



## Review Article

# Growing epidemic of Human papilloma virus associated malignant and premalignant lesions - A dental surgeon's perspective

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## Abstract

**Objectives:** To explore unique characteristics of HPV related oral malignant and premalignant lesions and to describe role of dental surgeons in prevention of this viral- induced carcinogenesis.

**Methods:** Extensive literature search was conducted to identify articles detailing HPV associated diseases. Data collected were categorised under relevant titles of clinical interest.

**Results:** Peculiarities of HPV linked cancers in head and neck include its different mode of transmission, younger age distribution, irrelevant habit history, good treatment response, better survival rates, less chance of local recurrence and low distant metastasis.

**Conclusions:** The most distinguishing feature of HPV related head and neck cancers is that it is vaccine preventable. Dental surgeons have got an influential role in creating patient awareness regarding this emerging epidemic. The article advocate further research in this regard.

**Key Message:** The carcinogenic potential of Human papilloma virus has been an interesting topic of research for the past few decades. This article discusses the recent epidemiologic and etiologic trends in Human Papilloma Virus – associated head and neck cancers, its presence in precancerous lesions and its implication in dental practise.

**Keywords:** Human papilloma virus, Head and neck cancers, Viral carcinogenesis.

## Introduction

Human papilloma viruses (HPV) are a group of viruses which are well known to cause sexually transmitted infections. Globally 5% of all cancers are caused by HPV, majority being cervical cancer<sup>(1)</sup>. In United States of America, at least

70% of reported oropharyngeal carcinomas are positive for HPV<sup>(2)</sup>. India has got a very high prevalence rate for Oropharyngeal Squamous Cell Carcinoma (OSCC), despite various laws and actions taken to control the use of tobacco and other deleterious carcinogenic substances. The

incidence of OSCC is increasing among younger population<sup>(3)</sup>, which is an alarming sign that shows role of other etiologic factors like HPV in oral carcinogenesis. American Joint Committee on Cancer revised the criteria for staging of oropharyngeal carcinomas to include Human papilloma virus associated (p16 positive) oropharyngeal cancer in its 8<sup>th</sup> edition<sup>(4)</sup>.

Aim of this review is to improve understanding of distinct epidemiologic trends, demographic and pathologic characteristics, molecular biology and prognostic features of HPV associated malignant and potentially malignant lesions, which will help to improve dentist's preventive, diagnostic and management approach towards the disease.

## Materials and Methods

### Literature search strategy

A computerized literature search was performed using PubMed and Google Scholar data bases, with restriction to English language, without time-limits and using the following search terms in various combinations- Human papilloma virus, oral carcinogenesis, viral carcinogenesis, oral cancer, oropharyngeal cancer, HPV induced malignant transformation, epidemiology, taxonomy, HPV in cervical cancer, prevalence, oral cavity, mouth, prognosis, treatment outcome. Moreover, reference lists of relevant papers were also hand searched. All 'related citations' for results found in PubMed were searched as well.

Articles detailing HPV's role in oropharyngeal carcinoma, including epidemiology, microbiology, pathogenesis, treatment and prognosis were included in this review. Articles without full text availability, abstracts, case reports, conference presentations, editorials, expert opinions were excluded.

### Human Papilloma Virus and its oncogenic potential

It is a common microbe in human body, first isolated from rabbit papillomatosis in 1933<sup>(5)</sup> coming under Papovaviridae family<sup>(6)</sup>. This epitheliotropic virus has a non-enveloped structure of 52 -55nm diameter with icosahedral shape<sup>(6,7)</sup>.

World health Organisation (WHO) has included many of  $\alpha$  papilloma virus types under human 'Carcinogens Type 1' and HPV 16 and 18 are established human carcinogens<sup>(8,9)</sup>.

It was Sur Hausenin 1970, who suggested a common viral etiology for cervical cancer and condyloma acuminata – HPV. Later, in 1983, Syrjanen<sup>(10)</sup> first suggested the link of HPV and oral carcinogenesis by considering the epitheliotrophism and oncogenic potential of the virus and similarity of oral and genital mucosa. Niedobitek et al<sup>(11)</sup> separated HPV 16 for the first time, which was from palatine tonsil, in 1990.

### Etiopathogenesis

The epitheliotropic virus commonly infects the basal and para basal cells of epithelium following the traumatic removal of superficial layer and HPV genome cause immortalization of primary human keratinocyte by altering the expressions of LCR and E6/E7 early genes. E6 cause cell cycle arrest by degradation of Tp53 and E7 trigger DNA synthesis. Thus, E6 compliments E7 function and cause pathological cell growth, transforming infected cell into a fully malignant one<sup>(12)</sup>. The process of carcinogenesis is also facilitated by actions on telomerase, Retinoblastoma(Rb) proteins and p53<sup>(2)</sup>.

### Epidemiology of HPV related head and neck cancers and premalignant lesions

HPV associated carcinomas follows a distinct epidemiologic profile. One feature is high incidence among those practising of oral sex and having multiple oral sexual partners<sup>(13-15)</sup>. However there are reported cases of HPV associated OSCC in patients (8-40%) who never had oral sex<sup>(16)</sup>. Habits of chewing tobacco and alcoholism can have a synergistic role in etiopathogenesis of HPV related cancers<sup>(17)</sup>, possibly by altering the host immune response<sup>(14)</sup>. Men are found to be having a higher risk for HPV associated OSCC, the reason for which is yet unknown<sup>(13)</sup>.

D'Souza et al's<sup>(18)</sup> study proved that oral HPV infection rates increase with oro- genital contact, and suggested a possibility for spread of virus

through direct mouth – to- mouth contact, signifying role of saliva in transmission of HPV. Different study findings of HPV related oropharyngeal carcinomas and premalignant lesions are listed in Table 1 and 2. These studies indicate that HPV status may be a risk factor for development of premalignant lesion, but warrants further studies for confirmation.

#### **Habit and HPV**

Reports regarding association between habits of using tobacco or alcoholism and HPV related cancer development are conflicting. Studies exploring influence of habit in HPV associated SCC is depicted in Table 3.

#### **Immunobiology**

The significance of cellular and humoral immune mechanisms in controlling the HPV infection have been studied and was found that person with good immunity can respond well against the virus, prevent HPV infection and probably HPV associated cancer as well<sup>(9)</sup>. A retrospective longitudinal study was conducted by Lindel et al<sup>(19)</sup> among patients having oral leukoplakia with malignant transformation, and found that 12 to 15 months preceding malignant transformation, these patients were having a shift from Ig A to Ig G plasma cell predominance. They suggest that this could be the result of change in the antigenic pattern of the overlying epithelial cell, which may be caused by HPV. It was proven from animal studies that, protection from HPV infection is possible by antibodies that can neutralize virus. Increased rate of infection of HPV in patients who are HIV positive<sup>(20)</sup> and transplant recipients<sup>(21)</sup> suggest that human papilloma viral infection pathway is largely mediated through cell-mediated immune mechanism.

#### **HPV vaccine**

Vaccines can have a role in HPV infection mainly by acting on virus- specific immune mechanism. The types of vaccines are, prophylactic HPV vaccines, therapeutic HPV vaccines and combined prophylactic and therapeutic vaccines. Beside these, there are many experimental vaccine strategies like vector-based vaccines, peptide-

based vaccines, protein-based vaccines, nucleic-acid-based vaccines, chimeric VLP-based vaccines, cell-based vaccines, pseudovirions, and RNA replicons. These are supposed to act by enhancing HPV-specific immune cell activity and anti-tumor responses<sup>(22)</sup>.

Three types of vaccines now available for HPV are<sup>(22)</sup> the bivalent HPV vaccine (against HPV 16 and 18), The quadrivalent vaccine (targeting HPV 6, 11, 16 and 18) and the 9-valent vaccine (targets HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58). Now only 9- valent vaccine is being used in United States<sup>(22)</sup>.

#### **Prognosis**

Current literature showed that HPV associated OSCC are a specific subgroup of OSCC with better survival rate, prognosis and favourable local recurrence hazard rate, disease- free and disease-specific survival rates (Table 4). This important finding may help oncologists to classify patients based on HPV status and habit history and to formulate a follow-up protocol accordingly.

Mechanism of good treatment outcome of HPV induced tumorigenesis may be its distinct etiology. In virus infected patients, immune reactions occur against viral specific tumor antigens. Moreover, there is no field of altered genetic activity (field cancerization) in these patients and their apoptotic mechanism will be functional, which maximize treatment response to radiotherapy<sup>(23)</sup>.

#### **Role of Dental Surgeon**

Majority of HPV associated OSCC are seen in oropharyngeal region<sup>(24)</sup>. As a primary health care provider of orofacial region, dental surgeons have to take a major role in controlling the HPV menace. It is very important to have a good relationship with patients to have discussions about this virus, its carcinogenic potential, increasing reports of oropharyngeal cancer, the risk factors, relationship between sexual behaviours and spread of HPV and methods of prevention. But knowledge about these facts among oral health care professionals is less<sup>(2)</sup> which has to be addressed positively.

Since sexual habit of a person is an important perspective in HPV infection, possible association of HPV 16 infection with oral sex practice was studied by Nguyen et al<sup>(25)</sup>. They concluded that individuals who are practising oral sex, especially with multiple partners have got a high risk for development of oropharyngeal carcinomas. Along with these, the fact that 60% of oropharyngeal cancer cases reported in US were positive for HPV16, strengthens the need for an intervention by family physicians to educate the individual about healthy and safe sexual behaviours and role of HPV vaccination to prevent the infection. It was also suggested to take necessary measures to educate the public regarding risk of unprotected oral sex and chance of oral HPV transmission.

Most of the professionals are facing difficulty due to their lack of knowledge base for addressing patient's queries. Some patients may not be comfortable with asking direct questions regarding their sexual behaviors. Therefore good quality knowledge should be provided to the health care professional to handle the circumstance.

Health literacy may be defined as "ability to access and effectively utilize health information"<sup>(26)</sup> and probably results in better health outcome<sup>(27)</sup>. Health literacy regarding knowledge of HPV in head and neck cancers has to be improved to effectively control the disease burden and for achieving a better outcome.

Daley et al<sup>(28)</sup> conducted a survey to evaluate the readiness of Dental professionals to act against increasing rate of HPV- associated OSCC. The results suggested that majority of the dentists are not keen on taking an active role in primary prevention of HPV- OSCC. This can be addressed by formulating guidelines for HPV- OSCC discussions by the professional organizations. The study also pointed out that as the awareness of patients regarding the relationship between HPV and oral cancer is increasing, dental surgeons have to answer and educate their patients in this regard and must be capable for the same. This can be

achieved through continuing educations, by keeping oneself up to date in the field.

Also one should work with their fellow healthcare professional to improve the public awareness about HPV infection. It is important to identify the individuals at risk and proactively address their issues and give necessary instructions. Male and female patients have to be questioned individually as men seems to be less informed about HPV<sup>(29)</sup>.

We also should advocate good research works that can lead to create more clear knowledge and idea about this pervasive disease which promote creating public awareness and formulation of preventive policies for this growing epidemic.

#### **Patient Information Sources**

The patient has to get good source of information that meet their needs and helps to prevent the disease. These resources should try to explain the mode of infection, risk factors, precautions to be taken and preventive measures which include vaccination etc. to the patient. Physician can advise their patients the following website for more information about HPV.

- Centers for Disease Control and Prevention, HPV Fact Sheet - <https://www.cdc.gov/std/hpv/stdfact-hpv.htm>
- National Cancer Institute, HPV and Cancer - <https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-fact-sheet#q8>
- Medical Institute for sexual health - <https://www.medinstitute.org/sti-wizard/hpv/>

**Table 1: Human papilloma virus status in head and neck cancer patients**

Author	Year	Country	Study period	Study population	Study design	Sample size	Age	Male: female	Mode of identification	Results
Licitra et al <sup>(30)</sup>	2006	Italy	1990 - 1999	OSCC	Retrospective cross sectional	100	57 (Median)	3:2	PCR & IHC	Positive HPV DNA-19%, TP53 mutations-39%. p16INK4a deletion-31%, p16 null immunophenotype -64%
Sannigrahi et al <sup>(31)</sup>	2015	India	2013-2014	HNSCC	Cross-sectional	226	<60-78% ≥60- 22%	25:7	PCR	Positive HPV DNA- 29.7%, Positive HPV16 -47.7%
Lassen et al <sup>(32)</sup>	2009	Baltimore, US	1986-1990	HNSCC	Prospective cohort study	156	57(Median)	23:12	IHC	p16INK4A positivity -in 35 tumors (22%), positive IHC for p16- 22%
Gillison et al <sup>(15)</sup>	2008	US	2000-2006	HNSCC	Case-control study	Cases 240 Controls 322	<50-30% 50-64- 58 ≥65 - 12	85:15	ISH	Positive HPV16- 38%
D'Souza et al <sup>(18)</sup>	2007	Baltimore	2000 - 2005	HNSCC	Case-control study	Cases 100 Controls 200	<50yrs- 34%,50-64yrs-51%, ≥65-15%	14:86	ISH	Positive HPV 16 -72%
Ibieta et al <sup>(33)</sup>	2005	Mexico City	1999 - 2001	OSCC	Cross-sectional	51	Not mentioned	15:6	PCR	Positive HPV DNA-42%, Positive HPV 16-66.7%

\*OSCC- Oropharyngeal Squamous Cell Carcinoma Patients HNSCC- Head and Neck Squamous Cell Carcinoma Patients  
 PCR -Polymerase Chain Reaction IHC- Immuno Histo Chemistry  
 ISH- In Situ Hybridization HPV -Human Papilloma Virus

**Table 2 : Human papilloma virus in oral potentially malignant lesions**

Author	Year	Country	Study setting	Study design	Study sample	Results
Bibjina et al <sup>(34)</sup>	2016	India	Department of Microbiology, KMC, Mangalore, India	Case -control study	20 Potentially malignant lesions & 47 Oral squamous cell carcinomas	HPV DNA in Potentially malignant lesions- 0% OSCC- 40.4%
Reed et al <sup>(35)</sup>	2015	Austria	Department of Craniomaxillo facial and Oral Surgery, Medical University of Innsbruck	Case control study	118 clinically diagnosed LKP or EP & 100 controls	Risk of having an LKP or EP is 3 to 4 times higher in patients with oral high-risk HPV infection
Kreimer et al <sup>(14)</sup>	2011	United States, Mexico, and Brazil	General population in United States, Mexico, and Brazil	Cohort study	1,688 Healthy men	HPV DNA in 4% of sample & HPV 16 in 0.6% of samples
Campisi et al <sup>(36)</sup>	2004	Italy	Unit of Oral Medicine, University of Palermo, Italy	Case - control study	Cases -139 Patients with 71 OLP &68 LKP Controls -90 without mucosal lesions	HPV DNA was found in 17.6% of LKP, in 19.7% of OLP, and in 5.6% of controls Positive HPV 16 in OLP -14.3% LKP- 16.7%
Giovanneli <sup>(37)</sup>	2002	Italy	Department of Oral Sciences, University of Palermo, Palermo, Italy	Case- control study	SCC-13, potentially malignant lesions- 59, benign erosive ulcerative lesions-49	HPV DNA- 61.5% in SCC, 27.1% in potentially malignant lesions, 26.5% in erosive ulcerative lesions
Lind et al <sup>(38)</sup>	1985	Norway	Department of Oral Surgery and Oral Medicine, University of Oslo, Norway	Retrospective longitudinal study	20 patients with LKP, out of which 10 developed SCC	Remarkable shift from IgA to IgG plasma cell predominance in the biopsies of the cancer series, not detectable in the non-cancer group

\*OLP- Oral Lichen Planus LKP- Leukoplakia EP - Erythroplakia SCC- Squamous Cell Carcinoma  
 HPV DNA- Human Papilloma Virus Deoxyribo Nucleic Acid



**Table 3:** Habit status in Human papilloma virus associated head and neck cancer patients

Author	Year	Results
Kumar <i>et al</i> <sup>(39)</sup>	2015	Significant association was observed between hr-HPV infection with alcohol consumption and tobacco chewing in HNSCC cases, especially HPV18 than HPV16
Jitani <i>et al</i> <sup>(40)</sup>	2015	Among cases of OSCC, 66.7% (n=6) of the HPV 16/18 positive cases were non-smokers, compared to 33.3% (n=3) smokers, and a statistically significant result (p=0.05) was observed
Wang <i>et al</i> <sup>(12)</sup>	2011	No significant statistical difference between hrHPV positivity and history of tobacco and alcohol use
Dahlstrom <i>et al</i> <sup>(41)</sup>	2007	NSND patients were more likely to be female and to present at extremes of age, but overall were significantly younger than ESED patients More than half the NSND patients with an oropharyngeal primary were serologically positive for human papilloma virus type 16.
Zhang <i>et al</i> <sup>(42)</sup>	2004	Statistical analysis indicates that age (<60 years) and gender (male) were significantly correlated with the presence of HPV16/18 DNA in the tumour. No significant association between HPV presence and other factors including tobacco and alcohol usage, tumour location, histologic grade or TNM staging
Giovannelli <sup>(37)</sup>	2002	HPV infection was related to older age but not to sex, smoking, or alcohol use; the presence of lesions in the oral cavity increased the risk of HPV infection

\*NSND – Non Smoker Non Drinker

HPV – Human Papilloma Virus

HNSCC- Head and Neck Squamous Cell Carcinoma Patients

ESED – Ever Smoker Ever Drinker

hr-HPV- High risk Human Papilloma Virus

OSCC – Oral Cavity Squamous Cell Carcinoma

**Table 4:** Studies on management and prognostic features of Human papilloma virus associated head and neck cancers

Author Year	Country	HPV 16DNA	p16 expression	p53 expression	TNM stage	Locoregional control	Survival rate	Distant metastasis	Tumor relapse	Result
Lohaus <i>et al</i> ,2014 <sup>(43)</sup>	Germany	33.5%	36.9%	38.5%	NA	89.6% (2year)	Overall survival(2yr)- 83.4%	85.1% (2yr)	Not mentioned	HPV16 DNA positivity was a strong independent prognosticator for loco-regional tumour control in oropharyngeal but not in oral cavity tumours
Lassen <i>et al</i> ,2009 <sup>(32)</sup>	Denmark	NA	22%	NA	Stage 1-2= 17 Stage 3-4= 83	58%	5year-58% disease-specific survival-72% overall survival – 62%	N0=37% N1-3=63%	Not mentioned	Statistically significant improvement in locoregional tumor control in p16INK4A-positive tumors as compared with p16INK4A-negative tumors (58% v 28%)
Fakhry <i>et al</i> , 2008 <sup>(44)</sup>	Baltimore	37.5%	37.5%	NA	Stage 3 =29% Stage 4=71%	Progression free survival-1yr& 2 yr-91%, 86%	1-year overall survival-97% 2-year overall survival- 95%	11% HPV positive & 5% HPV negative	Progression free survival-1yr& 2yr- 91%,86%	Higher response rate for HPV positive tumors -after induction chemotherapy (82% vs. 55%) & after chemoradiation treatment (84% vs 57%)
Licitra <i>et al</i> ,2006(30)	Italy	19%	35.5%	39%	NA	47.8(5.8 yrs)	3yr- 93% 5yr-79%	3yr-0% 5yr-0%	3yr-14% 5yr-21%	Favourable prognosis, including the reduced incidence of second tumors in hr-HPV SCCs

\*HPV – Human Papilloma Virus  
SCC- Squamous Cell Carcinoma

hr-HPV- High risk Human Papilloma Virus  
NA- Not Assessed

**Conclusion**

There has been an alarming increase in the number of HPV positive OSCC cases in these recent years. It has got an impact on diagnostic, preventive and therapeutic practices. The infections caused by HPV and its mechanism of carcinogenesis in oropharyngeal region are not well studied when compared to that of genital tract and cervical cancer. There are numerous studies regarding HPV and cervical cancer, which helped to develop criteria, classification systems and treatment protocols for the disease. More studies have to be done in the field of Oropharyngeal carcinoma and role of HPV to develop appropriate preventive and management protocol.

Dental community has to be more aware about this virus and their carcinogenic potential, since there is a major role to be played by them especially in the preventive aspect. Community – based educational approach is needed to make the public aware of this infection and its serious sequelae and possible methods of prevention, including vaccination.

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