

# **Human papillomavirus and carcinoma of the mucosal surfaces of the head and neck**

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## **ABSTRACT**

Human papillomavirus induced cervical cancer is the fourth most prevalent malignancy affecting females globally. Over the past two decades scientific information unveiled an increasing role for the virus in the pathogenesis of malignancies developing from the mucosal surfaces of the oropharynx. It is feasible to postulate that we may be in the beginning of a global pandemic of oropharyngeal cancer if the mode of transmission of the virus is taken into account. The main goals of this manuscript are to present a brief summary of the mechanisms of human papillomavirus induced malignant transformation, provide guidelines for the microscopic diagnosis of high risk human papillomavirus involvement in mucosal biopsies and highlight the implications thereof in cancers of the mucosal surfaces of the head and neck.

**Key words:**

High risk HPV infection, HPV 16, oropharyngeal cancer, p16.

**1. Introduction**

Human papillomavirus (HPV) infection is the most prevalent sexually transmitted disease in the world. Oncogenic strains of the virus are directly linked to malignant transformation of the squamo-columnar junction of the female cervix. Cervical cancer caused by HPV is almost three times more common than female breast cancer in developing countries and has a mortality rate of nearly 60% [1]. HPV spreads to the mucosal surfaces of the head and neck through open mouth kissing and/or oral sexual activity [2]. More than 200 HPV types have been recorded. Non-oncogenic varieties with an affinity for the mucosal surfaces of the head and neck include HPV 2, 4, 6, 11, 13 and 32 and cause benign proliferations such as verruca vulgaris, condyloma acuminatum, focal epithelial hyperplasia and recurrent laryngeal papillomatosis (for a review of the non-oncogenic HPV associated mucosal lesions readers are referred to Bharty et al 2013[3]). Although HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 are classified as high risk oncogenic genotypes for transforming epithelial cells into cancer, HPV type 16 is associated with most malignancies in the head and neck region in which the virus is implicated [3, 4]. HPV type 18, which has an affinity for glandular tissue and other oncogenic HPV types are rarely involved in mucosal malignancies in the head and neck region [5].

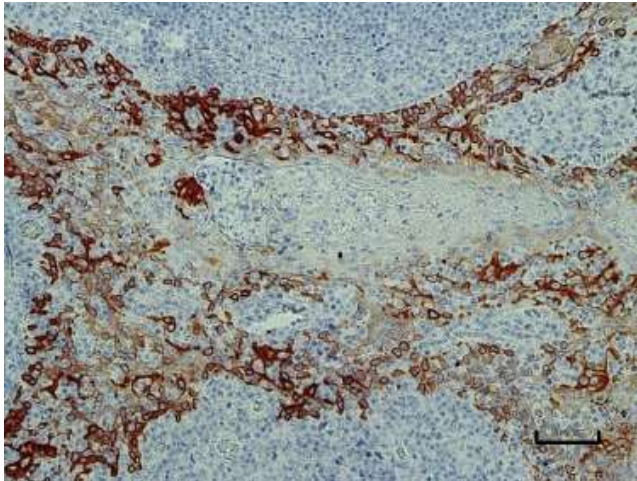
With 273 000 deaths and 482 000 new cases reported world-wide in 2008, oral and pharyngeal cancer has become the sixth most frequent malignancy affecting mankind [6]. Recent epidemiological studies showed that despite a decrease in the use of tobacco, there is a progressive increase in the incidence of head and neck cancer experienced globally [7]. This trend is attributed to the escalating prevalence of oncogenic HPV infections of the mucosal surfaces of the oropharynx [8]. Studies in North America and Europe claim a 70-80% association between cancer of the oropharynx and HPV [8-10]. World-wide trends in the incidence of oropharyngeal cancer in men between 1983 and 2002 showed a rise in developed countries and a shift towards involvement of a younger age group [11]. This is particularly evident in communities where the traditional risk factors of tobacco and alcohol

consumption are on the decline. Changing sexual practices play a defining role in the unfolding of the oral- and pharyngeal oncogenic HPV epidemic. Patients with HPV associated anogenital cancer, which is more common in male homosexuals, have a higher risk for HPV-associated tonsillar cancer than for non-HPV tobacco associated oral cancers [12].

It is feasible to postulate that developing countries with their burden of sexually transmitted diseases, could be on the forefront of the unfolding global epidemic of HPV associated oropharyngeal cancers. The main goals of this manuscript are to provide health care practitioners with an overview of the mechanisms of HPV associated malignant transformation and highlight the importance of determining the involvement of high risk HPV types in lesions affecting the mucosal surfaces of the head and neck.

## **2. HPV-induced malignant transformation**

A requirement for infection of an epithelial cell by HPV is binding of the virus to receptors in the epithelial basement membrane [13]. Most of the oral cavity, oropharynx and larynx are lined by stratified squamous epithelium with tight junctions that provide adequate protection against contact between HPV and the basement membrane. Mucosal ulcerations which are common in the oropharynx and areas in which the epithelium show a functional adaptation towards a loose arrangement such as the reticulated epithelial lining of the oropharyngeal- and lingual tonsillar crypts (Fig. 1), expose the basement membrane binding sites thereby facilitating viral entry into the basally located epithelial stem cells [14]. The ease of access to the basement membrane also apply to the squamo-columnar epithelial junction of the female cervix, which is the site of entry of HPV for the induction of cervical carcinoma. After the virus transfers from the basement membrane to the epithelial cell, it integrates into the nucleus, replicates and propagates in the daughter cells. Natural clearance of HPV occurs in most infected individuals within 2 years, although in some the clearance of HPV 16 takes nearly two times longer [3]. Those individuals in whom HPV type 16 persist, are subjected to a high incidence of malignant transformation.



**Fig. 1:** Loose reticulated epithelial lining of a crypt of a tonsil highlighted by an immunoperoxidase stain for cytokeratin (bar 100  $\mu$ m).

Due to the malignant potential of HPV 16, its influences on cell reactions have been studied extensively. The success of epithelial infection by HPV 16 is promoted by its ability to evade immune recognition. This occurs through a suspension of E-cadherin dependant Langerhans cell adhesion to epithelial cell surfaces [15], inhibition of Langerhans cell migration to the epithelium[16] and suppression of the release of pro-inflammatory cytokines by epithelial cells which harbour the virus [13].

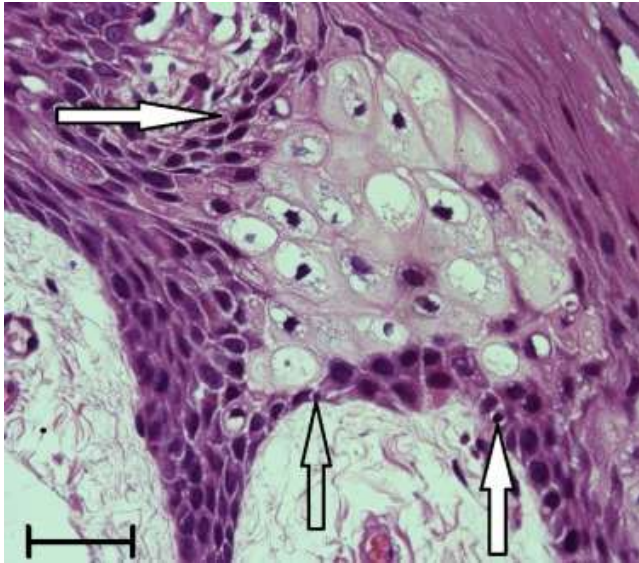
High risk HPV oncoproteins E6 and E7 play a pivotal role in malignant transformation of infected epithelial cells. These oncoproteins bind to- and inactivate p53 and the retinoblastoma protein (pRB) respectively [17]. During a normal mitotic cycle of an uninfected cell, p53 prevents neoplastic transformation through activation of DNA repair and blockage of cell division by arresting the process in the G1/S phase. When DNA damage is extensive, p53 initiates epithelial cell apoptosis thereby preventing the likelihood of mutations during DNA repair. In an uninfected cell, cycline dependant kinase 4 (CDK 4)-mediated phosphorylation of pRb is a requirement for induction of the mitotic cycle. P16, a tumour suppressor gene, inhibits CDK4-mediated phosphorylation thereby restraining cell division. HPV E7 binds to- and destabilizes pRB [18], the negative feedback of free pRB is subsequently reduced and p16 becomes over-expressed within the infected cell. P16 expression by epithelial cells therefore signals the incorporation of high risk HPV which

implies that malignant transformation is likely to follow if viral clearance does not occur [17,19].

Epidemiological studies indicate that the incidence of carcinomas of the mucosal surfaces of the head and neck is higher in HIV positive individuals. Although modified tobacco- related habits may play a role in initiating mucosal malignancies in this patient cohort, there is overwhelming evidence that oropharyngeal cancer in HIV positive patients is a consequence of concomitant HPV and HIV infection [17]. Although speculative, the higher rate of infection with HPV of the HIV positive individual is likely the result of a modified lifestyle, altered systemic immune response, breakdown of the innate mucosal immune barriers and suppression of the mucosa-associated adaptive immune response. The impact of HAART on HPV infection and the development of oral and pharyngeal cancer are not yet clarified.

### **3. HPV identification in biopsy samples**

During light microscopic examination of a biopsy or a cervical smear, koilocytes are generally regarded as the hallmark for both oncogenic- and non oncogenic HPV infection (Fig. 2). The appearance of HPV core gene E4, which prepares the cell for the release of viral particles through mediation of enzymatic fragmentation of keratin filaments within the cytoplasm of the infected cell [13], coincides with the onset of koilocytic vacuolation. As E4 expression intensifies, koilocytic vacuolation increases in prominence and cell proliferation declines. The pathognomonic vacuolation is probably a sequel to the cytoplasmic osmotic change resulting from the fragmentation of the filamentous cytokeratin proteins. In oncogenic HPV infection, p16 expression increases in intensity with progressive koilocytic change [20,21]. The morphological identification of koilocytes in microscopic sections of cancer is difficult due to the frequent occurrence of unrelated vacuolation and clear cell change in neoplastic epithelial cells.



**Fig. 2:** Microscopic appearance of a HPV infection of the surface epithelium of the oropharynx showing the vacuolated koilocytes and apoptotic keratinocytes (arrows) (H&E stain, bar 50  $\mu\text{m}$ )

Direct comparisons between studies on the prevalence of high risk HPV in cancer are confounded by the nature of the specimen examined (fresh frozen- vs paraffin wax embedded material) and the techniques- and primers used for the identification of the virus. The polymerase chain reaction (PCR) and in-situ hybridization (ISH) techniques, which provide comparable results [19], are significantly more sensitive than immunohistochemistry for the demonstration of p16 in tissues. The benefit of ISH is that microscopic localization of the viral protein is possible, which is not the case with PCR where the architecture of the tissue is destroyed. ISH for high risk HPV E6/E7 ribonucleic acid has a high degree of specificity for the recognition of high risk HPV transcription in biopsies of carcinomas [22] and is the method of choice in the well-equipped histopathology laboratory. Although PCR destroys the micro-architecture of tissue, it is extremely sensitive which makes it vulnerable to cross contamination leading to false positive results if strict protocols are not followed.

Immunohistochemistry for p16 on routine processed biopsies is however the most appropriate technique for the screening for high risk HPV involvement. The cost is a fraction of PCR- and ISH- based techniques, laboratory staff requires no additional training and the stains can be performed on routinely processed tissue in most histopathology laboratories with reserve tissue remaining in the wax block for further studies. Although p16 reactivity correlates well with the presence of high risk HPV in oropharyngeal squamous cell carcinoma, the relationship is not absolute [23,24]. Differences in opinion on the reliability of p16 as a

marker are related to the interpretation of the stain. In a systematic review, nuclear- and cytoplasmic staining of a minimum of 70% of cells for p16 has been recommended as the most appropriate level of sensitivity for confirmation of the presence of high risk HPV protein [18]. This correlates with 3+ staining where more than two-thirds of cells show nuclear- and cytoplasmic staining [22].

#### **4. Mucosal pre-malignancy and HPV**

The scientific literature focusses on HPV's role in cervical pre-cancer and cancer. Involvement of HPV in colorectal-, oral- and oropharyngeal malignancies have been studied less frequently. Labelled DNA of HPV 6, 11, 13, 16, 18 and 30 was demonstrated in one quarter of 22 biopsies of oral dysplastic lesions in the classic study performed by Syrjänen in Finland in 1988 [25]. The presence of non-oncogenic HPV types in dysplastic lesions suggests the possibility of a non-aetiological (passenger) status for several of the HPV types. High risk HPV involvement is more frequently recorded when the microscopic criteria for the selection of a biopsy for p16 staining are narrowed down to severe dysplasia with marked apoptosis, koilocytes and brightly eosinophilic cells distributed throughout the thickness of the epithelium (Fig. 2). Only scattered typical koilocytes are generally present in HPV-associated dysplasias. The term "HPV-associated Oral Intraepithelial Neoplasia" (HPV-OIN) was recommended for lesions compatible with this microscopic description [20]. The presence of HPV DNA in the oral mucosa of tobacco chewers suggests that both of these factors may be implicated in the high incidence of oral cancer in parts of Pakistan. It was proposed that tobacco chewing causes mucosal abrasions which expose the epithelial basement membrane to HPV binding and epithelial viral integration [26].

No malignant transformation has been reported in non-oncogenic low risk HPV associated lesions of the oropharyngeal- and laryngeal mucosal surfaces (condyloma acuminatum, verruca vulgaris, focal epithelial hyperplasia and laryngeal papillomatosis). The risk of a malignancy developing in inverted papillomas is approximately 10% [27]. Thirty eight percent of inverted papillomata express HPV, the majority HPV types 6 and -11 and a minority the high risk HPV types 16 and -18. Those with HPV type 16 and -18 often show severe dysplasia, increased apoptosis and mitotic activity and p16 positivity and represent the group of inverted papillomas which is associated with a higher tendency to undergo

malignant change [28]. A stain for p16 is therefore recommended on all inverted papillomas and positive lesions should be followed up regularly.

## **5. Mucosal carcinoma and HPV**

Tobacco and alcohol are implicated as etiological factors in most squamous cell carcinomas of the oral cavity which includes the mucosal surfaces of the floor of the mouth, anterior two thirds of the tongue, buccal mucosa and alveolar mucosa. High-risk HPV's play a lesser role in the induction of carcinomas at these sites [29]. As an external chemical carcinogen, the pre-cancerous stages of tobacco induced carcinoma show microscopic changes in the overlying epithelium which are distinct from HPV-OIN. Unlike the belief in the past, no role for HPV could be found in the development of verrucous carcinoma [30].

The 2017 edition of the World Health Organization (WHO) reference book on head and neck tumours [31] separates the oropharynx (palatine tonsils, soft palate, tongue posterior to the circumvallate papillae and posterior pharyngeal wall) as an anatomical site distinct from the oral cavity. The rationale for this division is the important role HPV plays in the unique carcinomas induced the oropharynx. Of the extra-genital carcinomas, non-keratinizing carcinoma of the oropharynx has the strongest association with high risk HPV. The most feasible explanation for this is the loosely arranged reticular nature of the epithelium lining the oropharyngeal- and lingual tonsillar crypts (Fig. 1) which, as explained earlier, provides access for the virus to the basement membrane binding sites. Unlike the cervix, the inaccessibility of the precursor lesions within the tonsillar crypts renders a cytology based pap-smear equivalent for the diagnosis of the early pre-cancerous stages ineffective. HPV-related carcinomas of the tonsils are therefore often diagnosed at a late stage with lymph node metastases (which are frequently cystic), in contrast to HPV negative tumours [32]. The p16 positive neoplastic cells show a high nuclear-cytoplasmic ratio, brisk mitotic activity, apoptosis and tumour necrosis, lack keratin production and are associated with a lymphoid infiltrate. These microscopic features linked to their p16 reactivity are helpful in establishing the oropharynx as a probable site of origin of a metastatic deposit in a neck lymph node with an undisclosed primary [33]. There is general agreement that HPV positive non keratinizing oropharyngeal cancers have a better prognosis than those that are negative [18] despite their aggressive microscopic features and propensity to metastasize early in their progression. For



this reason, it is recommended in the WHO 2017 reference book on head and neck tumours [31] to sign the HPV positive oropharyngeal carcinomas out as “squamous cell carcinoma, HPV positive” and avoid the use of the term “poorly differentiated non-keratinizing carcinoma” as the latter does not reflect its favourable biological behaviour.

Other microscopic growth patterns of carcinomas of the mucosal surfaces of the head and neck frequently associated with HPV 16 are basaloid squamous cell carcinoma [34-36], papillary squamous cell carcinoma [37], adenoid cystic-like carcinoma of the sinonasal tract [38,39], adenosquamous cell carcinoma [40] and primary small cell carcinoma [41] (the latter which is now classified as a distinctive entity in the 2017 WHO reference manual on head and neck tumours [31]). In all growth patterns, p16 positivity, which indicate involvement of an oncogenic HPV, correlate with a more favourable prognosis than those that are HPV negative, except for primary small cell carcinoma where the presence of HPV viral protein does not correlate with a better prognosis than negative cases [42]. Due to prognostic implications, it is advised to include the HPV status in the signed-out diagnosis of all these growth patterns [31]. A systematic review of 55 studies of laryngeal cancer found a 19.8% association with HPV type 16 [43]. Only one paper reported a more favourable prognosis for laryngeal squamous carcinomas with HPV 16 expression [44]. Long term follow-up studies are however required to determine the prognostic significance of laryngeal carcinomas associated with the HPV 16.

## **6. Conclusions**

The increasing rate of occurrence of oropharyngeal carcinomas globally is mainly the result of a higher rate of infection of the oropharynx with HPV 16. Preliminary indications are that patients with HPV 16 positive squamous cell carcinomas, with the exception of a few rare growth patterns, enjoy a more favourable prognosis than those with HPV 16 negative tumours. Staining for p16 is a cost-effective marker for high risk HPV transcriptional activity. The stain is useful for the prediction of malignant transformation of inverted nasal papillomata, identification of high risk HPV involvement in mucosal dysplasias and confirmation of oropharyngeal origin of a metastatic deposit in a cervical lymphnode with an undisclosed primary.

Due to the direct mode of spread, the oropharyngeal implications for persons in close contact with both females and males with high risk HPV positive lesions need to be researched further. Immunization of females against high risk HPV infection is safe, successful and national immunization programs which have been instituted in several countries will lead to a reduction in the burden of cervical carcinoma [45]. The female vaccination program will induce a male bias in the incidence of HPV 16 related oral- and pharyngeal cancers unless the vaccination programs are extended to include teenage boys. Furthermore substitution of HPV 16 by one of the other high risk HPV types not included in the vaccine cocktails is predictable in vaccinated individuals and the hope of eradicating HPV involvement in the induction of mucosal malignancies may be a delusion.

### **Conflict of interest**

The authors declare no conflict of interest.

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