ROLE OF HUMAN PAPILLOMAVIRUS (HPV) IN ORAL PRECANCEROUS DISORDERS AND ORAL CANCER - A REVIEW OF LITERATURE

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ABSTRACT
Oral cancer is a major global health problem and affects more than 200000 people worldwide. These are often led by preexisting oral lesions termed as potentially malignant disorders of the oral mucosa. Oral cancer is associated with multiple risk factors. Though tobacco and alcohol consumption are the most common risk factors, studies have also revealed that DNA viruses, especially human papillomavirus (HPV) may be an important etiological factor for head and neck malignancy. HPV infection is a significant risk factor for cervical carcinoma; however, the role of HPV in OSCC is less well defined. Hence this article throws light on various studies which were done previously to show an association between HPV and potentially malignant disorders and oral cancers.

Keywords: Human papillomavirus (HPV), oral premalignant disorders, oral squamous cell carcinoma (OSCC).

INTRODUCTION
Oral cancer is the 6th most common malignancy in developed countries, representing almost 3% of all malignancies, accounting for 50% of all cancers especially in India and other regions of Southeast Asia. Besides the main risk factors of tobacco, smoking and alcohol, infection by human papillomavirus (HPV) and genetic alterations are likely to play an important role in these lesions. More than 90% of these malignancies are often preceded by preexisting oral lesions termed as potentially malignant disorders of the oral mucosa. In several epidemiological studies, the role of tobacco smoking and alcohol consumption as major risk factors for potentially malignant disorders and oral cancer is well documented. Literature reveals that oncogenic HPVs are main causative agent for cervical cancer, but its role in potentially malignant disorders and carcinomas of the oral cavity is less established. Association of HPV with oral and pharyngeal carcinogenesis was first proposed in 1983 by Syrjanen et al. HPV genotypes vary, with different genotypes affecting different anatomical sites. For instance, HPV genotypes 16 and 18 are associated with oral and oropharyngeal squamous cell carcinoma while HPV genotypes 58 and 59 are associated with oropharyngeal squamous cell carcinoma. hpv 16}
population, with different sample size and different assays to detect viral DNA. Hence a retrospective review of the existing epidemiologic data was compiled to highlight the relationship of HPV in the development of potentially malignant disorders and OSCC.

Syrjanen K and Syrjanen Set al. in 1983 assessed biopsies from 40 cases of OSCC and observed association of HPV with malignancy. Morphological signs of the flat-type HPV lesion were found in 4 cases (10%), inverted type in 3 cases (7.5%), and papillomatous type in 9 cases (22.5%). Epithelial cells (mostly koilocytes) showing HPV-positive nuclei were disclosed in 5 papillomatous lesions, in 2 inverted lesions and in 1 flat lesion. Thus according to them HPV could be the etiological factor for certain types of OSCC.4

Shroyer KR and Greer RO in 1991 compared the sensitivity of detection of HPV DNA in premalignant and malignant oral lesions by in situ hybridization (ISH) and polymerase chain reaction (PCR). As per his observations HPV DNA was found among 4 of 24 cases of epithelial dysplasia, 4 of 14 cases of verrucous hyperplasia, and 1 of 10 cases of squamous cell carcinoma. The 10 cases of smokeless tobacco keratoses and 3 cases of verrucous carcinoma were all negative for HPV DNA. According to them, PCR was an effective technique for identifying HPV 16 DNA from premalignant and malignant oral lesions.6

Young SK and Min KW et al. in 1991 evaluated potentially malignant and malignant lesions with biotinylated double-stranded DNA probes for detection of HPV types 6/11, 16/18, and 31/33/35. According to his observations 62% (13/21) of oral squamous papillomas were positive for HPV DNA among which 6 and 11 HPV types demonstrated the strongest reactivity. Of the 13 cases, 10 also showed some reactivity with HPV-16/18 and -31/33/35. This study thus confirmed that HPV DNA is frequently found in oral squamous cell papillomas and may not be detected in keratotic, premalignant, or cancerous lesions of the oral mucous membranes.7

The studies by Chang et al in 1991, Yeudall in 1992 and Miller and Johnstone in 2001 detected many low risk types of HPV (6 and 11) with benign lesions and HPVs (16, 18 and 33) with malignant lesions.8-10

Shindoh Met al in 1992 studied an association of HPV DNAs in carcinomas of the oral cavity. According to their observations HPV-16 DNA sequences may have the capability to maintain the proliferative state of epithelial cells, and thus may contribute to the production of malignant phenotypes.11

Yeudall WA and Paterson IC et al in 1995 studied patients with tobacco history and their association with HPV. They suggested that though p53 mutation was a frequent genetic event in oral cancer, this does not preclude a papilloma viral etiology for these tumors.12

Zhonghua Kou et. al. in 1996 detected HPV 16 and 18 type DNA in OSCC and normal mucosa (NOM) by PCR, and then analyzed the PCR products using southern blot hybridization. They observed that the positive rates of HPV DNA were 47.8% (11/23) in OSCC, including HPV16 in 6 samples, HPV 18 in 3 samples and 16, 18 co-infection in 2 samples. Whereas HPV16 DNA was found to be 20% (2/10) in normal oral mucosa, thus suggesting that HPV may play a role in carcinogenesis of OSCC.13

Bustos D.A et al in 1999 studied association of HPV with cervical and oral cancer. According to their observations, HPV DNA in cancer biopsy specimens were detected less frequently among tobacco smokers and pan chewers and more frequently among heterosexuals or those who practiced oral sex.14

Martha Bouda et. Al. in 2000 conducted a study to examine HPV infection in oral hyperplasias, dysplasias and squamous cell carcinomas as well as in normal oral mucosa by nested polymerase chain reaction (NPCR), type specific PCR (TS-PCR), restriction fragment length polymorphism
(RFLP) analysis, dot blotting (DB), and nonisoropic in situ hybridization (NISH). They suggested that, association of high risk HPV types with oral carcinogenesis and high percentage in hyperplasias and dysplasias to be an indicator of an early involvement of HPV in oral neoplasia.\textsuperscript{15} Scully \textit{et al.} in 2000 also suggested that viral factors like HPV may contribute to the etiology of OSCC.\textsuperscript{16} Klussmann JP and Weissenborn SJ \textit{et al.} in 2001 reported 25 Head and Neck Squamous Cell Carcinomas (HNSCCs) (26%) to be HPV positive. The frequency of HPV positive lesions was 18\% in the oral cavity, 45\% for oropharynx, 25\% for hypopharynx, 8\% for nasopharynx, and 7\% for larynx.\textsuperscript{17} Nagpal \textit{et al.} in 2002 analyzed the genetic predisposition of Indian population to HPV infection and oral carcinogenesis. They screened 110 patients of oral cancer, who were highly addicted to betel quid and tobacco chewing for HPV 16/18 infection and its association with polymorphism at p53 codon. Total 37 patients (33.6\%) showed the presence of HPV 16 in 22.7\%, HPV 18 in 14.5\% and HPV 16/18 co-infection in 10\%.\textsuperscript{18} Hansson BG and Rosenquist K \textit{et al.} in 2005 demonstrated a strong association between infection with high-risk types of HPV and oral and oropharyngeal squamous cell carcinoma (OOSCC), suggesting that high-risk HPV types play a key role in carcinogenesis.\textsuperscript{19} Syrjanen S. \textit{et al.} in 2005 were the first to present evidence on the involvement of HPV infections in both laryngeal and oral carcinogenesis. Until 2002, 4768 oral carcinomas had been analysed for HPV DNA, and 22\% were reported to contain HPV. Tonsillar carcinomas appeared to have the highest prevalence of HPV among all non genital cancers. By the end of 2002, 422 cases of tonsillar carcinoma were analyzed for the presence of HPV DNA, with the overall detection rate of 51\%. HPV 16 was the most prevalent type found in 84\% .The role of HPV in laryngeal squamous cell papilloma and recurrent respiratory papillomatosis (RRP) is well - established, whereas the role of HPV in laryngeal carcinomatosis remains controversial. The molecular mechanism of HPV-associated carcinogenesis of the head and neck is still not understood.\textsuperscript{20} Koppiar P \textit{et al.} in 2005 studied HPV DNA in oral carcinoma by polymerase chain reaction (PCR) amplification and reported that HPV contributed to carcinogenesis. High risk HPV\textsubscript{s} are predominantly found in oral cancer and may play a role in its progression, while low risk subtypes are usually associated with oral precancerous lesions.\textsuperscript{21} Chen PC and Pan CC \textit{et al.} in 2006 analyzed the association of potentially malignant lesions with HPV. According to them HPV 16 and 18 were frequently identified with all potentially malignant lesions, whereas HPV 6 and 11 were found only in squamous papilloma. HPV 18, betel quid chewing and smoking were significantly associated with leukoplakia and squamous papilloma, while only betel quid chewing and smoking were significantly associated with oralsubmucous fibrosis (OSMF).\textsuperscript{22} Chen SL \textit{et al.} in 2007 suggested that the role of HPV infection is due to oncoproteins E6 and E7 which inactivate p53 and pRB respectively. The oncogene E5 has also been found to transform cells by modulating growth factor receptors, thus suggesting that several oncoproteins contribute in carcinogenesis.\textsuperscript{23} Katie M. Applebaum and C. Sloane Furniss \textit{et al.} in 2007 suggested HPV 16 seropositivity and alcohol and tobacco use to be associated with risk of Head and Neck Squamous Cell Carcinoma. According to them, the strongest risk factors by tumor site were smoking for laryngeal cancer, alcohol for cancer of the oral cavity, and HPV16 for pharyngeal cancer. For pharyngeal cancer, risk increased with increasing alcohol consumption and smoking among HPV16-seronegative subjects but not among HPV16-seropositive subjects. Among light drinkers or never smokers, HPV16 seropositivity was associated with a 30-fold
increased risk of pharyngeal cancer. They concluded that alcohol or tobacco use does not further increase risk of HPV16-associated pharyngeal cancer and the risk of Head and Neck Squamous Cell Carcinoma associated with smoking, alcohol, and HPV16 differs by tumor site.24

Liang XH and Lewis J et al. in 2008 carried out a study to examine the prevalence and significance of HPV infection and its clinical significance in patients with oral tongue cancer. They suggested that the incidence of HPV in oral tongue cancer was low and was unlikely to play a significant role in etiology, pathogenesis and clinical outcomes of oral tongue cancer, as there was a rising trend of oral tongue cancer in the young populations.25

Scapoli L and Palmieri A et al. in 2008 carried out a study to evaluate the prevalence of high-risk HPV in a large, well defined sample of oral squamous-cell carcinoma. Data obtained from 314 oral squamous-cell carcinoma, indicated that the prevalence of high-risk HPV was as low as 2% and thus did not support a major role of HPV in the etiology of oral squamous-cell carcinoma.26

Jalouli J and Ibrahim SO et al. in 2010 illustrated human simplex virus (HSV), HPV and Epstein Barr virus (EBV) infections to be common and may influence oral health and cancer development. According to them, there was a high prevalence of HPV in Oral Sub Mucous Fibrosis and the etiologic implication of this finding warrants further studies.27

CONCLUSION
The role of HPV in Oral Squamous Cell Carcinoma has gained attention due to biological similarities between the epithelium of the cervix and the oral cavity. HPV is an important risk factor for potentially malignant disorders and Oral Squamous Cell Carcinomas. HPV 16 and 18 were detected more frequently in Oral Squamous Cell Carcinoma than potentially malignant disorders and absent in the normal samples. This suggests an association of the virus with oral carcinogenesis. Data pertaining to prevalence of HPV in patients with Oral Squamous Cell Carcinomas, without history of smoking, alcohol or betel nut habit is limited. Hence, further studies need to be carried out to find the prognostic value of HPV infection as a biomarker for early diagnosis of potentially malignant disorders and Oral Cancer.

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