenesis from increased cytokines related to nearby lymphoid tissue<sup>[170]</sup>. The recent observation of a distinct set of embryonic cells at the squamocolumnar junction of the cervix, which seem to confer a particularly high risk of malignancy, has led to a “top-down” theory of malignancy at this site, although it remains to be seen if this model translates to the oropharynx<sup>[171-173]</sup>. Despite being full of lymphatic tissue, the tonsils are known to harbour pathogenic viruses such as Epstein Barr virus, adenoviruses and herpes simplex virus<sup>[174]</sup>, and it is the mechanisms of immune evasion that allow persistent infection and carcinogenic potential at these sites, hence immunosuppressed individuals are particularly at risk.

From cervical models, we understand that most HPV infections last no more than a few months and are eliminated by the immune response, with 90% of infections cleared within two years, although high risk HPV tends to persist longer than low risk<sup>[175,176]</sup>. Once immune evasion is established, integration of HPV DNA into the cellular genome likely represents a critical step for malignant transformation in those individuals who harbour HPV in their tonsils<sup>[25]</sup>, with HPV integration representing a stochastic process resulting in clonal selection of aggressively expanding cells that display altered gene expression of integrated HPV genomes and potential perturbations of cellular genes at or near viral integration sites<sup>[177]</sup>. Viral integration can also lead to loss of E2-mediated inhibition of viral oncoprotein expression<sup>[178]</sup>. Furthermore, it has been shown that this HPV DNA integration is consistently centred on tonsil crypt epithelium<sup>[25]</sup>, however the factors allowing transformation from episomal HPV infection, whether active or latent, to DNA integration remain poorly understood. It has also been noted that much of the HPV that is detected in oropharyngeal cancers seems to be episomal.

Based on cervical cancer models, high-risk HPV can induce genetic changes in a small number of those with persistent infection which leads to precancerous lesions, a fraction of whom will develop cancer many years after the original infection. While HPV-related precursor lesions in the oral cavity have been identified<sup>[179]</sup>, there is an absence of detectable precancerous lesions in the oropharynx<sup>[41]</sup>, perhaps related to the difficulty in assessing and sampling deep tonsillar crypts, the predominant location of HPV-related SCCs<sup>[180,181]</sup>. Nevertheless, HPV-related oropharyngeal SCCs present with distinct molecular profiles, more comparable to cervical SCC than to non HPV-related HNSCC<sup>[55]</sup>. Infection with HPV is likely an early oncogenic event in HNSCCs. The viral oncoproteins E6 (151 amino acids) and E7 (98 amino acids) of high risk HPV types, particularly HPV-16, are implicated as the drivers of transformation in HPV-related oropharyngeal SCCs<sup>[182]</sup>. These proteins help to re-program postmitotic terminally differentiated epithelial cells to re-enter the cell cycle and express proteins that are required for viral genome replication<sup>[183]</sup>. They also disrupt a num-

ber of cellular mechanisms through a wide variety of downstream effects.

The E5 oncoprotein co-operates with E6 and E7 to promote proliferation of infected cells and is likely to facilitate malignant progression<sup>[184]</sup>, although this process is likely to take place in the early stages of carcinogenesis because viral integration frequently leads to loss of E5 gene expression<sup>[185]</sup>. Transcription of E6 and E7 viral oncogenes can occur when the virus is episomal however, in cervical SCC, alteration of E2 on integration may facilitate increased expression of E6 and E7 oncogenes, although this may not be the case in oropharyngeal SCC<sup>[186]</sup>. Viral integration is thought to play an important role in cervical SCC but the relevance of viral integration is not fully clear in oropharyngeal SCC<sup>[187]</sup>. Some studies suggest that viral integration in the tonsillar crypts plays an important role in carcinogenesis<sup>[165,188]</sup>, which may explain the predilection of HPV-related HNSCCs at this site, while other studies suggest that episomal HPV alone contributes to the development of most oropharyngeal SCCs in contrast to SCCs of the cervix<sup>[186,187]</sup>.

In cervical lesions, it is not possible to predict tumour progression based on HPV viral load<sup>[189]</sup>. It has been suggested that high HPV viral load (at least one HPV copy per tumour cell) in oropharyngeal SCC predicts active HPV infection<sup>[190-192]</sup>. The proportion of HPV-positive SCCs with high viral load varies between studies from 33%-77.5%<sup>[59,190]</sup>. It is possible that in cases of low viral load that HPV presence is coincidental and alternative mechanisms of carcinogenesis are implicated. However, gene expression varies widely and so a constitutive rather than a high expression of viral oncogenes may be all that is required for HPV-related oropharyngeal carcinogenesis<sup>[187]</sup>.

The major role of E6 oncoprotein is induction of ubiquitin-mediated proteolysis, through E6 associated protein, leading to degradation of tumour suppressor p53. As p53 usually facilitates repair to damaged host DNA by arresting cells in the G1 phase (or else inducing apoptosis), E6 expressing cells face increased mitotic stress and genomic instability<sup>[193]</sup>. E6 aids cellular proliferation by up-regulating transcription of telomerase<sup>[194]</sup> and also, through the presence of the PDZ binding motif, high risk HPV E6 proteins bind to a number of PDZ domain containing proteins with presumed tumour suppressor activity that have diverse functions<sup>[183,195]</sup>. E6 also targets the Wnt and Notch signalling pathways<sup>[183]</sup>.

The E7 oncoprotein causes cell cycle disruption by binding and inactivating tumour suppressor proteins of the retinoblastoma family (pRb) that regulate cellular senescence. E7 thereby causes cell proliferation through abnormal entry into the S-phase by the overexpression of released transcription factor E2F<sup>[196]</sup>. This functional inactivation of pRB also results in overexpression of p16 tumour suppressor protein, which is a CDK4A inhibitor, allowing the use of p16 as a surrogate marker for HPV-related oncogenesis<sup>[59,197-200]</sup>, which will be discussed further below. E7 proteins also alter cell cycle control through interactions with histone deacetylases, cyclins

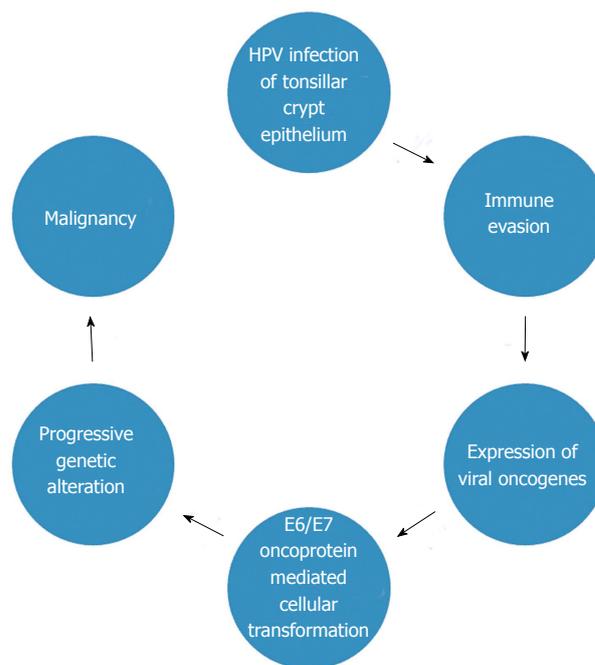
and cyclin-dependent kinase inhibitors<sup>[201]</sup>.

Animal models suggest that E7 is the dominant HPV oncoprotein in HNSCC<sup>[202]</sup>, but both E6 and E7 directly impact upon a number of apoptotic mechanisms; interaction with extracellular matrix adherence proteins to allow anchorage independent growth; interaction with cell surface receptors to resist cytokine induced extrinsic apoptosis; and interaction with proteins involved in interferon signalling and interleukin to allow immune evasion<sup>[201,203]</sup>.

Genomic instability underpins the development of dysplasia, malignancy, invasion, and metastasis in cancers<sup>[204]</sup>. While aberrant proliferation induced by E7 is facilitated by suppression of apoptosis by E6 mechanisms, it is the additional functions of E6 and E7 to induce genomic instability by multiple mechanisms that lead to chromosomal mutations. These include centrosome abnormalities or spindle checkpoint failure leading to polyploidy, aneuploidy and chromosomal rearrangement<sup>[205,206]</sup>, direct DNA damage<sup>[207]</sup> (which also occurs with viral integration<sup>[208]</sup>), variation in the Fanconi anaemia DNA repair pathway and induction of the ATM-ATR DNA damage repair pathway with concomitant disruption of checkpoint control mechanisms<sup>[201]</sup>. Tobacco exposure also causes genomic instability and so may help to induce malignancy on the background of E6 and E7 effects, allowing for a role of tobacco exposure in the potentiation of HPV-related HNSCC, which has been suggested from mouse models<sup>[209]</sup>.

Different patterns of DNA methylation have been demonstrated between HPV and non HPV-related HNSCCs, with methylation patterns in HPV-related HNSCCs more analogous to cervical SCC patterns than non HPV-related HNSCCs<sup>[210]</sup>. Excess DNA methylation could be recruited by the integrated viral genome rendering it invisible to host immune responses or it could be an attempted defence mechanism by the host cell<sup>[210]</sup>. HPV-related HNSCCs also have a distinct miRNA profile, also more analogous to cervical SCCs, in comparison with non HPV-related HNSCCs<sup>[211]</sup>. Furthermore, differences in DNA methylation rate have been identified between HNSCCs in tobacco users versus nonusers as well as specific mRNA and microRNA clusters<sup>[212]</sup>.

While distinct methods of carcinogenesis are evident between HPV-related and non HPV-related HNSCCs, the effects on downstream pathways are often the same, such as in the case of mTOR inhibition, either from TP53 mutations in tobacco related cases or from E6 induced degradation of p53 in HPV-related cases<sup>[150]</sup>. It is also important to note that E6 and E7 proteins expressed in low risk HPV types do not induce the same changes and that HPV present in some HNSCCs may exist as a latent passenger virus with no transcriptional activity<sup>[213,214]</sup>. New roles for HPV oncoproteins are continually being identified, offering many future potential therapeutic targets<sup>[215]</sup>. In any case, there is a distinct group of HPV-related tumours arising from the epithelium of lymphoid tissue characterised by viral oncoprotein expression, rather than SCCs that arise on a background of a long history of somatic mutations due to carcinogenic exposures. A



**Figure 2 Proposed Theory of human papillomavirus-related carcinogenesis.** HPV: Human papillomavirus.

proposed model of carcinogenesis in HPV-related oropharyngeal SCC is shown in Figure 2.

## BIOMARKERS

Studies have had difficulty identifying clinically useful biomarkers in HNSCC<sup>[216]</sup>. A high degree of heterogeneity is evident in HNSCC, with different prognosis described for different subsets of tumours. This includes a favourable prognosis for the growing cohort of HPV-related SCCs, particularly oropharyngeal<sup>[217]</sup>, often despite a more advanced presentation. This is due to a number of factors including the sensitivity of this subset to chemotherapy<sup>[133]</sup>, the lower likelihood of loco-regional recurrence<sup>[217]</sup> and a younger cohort of patients with fewer comorbidities as well as a possible decreased risk of second primary tumours.

HPV status and p16 status have each proven useful as biomarkers in HNSCC. The tumour suppressor p16 binds to the cyclin D1 CDK4/CDK6 complex, thereby helping to keep the Rb protein in its active hypophosphorylated form. With pRb functionally inactivated by the binding of HPV E7 oncoprotein, p16 expression is upregulated by its corresponding gene being released from transcriptional inhibition. In non HPV-related HNSCC, downregulation or loss of p16 protein expression is a common early event and is associated with a worse prognosis, consistent with the tumour-suppressor role it has<sup>[204]</sup>, and oral cavity and hypopharyngeal SCC show lower levels of p16 positivity<sup>[218,219]</sup>. However, a strong correlation has been observed in numerous studies between integrated HPV detection and p16 protein overexpression. As such, p16 has been adopted as a surrogate biomarker for HPV-related HNSCC<sup>[139,197-200,220,221]</sup>, with

immunohistochemistry for p16<sup>INK4A</sup> now routinely performed in many laboratories and guides for interpretation have been described<sup>[199]</sup>.

Not only can p16 act as a surrogate biomarker for HPV status, with 46%-98% of HPV positive oropharyngeal SCCs demonstrating p16 positivity on pooled analysis<sup>[200]</sup>, but, with 3%-51% of HNSCCs being p16 positive and HPV negative<sup>[200]</sup>, p16 status can also act as an independent prognosticator, regardless of HPV status<sup>[222-225]</sup>, although not all studies agree on the specific effect<sup>[214]</sup>. Overexpression of p16 has been found in normal tonsillar tissue<sup>[25,226]</sup> and HPV negative tumours, with dysregulation of epigenetic control or multiple transcription factors being other mechanisms that lead to aberrant expression of p16<sup>[227]</sup>, some of which are associated with non HPV-related HNSCC carcinogenesis. The lack of clarity on p16 expression and discrepancies in interpretation of p16 IHC have led to controversy surrounding its use as a surrogate biomarker.

Overexpression of p16 is not evident in a subgroup of HNSCC with active HPV infection<sup>[228]</sup>, 2%-54% in pooled analysis<sup>[200]</sup>. With overexpression of p16<sup>INK4A</sup> thought to represent activity of viral oncogenes, it is possible that HPV positive/p16 negative may represent latent HPV infection, which could explain why HPV positive/p16 negative HNSCCs have a slightly worse prognosis<sup>[229,230]</sup>. Therefore, by combining testing for HPV DNA positivity and p16 overexpression, one can eliminate cases related to inactive infection, improving specificity of p16 a surrogate biomarker for detection of biologically relevant HPV infection<sup>[200]</sup>. This has been shown to be as reliable as detection of HPV E6/E7 mRNA expression by polymerase chain reaction, which is considered the gold standard of testing for transcriptionally active virus because HPV-negative HNSCCs and HPV-positive/E6 and E7 mRNA-negative HNSCCs show similar survival curves<sup>[191]</sup>; however E6/E7 mRNA is only used in a small number of centres and is mostly restricted to the research laboratory<sup>[231]</sup>. Equivalent detection may also be possible with HPV mRNA ISH and this may be of more practical clinical use<sup>[232,233]</sup>. However, there is currently a great degree of heterogeneity of HPV assessment techniques used in clinical practice depending on location<sup>[234]</sup>.

A large number of alternative prognostic or predictive biomarkers in HNSCC have been studied, such as EGFR, cyclin D1, Bcl-2, cyclin-dependent kinase inhibitor p27, MCM7, DSG3, vascular endothelial growth factor, p53, ERCC1, RRM1,  $\beta$ -catenin and MET<sup>[209,235-240]</sup>. Some examples of studies on biomarkers related to treatment response found MMP-7 and EGF to be predictive markers of, respectively, resistance to cisplatin and poor response to cetuximab<sup>[241-243]</sup>, while survivin overexpression predicted improved response to radiotherapy<sup>[244]</sup>. However, findings in many of the studies on biomarkers have been either inconsistent or often even contradictory. Some biomarkers have not been studied in sufficient detail to draw a firm association<sup>[216]</sup>. However, EGFR positivity has been associated with poor survival in HNSCC in a number of studies<sup>[245-247]</sup>, including in HPV-related

HNSCCs<sup>[167,235]</sup> (although these tumours generally tend not to overexpress EGFR<sup>[248]</sup>), and an EGFR-targeting antibody, cetuximab, has shown benefit in combination with radiotherapy for patients with HNSCC<sup>[249]</sup> so is approved for clinical use alone or in combination with radiotherapy or chemotherapy. Evidence suggests p16 may be useful in the context of analysing treatment response to cetuximab<sup>[250]</sup>. Besides EGFR inhibition, new molecular targeted therapies that have an effect on other activated molecular signalling pathways such as mTOR, Src kinase and IGF-1R inhibitors are being developed<sup>[251]</sup>.

In HPV-related oropharyngeal SCC, there is the potential for translation of cervical biomarkers given the similarities in carcinogenesis between these sites. New biomarkers are continually emerging from molecular biological research which are of as yet uncertain relevance, such as recently discovered distinct squamocolumnar junction-related biomarkers<sup>[171-173]</sup>.

It has been suggested that the programmed death 1 (PD-1):PD-L1 pathway plays a role in HNSCC, particularly in HPV-related oropharyngeal cases<sup>[252]</sup>, by facilitating HPV-related carcinogenesis in an immune-privileged site<sup>[253]</sup>. Furthermore, an investigation into a panel of serum cytokine and chemokine markers revealed significantly decreased IFN- $\gamma$  in HNSCC patients<sup>[254]</sup>, which may be caused by inhibition of T-cell regulation from increased expression of PD-1:PD-L1. Immune checkpoint blockade through a monoclonal antibody that inhibits the PD-1 receptor has the potential to play a big role in future therapy, because initiation of anti-tumour response is observed on PD-1 blockade in animal studies<sup>[255]</sup>.

Personalised therapy may be possible with robust biomarker panels and it is detailed molecular analysis, such as DNA profiling<sup>[204]</sup>, that may guide biomarker development. Limited success of individual markers to predict tumour behaviour has led to attempts to classify biomarker "signatures" such as panels of RNA or protein expression alterations<sup>[256]</sup>. It is possible that miRNA panels associated with HNSCC subsets may also act as biomarkers to improve diagnosis and management<sup>[257]</sup>. Some studies have investigated panels of predictive biomarkers in both HPV-related oropharyngeal SCC<sup>[258]</sup> and non-HPV related oropharyngeal SCC<sup>[259]</sup>, however few of these are validated<sup>[239]</sup>.

Research on biomarkers in HNSCC is a rapidly expanding field, with new potential markers that may provide valid therapeutic targets<sup>[260]</sup>, however it is difficult to demonstrate clinical utility without well designed biomarkers or panels undergoing rigorous assessment in clinical trials. Hence many questions remain, with HPV infection as yet not formally validated as a predictive biomarker for any specific treatment modality or agent<sup>[256]</sup>. More practical diagnostics could be achieved through serum<sup>[137,239]</sup> or radiological<sup>[256]</sup> biomarkers, however clinical utility of these remains to be proven. There is no standardisation of detection and when p16 expression is used as a marker for HPV infection, approximately 10% of cases may be false positives<sup>[167]</sup>, such that a combination of p16 overexpression with HPV DNA positivity may currently

represent the most practical investigation for biologically relevant HPV infection<sup>[200]</sup> and this has been shown to be the most relevant group in terms of prognosis<sup>[261]</sup>. The relevance of infection in head and neck cancer outside the oropharynx is unestablished and identification of robust fingerprints of HPV carcinogenesis will help to improve the estimate of HPV-related non-oropharyngeal HNSCC.

## CLINICAL IMPLICATIONS

HNSCC has a huge impact upon quality of life and longevity. Improvements in clinical outcome have been forthcoming through advancements in surgical technique, radiation oncology and emerging chemotherapeutic and biologic agents, however, despite a multidisciplinary team approach, treatments remain complex with an associated high morbidity and only two new treatments (EGFR antibodies and robotic surgery) have been approved in the past 30 years<sup>[262]</sup>.

HPV-related oropharyngeal SCC, distinct from other HNSCC<sup>[39,263]</sup>, generally presents with a more advanced clinical stage, with a higher nodal category<sup>[248,264]</sup>, despite lower tumour extent<sup>[133,264]</sup> and have different tendencies for extracapsular spread and perineural invasion<sup>[265]</sup>. These HPV-related tumours may even be clinically occult, but often present with early lymph node metastases<sup>[14,266]</sup>, which can be confused with branchial cleft cysts<sup>[267]</sup>. However, tonsil SCCs are long known to present with early lymph node metastases<sup>[268]</sup> and it may be that the characteristics of the affected site itself facilitate early spread or else potentially the depth of invasion<sup>[266]</sup>.

As stated above, these patients tend to be younger and are less likely to have significant exposure to tobacco and alcohol. Despite more advanced presentation, improved survival, consistently higher than 30%<sup>[269]</sup>, is evident in HPV-related oropharyngeal SCC<sup>[66,266,270,271]</sup>, irrespective of treatment modality<sup>[133,220,272-276]</sup>. It has been suggested, therefore, that the current classification system for HNSCCs be altered to reflect the different status of HPV-related HNSCCs<sup>[273]</sup>.

Detection of biologically relevant HPV infection is best accomplished using HPV E6 and E7 mRNA, however p16 in combination with HPV DNA correlates well and can be a practical alternative<sup>[277]</sup>. Studies have also shown an improved response to therapy from HPV-related HNSCCs<sup>[16,133,278-280]</sup>. As a result of this, it is possible that de-escalation of therapy would be appropriate for these tumours to improve associated morbidity and quality of life. Considering this, there are currently a number of ongoing trials. A summary of some of these trials is shown in Table 1.

There have been conflicting reports on the benefit of cetuximab in HPV-related oropharyngeal SCC. While subset analysis in one study suggests improved survival for oropharyngeal SCCs in the cetuximab group (although not necessarily HPV-related)<sup>[281]</sup>, others including the RTOG 0522 and SPECRUM trials disagree<sup>[269,282]</sup>. Preclinical investigation on treatment effects are limited

by the sparse number of HPV-related HNSCC cell lines available.

While organ-preservation trials have led to primary chemoradiotherapy superseding surgical management in HNSCC, there has been renewed interest in transoral techniques for oropharyngeal SCC, particularly with the introduction of robotic surgery. Equivalent early oncologic outcomes to chemoradiotherapy and improved functional outcomes are promising<sup>[283]</sup>. Some trials involving transoral surgery are shown in Table 1.

Therapeutic vaccines are novel strategies aimed at improving the T-cell mediated immune response to HPV-related SCCs. Recent phase I and II clinical trials, some in combination with chemotherapy to boost effectiveness, are investigating these<sup>[269,284]</sup>.

There is currently no single standardized treatment for oropharyngeal SCCs, but before recommended management strategies are altered, results from randomized controlled trials are needed to assess the efficacy of the different treatment modalities available for both HPV-positive and HPV-negative oropharyngeal SCC<sup>[285]</sup>, although recruitment of sufficient numbers remains difficult<sup>[265]</sup>.

Induction of HPV-specific immune responses by prophylactic vaccination with recombinant HPV virus-like particles is likely the key to successful prevention of persistent HPV infection and the subsequent consequences. As such, bivalent and quadrivalent vaccines are now widely available and have shown efficacy in prevention of anal, cervical, vaginal, and vulvar pre-cancers in unexposed individuals<sup>[94,286,287]</sup>. Unfortunately, present vaccines are only proven to be effective if given before genotype-specific infection is established<sup>[288]</sup>, duration of protection remains unclear and cost is high. Given the high specificity of oropharyngeal cases linked to HPV-16, it is unlikely that other genotypes would replace HPV-16, particularly in view of evidence for induction of cross-genotype immunity with genotype-specific immunisation<sup>[289]</sup>.

In relation to the oropharynx, animal model investigation has revealed reduction in development of HPV-related oral lesions in immunised cases<sup>[290]</sup>. Recently, an IARC-led study established that a bivalent vaccine used for cervical cancer prevention also reduced oral infections with HPV 16 and 18 by 93.3%<sup>[291]</sup>. While oral HPV infection is a risk factor for development of HPV-related oropharyngeal SCC, pathogenesis is unclear and the lack of an obvious HPV-related precancerous stage does not facilitate screening and makes evaluation of vaccine effectiveness difficult. Accurate estimates of HPV-related oropharyngeal SCC will help determine the potential role of prophylactic vaccination. It is likely that the effects of vaccination on oropharyngeal SCC will only be revealed over time through longitudinal studies on incidence before and after vaccine introduction.

Treatment of HPV-related oropharyngeal SCC is currently varied geographically depending on tumour stage, patient status including age and co-morbidities, facilities available and HPV or p16 status. There remains uncertainty regarding vaccination, cetuximab and de-escalation

**Table 1 Ongoing clinical trials pertaining to treatment of human papillomavirus-related oropharyngeal squamous cell carcinoma**

Trial	Phase	Inclusion	Arm 1	Arm 2	Outcomes
RTOG 1016	III	p16 positive locally advanced oropharyngeal SCC	Radiation and concurrent chemotherapy	Radiation and concurrent cetuximab	Survival, toxicity, locoregional recurrence and quality of life
ECOG E1308	II	Stage III-IVa HPV positive oropharyngeal SCC	Complete response to induction chemotherapy and reduced dose radiation with concurrent cetuximab	Incomplete response to induction chemotherapy and standard dose radiation with concurrent cetuximab	Survival, toxicity, response, quality of life and biomarker correlation
De-ESCALaTe HPV	III	Stage III-IVa HPV positive oropharyngeal SCC	Cetuximab and concurrent radiotherapy	standard concurrent cisplatin and chemoradiotherapy	Morbidity, quality of life, cost, survival and recurrence
QUARTERBACK	III	Locally advanced HPV-16 positive oropharyngeal, unknown primary or nasopharyngeal SCC showing complete or partial response to induction therapy	Reduced dose radiation with cetuximab and chemotherapy	Standard dose radiation with chemotherapy	Survival, locoregional control, toxicity and biomarker correlation.
LCCC 1120	II	HPV positive and/or p16 positive low-risk oropharyngeal SCC	Decreased dose of radiation and chemotherapy	Standard radiation and chemotherapy	Pathological response rate, locoregional control, survival and quality of life
NCT01221753	II	Locally advanced HPV positive oropharyngeal SCC	Docetaxel/cisplatin/5-fluorouracil (TPF) induction chemotherapy followed by concurrent chemoradiation using a modified radiation dose	N/A	Locoregional control, survival and toxicity
SIRS	II	Early to mid-stage HPV positive oropharyngeal SCC who receive transoral robotic surgery plus a neck dissection, where clinically indicated	Observation only	Low dose postoperative radiation only Arm 3: Chemoradiation	Rates of locoregional control, overall survival and use of salvage chemoradiation in the observation group
TROG 12.01	III	HPV positive oropharyngeal SCC	Radiation and cetuximab	Radiation and cisplatin	Symptoms severity, swallowing, quality of life, toxicity, survival, locoregional recurrence
ADEPT	III	p16 positive oropharyngeal SCC that has undergone transoral resection with negative margins	Postoperative radiation alone	Postoperative radiation with cisplatin	Survival, locoregional control, toxicity and quality of life
NCT01088802	I / II	HPV positive T1-3 oropharyngeal SCC	De-escalated radiation from 70 Gy to 63 Gy with concurrent chemotherapy	De-escalated radiation from 58.1 Gy to 50.75 Gy with concurrent chemotherapy	Toxicity, quality of life and adverse events
ECOG E3311	II	Stage III-IVa HPV positive oropharyngeal SCC after transoral surgery and neck dissection with negative margins, no extracapsular spread and less than 4 lymph nodes involved	Transoral surgery with standard radiation	Transoral surgery with low-dose radiation	Survival, surgical complications, toxicity and swallowing

SCC: Squamous cell carcinoma; HPV: Human papillomavirus.

of therapy, which will be made clearer through current prospective trials, leading to better delineation of therapy for HNSCC subsets. Accurate assessment for biologically relevant HPV will be critical to improvement in treatment approaches.

## CONCLUSION

HPV has been established beyond doubt as a causative agent in oropharyngeal SCC and biologically active HPV can act as a prognosticator with better overall survival than HPV-negative HNSCCs. A distinct group of younger patients with limited tobacco and alcohol exposure have emerged as characteristic of this HPV-related subset

of HNSCC. However, the exact molecular mechanisms of carcinogenesis are not completely described and further studies are needed to assist development of optimal prevention and treatment modalities.

Despite the large pool of research on HPV in HNSCC, great variation exists in detection techniques. Detection of biologically relevant HPV infection will be important for clinical trial design. Also, biomarker discovery will be important not only to identify specific SCC subsets, including those that are HPV-related, to allow for individualised treatment strategies aimed at decreasing morbidity, but also to clarify the role of HPV in non-oropharyngeal sites.

With stored tissue available from the SEER database

in only 271 patients<sup>[265]</sup>, there needs to be greater cooperation between institutions to improve research into understanding this disease. Nevertheless, it is likely that the key approach in future will be prevention and so further studies in prophylactic vaccination, specifically in relation to oropharyngeal SCC, are needed.

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