Original Research Article

Role of human papilloma virus in oral squamous cell carcinoma: Review of literature

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Abstract

Head and neck cancer is a major problem in our country constituting around one-third of all cancer cases in contrast to 4-5% in the developed world. The incidence of tobacco-related head and neck cancers in the western countries has declined due to decreased use of tobacco. Parallel to this decrease, there has been an increase in Human Papilloma virus (HPV) related oral cancers. In India also some attempts are made by the government to decrease the use of tobacco. However, the changing epidemiology seen there, is not seen here. We searched Pub Med database for literature published from 1985 to 2013 reporting any relationship between HPV and oral cancers to know why there is this difference in carcinogenic process.

Key Words: HPV infection; Head Neck Cancers; Oral Squamous Cell Carcinoma (OSCC); Oropharyngeal Squamous Cll carcinoma (OPSCC).

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INTRODUCTION

Head and neck cancer is the sixth most common cancer worldwide[1]. These tumours share common characteristics like a male predominance, occurrence in the 5-6th decade of life, a strong a etiological link with tobacco, and a histo-pathological resemblance (SCC)[2]. In India, Oral and Oropharyngeal squamous cell carcinoma is the commonest malignancy and constitutes 20–30% of all cancers[3]. It accounts for 1/3rd of the global burden. Tobacco, alcohol and betel nut chewing are well-established risk factors. However recently we are coming across a small proportion (15–20%) of cases without risk factors. Hence, there must be a role of other risk factors namely viruses such as human Papilloma virus (HPV) and Epstein–Barr virus, poor oral hygiene, sharp dentures, and micronutrient deficiencies[4]. A recent meta-analysis showed HPV plays an significant role in Head and neck cancers[5].

HPV as risk factor: Over the last 10-15 years HPV infection has been increasingly recognized as a major etiological factor for HNSCCs[6-9], mostly OPSCC. HPV infection in the etiology of OPSCC was first shown by Gillison *et al*[10]. Numerous case series and studies conducted in the late 1990s and early 2000s also evaluated the prevalence of HPV infection in oropharyngeal cancer[7,11,12]. This has created new opportunities for improved therapy and primary prevention for HNSCCs[13]. HPV is a DNA oncovirus and is epitheliotropic. Approximately 200 HPV genotypes have been sequenced and classified according to their phylogenetic position, biological niche and oncogenic potential. The genera alpha, beta, gamma, mu and nu types infect the humans. Novel γ-HPV types are believed to be present in oral cavity of healthy individuals also. Most recently, a novel HPV type 199 (HPV199) was Identified in a nasopharyngeal swab sample[14]. Based on their oncogenic potential, they can be subdivided into low- and high-risk types. Low-risk HPV types include

HPV6 and 11 and are associated with benign warts or condylomata. By contrast, there are at least 12 high risk HPV types, HPV[16,18,31,33,35,39,45,51,52,56,58,59]. They are associated with six different cancers as well as precursor neoplastic lesions. HPV 16 and 18 are the initiators of 90% of cervical cancers, 70% of anogenital cancers, 5% of non-oropharyngeal SCC [16] and 20-72% of OPSCC[15,16,17,18]. The oncogenic nature of high risk HPVs is due to the immortalizing and transforming properties of HPV oncoproteins E6 and E7. They target the p53 and pRB tumor suppressor pathways, respectively, rendering them susceptible to mutations and cancer formation[19,20].

Tests for Detection of HPV: Detection techniques of HPV have evolved a long way from the primitive and most commonly used reverse line blot technology (RLB) based tests to more advance tests based on real-time PCR and DNA sequencing. RLB-based tests are not able to determine viral load and hence unable to give a diagnosis for borderline cases. The recent more advanced real-time PCR based detection assays are cost-effective, more sensitive and swift. A**s** of 2016,193 distinct commercial HPV tests and at least 127 test variants are available in the market for HPV detection[21].Though, there are various tests for HPV detection, there is no standardized test or published guidelines for the same. The same methods used for genital HPV detection, are applied to detect oral HPV[22,23.] HPV 16 represents the majority of HPV present in oral cavity. But, oral HPV viral loads tend to be much lower than in genital tracks. So, HPV 16 type-specific assay along with viral load information should be used to identify clinically significant HPV infection. Oral swab, rinse samples or oral tissue samples from biopsy can be used for HPV detection. Future systematic studies are needed to identify and standardize the optimal sample collection method for oral HPV detection.

Epidemiology: Existing epidemiological studies suggest that oral HPV is rare in the general population and its infection is strongly associated with oral sex[24]. The studies done till now in India as well as in western countries shows that, HPV-positive patients are younger with a median age of diagnosis of 54 years, less or no exposure to tobacco and alcohol[25,26,27], and higher socioeconomic status and education[26]. HPV positivity is less frequent in blacks than in Caucasians (4% of HNSCC in blacks vs. 34% in whites)[28]. There is a threefold higher incidence in males as compared to females[26,29,30.] HPV 16 is the most commonly detected oral HPV infection; but other high risk HPV types have also been detected[31]. Hang *et al* determined the prevalence of oral HPV infection among 5410 healthy individuals in the Chinese population using general PCR and sequencing on oral swab specimens[32]. The study showed that the prevalence of alpha HPV types is 0.67% with HPV 16 being the most prevalent type. Cook *et al* determined oral HPV prevalence in 1010 healthy women in US using Roche Linear Array assay genotyping 37 mucosal (alpha) HPV types on oral samples[33]. They found that only 1.9% is infected with HPV. A cross-sectional study of oral HPV infection in US men and women, aged 14 to 69 years, determined that the overall prevalence of HPV DNA in oral exfoliated cells was 6.9 percent with HPV 16 comprising 14.5% of total oral HPV infection. Scandinavian study by Mork *et al*, showed that the presence of HPV 16 L1 antibodies in pre-diagnostic serum samples was associated with a 14.4-fold increased risk of oropharyngeal cancer[34]. Study done by Juliet Dang *et al*, on the incidence and prevalence of oral HPV infection in a cohort of male university students is consistent with these findings: with the prevalence at enrollment of 7.5% and 12- month cumulative incidence of 12.3% [35]. A recent systemic review of literature done by Kreimer AR *et al* reported the prevalence of any oral HPV detected below 5%, and HPV 16 accounted for 28% of all HPV detected in the oral region [36].

HPV Infection and Anatomical site

Multiple studies reported an increased incidence of HPV-associated oropharyngeal cancers, especially tonsillar and tongue cancer. Why HPV is more common in the oropharynx is still a question. The unique presence of transitional mucosa in the oropharynx, especially in the tonsillar tissue which shows histological similarities to the cervical mucosa may be the reason. One more factor is the genetic features of HPV 16, which may facilitate survival in the tonsillar crypt epithelium[37,38]. One of the possibility is that the invagination of the mucosal surface of the tonsil may favour virus capture and maintenance by promoting its access to basal cells (the only dividing cells in the epithelium)[39]. If this is true, tonsillar tissue may act as a reservoir for HPV in the upper aerodigestive tract. This theory is partly supported by the fact that when oral samples are collected by oral rinse, the detection rate of HPV is much higher than with swabs. Finally, the persistence of HPV in tonsillar tissue might be of importance in the immune response to HPV[40].

CLINICAL STAGE AT PRESENTATION

Review of literature shows that HPV-positive tumours are more likely to present with early T stage (T1-T2)[41] and higher N stage (usually cystic and multilevel)[42,43]. They have distinct histological features, like moderate/poor tumour differentiation and non-keratinising or basaloid pathology[41,43,44].

Radiological imaging: HPV-positive and HPV-negative oral cancers can be differentiated radiologically. HPV-positive carcinomas often had small or even occult primary lesions with well-defined borders and cystic

nodal metastases, whereas HPV-negative primaries more often had poorly defined borders and invasion of adjacent muscle[42,46].

Prognosis: Recent studies suggest that HPV is a better prognostic marker than tumor stage in HNSCC, especially for oropharyngeal cancer[47,49]. This holds true even after adjustment for differences in favorable prognostic factors associated with HPV positive patients (younger age, better performance status, fewer co morbidities, less smoking). Ang *et al*. reported that these prognostic factors explained only 10% of the observed survival differences between two subgroups[50]. However, other studies reported that survival rates improved among non-smoker HPV positive patients compared to smokers patients[51,52]. HPV-positive oropharyngeal cancer had a 28% reduction in the risk of death and a 49% reduction in the risk of disease recurrence[45]. Secondary primary tumour (SPT) in patients with HPV-positive cancer is very rare, and has improved better survival rate compared to patients with HPV negative tumours[39]. The reasons for a better prognosis in HPV positive patients may be as follows

- These tumours may harbour fewer or different genetic alterations, which can be associated with better response to therapy[53,54].
- The tumours have higher radiosensitivity, probably due to intact apoptotic response to radiation[55,56].
- Immunologic response may play a role in the improved response to radio- and chemotherapy in HPV positive tumours. This may be because of stimulation of immune response directed to viral specific tumour antigens[57].
- Younger age leading to good performance status because of fewer co-morbidities may also contribute to improved survival[58].

HPV and clinical management: Multiple studies have shown that patients with HPV-positive OSCC had a better 5-year survival upon treatment than those with HPV negative OSCC i.e. 70-80% vs. 25-40% respectively, and this was independent of age, gender, tumour stage and grade of differentiation, or ploidy[59,60,61]. It was also shown that patients with HPV-positive OSCC without history of smoking had a better prognosis than that with smoking[62,63]. Alternatively, smoking together with the presence of HPV may induce another tumour category, with additional genetic alterations, as is suggested in several reports[62,63,64,65,66]. Achievement of acceptable cure rates with minimal long-term morbidity with HPV positive oral cancer is possible. HPV status can be used in the clinical decision-making processes to select patients for less aggressive non-surgical treatment. Thus, assessing HPV presence is important. This is especially true considering long-term outcomes of HPV-positive younger patients, since they are at risk of a lifetime compromised quality of life as a result of chronic toxicities due to chemo-radiotherapy. Literature available now suggest that HPV-positive OSCCs are different from HPV-negative OSCCs [67] in various ways.

- OSCC patients infected with HPV are approximately 10 years younger than HPV-negative patients and not associated with tobacco and alcohol consumption
- HPV positive OSCCs predominantly arise in the base of the tongue or the tonsillar region;
- HPV-positive OSCCs display a poorly differentiated basaloid-like histology[68];
- Although HPV-positive OSCCs represent biologically more aggressive form of cancer, they have better prognosis: lower incidence of distant metastases, less likelihood to develop second malignancy, and better responsiveness to therapy.

CONCLUSION

In conclusion, the evidence argues for differentiation between HPV-positive and HPV-negative OSCCs. In India, majority of oral cancers present as locally advanced Stage III/IV disease as compared to early presentation of HPV positive cancers. Most efforts are usually focused on therapy and outcomes rather than early diagnosis and prevention. Hence, there is a need for more analytic epidemiological studies.

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