# Oropharyngeal carcinoma: a sexually transmitted disease

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## Abstract

Human papillomavirus (HPV)-associated oropharyngeal cancer (OPC) is on the increase and accounts for 18% to 63% of OPC. It occurs mostly in young males with no other identifiable risk factors. The vast majority of HPV-associated OPC is attributable to HPV16. The prognosis of patients with HPV-positive OPC is better than patients with HPV-negative OPC. Oral HPV infection is linked to sexual transmission. The natural history, prevalence and possible risk factors in local communities should be studied to implement appropriate prevention strategies.

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## Introduction

Head and neck squamous cell carcinoma (HNSCC) is often considered a single entity associated with tobacco and alcohol consumption. Recent studies highlighting clinicopathological differences are supportive of the fact that subsets of HNSCC exist that warrant separation from a generic group.

An increase in the incidence of HNSCC between 1973 and 2001 was observed in a study from the USA.[1] This was mainly due to a significant increase in incidence of oropharyngeal carcinoma (OPC), a subset of HNSCC. OPC includes carcinomas developing from the soft palate, base of tongue, palatine tonsil area and posterior pharyngeal wall. The incidence of squamous cell carcinomas (SCC) in other head and neck sites remained unchanged.[1] The increase in OPC was predominantly observed in young adults (20–44 yrs of age). Many of these cancers were not associated with a known risk factor and affected mostly males.[2] A similar increase was also reported in a study from Sweden, also with a male predominance.[3] This has prompted several authors to suggest a common aetiological factor for OPC in this specific group.[2–4]

## Human papillomavirus

Human papillomaviruses (HPVs) are small DNA viruses that characteristically infect epithelium to induce a variety of skin or mucosal lesions.[5] More than 100 different types of HPVs have been identified, and are classified as low-risk and high-risk types based on their potential to cause malignancy.[6] Low-risk types are linked to benign lesions, such as warts and papillomas, while high-risk types are strongly correlated with malignancy. High-risk types include HPV16, -18, -31, -33 and -45, with HPV16 and -18 linked to the majority of cervical cancers.[7]

The relationship between HPV and HNSCC has been studied extensively over the last decade or so. Conflicting results have been reported on the role of HPV in oral SCC,[8–9] while much stronger support of HPV involvement in SCC from the oropharynx exists.[10–11] HPV-associated cancers occur mostly in patients who have no other identifiable risk factors and who have pursued a healthy lifestyle, avoiding tobacco and excessive alcohol use.[10, 12] HPV was found in a higher percentage of non-smokers than in smokers, current or past, in a recent study.[10] The proportion of OPC attributable to HPV infection varies between 18% to 63%.[10, 13] This variability may be the result of different techniques used to identify HPV infection although differences regarding HPV involvement in tonsillar carcinomas have been ascribed to possible environmental, cultural or genetic variation.[14] The vast majority (90–95%) of HPV-associated OPC are attributable to HPV16.[15] The International Agency for Research on Cancer has furthermore accepted HPV16 as an aetiological factor for OPC based on epidemiological evidence.[16]

### HPV oncogenesis

The mechanism of HPV carcinogenesis has been well documented.[17–18] The HPV genome consists of a number of early (E) and late (L) genes that are essential for the life cycle of the virus. Two proteins (E6 and E7), coded by the respective early genes, are important in HPV carcinogenesis. The E6 protein binds with p53 and targets this protein for degradation.[19] The p53 protein is a product of the TP53 tumour suppressor gene that guards the integrity of the genome by allowing DNA repair or to induce apoptosis if the repair process is unsuccessful.[20] The E7 protein of high-risk HPVs binds and inactivates retinoblastoma protein (pRb) and thereby inhibits

the function of pRB to prevent cells with damaged DNA to divide.[17] Cells infected with high-risk HPVs are, therefore, undergoing uncontrolled cell division and replication and can survive with accumulated mutations that may eventually lead to malignant change. It has, however, been demonstrated that the E6 and E7 genes of high-risk HPVs are necessary, but not sufficient, for the progression to malignancy.[21] The E6 and E7 of low-risk HPVs also bind to p53 and pRb respectively, but at a lower affinity and are unable to promote degradation of the p53 and pRb proteins.[22–23]

### HPV-associated OPC

HPV status is an important prognostic biomarker for OPC. A recent literature review with meta-analysis found that patients with HPV-positive OPC have a 28% reduced risk of death compared to HPV negative OPC.[24] It is, therefore, important that the technique for determination of HPV involvement be accurate, highly sensitive and specific. One of the consequences of the inactivation of pRb through interaction with the E7 viral oncoprotein is the upregulation of p16 expression to levels that can be detected with immunohistochemistry.[17] This is a very sensitive technique but only about 80% specific for HPV involvement.[25] The development of signal amplification techniques, and the fact that paraffin-embedded tissues can be used, have contributed to the acceptance of in situ hybridisation technique to confirm HPV involvement. Detection of punctuate hybridisation signals indicate HPV DNA integration[26] and, with a specificity of almost 100%, is the ideal technique to perform on p16-positive cases for final confirmation of the presence of HPV.

There are many misconceptions about the histological features of HPV-associated OPC. The lack of keratinisation, together with the high nuclear cytoplasmic ratio seen in HPV-positive OPC, actually represent the epithelial lining of the tonsillar crypts and should not be interpreted as poorly differentiated features. These tumours also have a lobular growth pattern leading to the diagnosis of a basaloid squamous cell carcinoma (BSCC). BSCC are high-grade tumours with an aggressive behaviour. Studies have confirmed that BSCC consist of HPV-positive and HPV-negative groups with different biological behaviour, with HPV positivity linked to the better prognosis.[27]

### HPV epidemiology

The prevalence and risk factors for oral HPV infection in the general population have not been studied extensively. Initial research, however, suggests that oral HPV infection is sexually transmitted with the odds of infection linked to the number of oral sex partners as well as open-mouth kissing partners.[28] Oral HPV prevalence is linked to male gender and is higher in HIV-positive individuals.[29] Although oral HPV infections are more common in women with cervical HPV infection than women without an HPV cervical infection,[30] there is currently no evidence to support autoinoculation between different sites on the body.

The increase in oral HPV infection may be extrapolated to changes in sexual behaviour. Several case-control studies have reported strong trends between the odds of OPC and the number of oral sex partners,[31–32] implying oral-genital contact as the principal means of acquiring oral HPV infection. Men and women who reported having six or more oral-sex partners during their lifetime had a nearly nine-fold increased risk of developing OPC while those infected with HPV16 were also 32 times more likely to develop OPC compared to those who were HPV16-negative.[31]

Young people who decide to abstain from sex until marriage, are more likely to view oral sex as an acceptable safe sex practice, as virginity is usually linked to vaginal sex only.[33] Most strategies for the prevention of sexually transmitted diseases focus on vaginal intercourse only, even though it has been shown that a high number of young people engage in non-coital sexual practices such as oral sex.[34] Up to 50% of adolescents have had oral sex before their first coital sex.[35] This implies that thousands of adolescents in South Africa are at risk of being infected with HPV intraoral through oral sex, as they might perceive oral sex as being safe.

The earlier young people engage in sex, the higher the number of lifetime partners[36] resulting in a higher likelihood of HPV transmission to the oral cavity.[37] With a younger age of first sexual experiences there is also a more likelihood of no condom protection during subsequent sexual encounters,[38] exposing young people to an even higher risk of sexually transmitted diseases.

In a recent study on the use of condoms, it was found that only 28.6% of women and 39.2% of men aged 15–24 reported consistent use of a condom with their last partner.[39] This, despite the fact that HIV has a prevalence of 15% in women and 5% in men of the same age.[40] This illustrates the low use of condoms in high risk sexual activity and one can assume a much higher percentage of youths not using condoms during oral sex, which is perceived as a low risk sexual activity concerning HIV transmission. This was confirmed by a recent study reporting that only 4% of respondents used condoms for the first oral sex encounter.[41] This can in part be ascribed to the fact that it is perceived as a safer sexual activity.[41] In South Africa, an estimated 50% of young people are sexually active by age 16.[40,42] Orphans show earlier sexual activity than non-orphans, with a higher number of risk factors for earlier sexual activity.[43] There are an estimated 3.5 million orphans in South Africa,[44] with many of these children exposed to early and often unwanted sex. This puts this vulnerable group of young people at even more risk of acquiring HPV.

Education of young people about sexual practices is something which is taught at school, in the form of the compulsory subject, Life Orientation. In a recent study, it was found that differences in the success of such teaching existed between different areas within South Africa.[45] This illustrates the immense difficulties experienced with sexual education by culturally different

teachers to culturally different adolescents regarding education about the dangers of HIV/AIDS.[45] From this can be concluded that educating them about the dangers of HPV transmission is going to more difficult as it is an even more abstract enemy than HIV.

## Conclusion

HPV-associated OPC is an emerging disease which differs from other HNSCC. The evidence that oral HPV infection is sexually transmitted should lead to studies examining the natural history, prevalence and possible risk factors in local communities in order to implement appropriate prevention strategies.

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