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REVIEW ARTICLE

Human Papilloma Virus in Head and Neck Cancers—Role and Relevance in Clinical Management

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Abstract The biology and clinical behavior of Head and Neck Squamous Cell Carcinomas (HNSCCs) is very distinct within different subgroups due to the distinct molecular profiles for the HPV positive versus HPV negative tumors. HPV status is the most important independent prognostic variable in multivariate analysis taking into account all other prognostic factors like tumour stage, smoking status, age and performance status. The debate today is whether the intense therapy is too aggressive in this group of patients since they show a superior survival regardless of treatment strategies. A highly divergent prognosis and distinct biology of HPV positive and HPV negative HNSCCs underlines the fact that treating them as distinct diseases is the need of the hour. Infection with HPV is associated with less aggressive disease, better loco regional control and lower rates of second primary cancers. An important caveat that remains is the emergence of intermediate prognosis of HPV positive smokers and HPV negative non smokers. Though molecular biology has provided important data on the interaction of the HPV onco proteins with genes important in cell cycle control, also speculated to be involved in pathogenesis of HNSCC, more basic research is needed to describe the differential mechanisms of tumorigenesis among the HNSCCs that show presence and absence of HPV. This is clinically relevant to reduce morbidity without compromising tumour control in HPV positive patients and improving tumour control and co-morbid illness that could be pre-existing or treatment related in HPV negative patients. There may be a need for treatment intensification and incorporation of newer agents into induction chemotherapy protocols for the HPV negative patients and so HPV detection is important to aid in this selection. HPV tumour status is therefore more important than just providing the prognostic information in these classes of tumours. This article discusses the role and clinical relevance of HPV in HNSCCs.

Keywords HPV status · Head and neck squamous cell carcinoma · Prognostic indicators · Tumorigenesis mechanism in HPV positive head and neck cancers

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Introduction

Head and Neck Squamous Cell Carcinomas (HNSCCs) is the sixth most common cancer and the eighth most common cause of cancer death worldwide. Its incidence varies widely among different regions [1]. In North America and the EU, HNSCC accounts for 3 % to 4 % of all cancer diagnoses whereas in India, it accounts for 30 % of all cancers in males and in 11–16 % in females. HNSCCs are a heterogeneous group of neoplasms that differ greatly in tumor aggressiveness and response to treatment. About 80–90 % of head and neck cancer cases are considered to be associated with known risk factors, such as smoking, oral tobacco or betel nut chewing, and alcohol abuse. Carcinogens produced by tobacco such as nitrosamines and benzopyrene produce the types of guanine nucleotide changes found as p53 mutations seen in HNSCC. Effects of alcohol are less understood but it may get metabolized to acetaldehyde thus damaging DNA and also traps glutathione which is important for detoxication of carcinogens.

Recent epidemiological and experimental data has implicated infection with human papilloma virus (HPV,

specifically, HPV 16 and 18) in the pathogenesis of HNSCC. Since survival of HPV positive HNSCC patients have been shown to be notably better than survival of HPV negative HNSCC patients; the significance of HPV detection and the molecular aspects of the roles related to HNSCC tumorigenicity assumes great clinical relevance.

HPV and HNSCC

HPV positive HNSCC represents a separate entity with a distinct pathway of malignant transformation with characteristic clinical and pathological features. The HPV involvement in oral and oropharyngeal carcinogenesis was first proposed in 1983 by Syrjanen et al. [2]. and then supported by several other authors on the basis of the following evidences: the well-assessed broad epithelial-tropism of HPV; the morphological similarities between oropharyngeal and genital epithelia; the ability of immortalizing human oral keratinocytes in vitro; the strongly established etiological role of high risk HPV in cervical SCC and finally the detection of HR HPV genotypes in samples of HNSCC [3–6].

An epidemiological review also suggests, HPV positive cancers to be a distinct type of tumor with numerous important differences reported in the type of affected patient (generally, never married younger males, < 40 years.); who have had less exposure to tobacco and alcohol use, but who may have had more marijuana exposure and/or higher numbers of sexual partners, a favorable histological grading, with better responses to chemo-radiotherapy, innovative targeted therapy and better clinical outcomes [7].

Both serological and molecular markers of HPV infection is associated with increased risks of HNSCC. With the implication of HPV infection as an emergent risk factor for HNSCC, it is crucial to describe the distribution and incidence of HNSCC by sub-sites potentially associated with HPV and those not associated with HPV. The International Agency for Research on Cancer recognizes HPV as a risk factor for oropharyngeal cancer and accumulating molecular and epidemiological data now show that high-risk types of HPV are responsible for a subset of oropharyngeal cancer [8]. A population-based case–control study in southern Sweden [9] found a strong association between the detection of high risk HPV DNA in the oral cavity and oropharyngreal carcinoma (OR 230; CI- 45–1200) after adjustments for alcohol and tobacco usage.

HPV Detection Methods

As an indicator of prognosis, HPV detection methods that are sensitive and specific are very crucial. There are currently no internationally accepted standards to undertake HPV testing for head and neck cancers within the diagnostic setting and for clinical trials. Currently, Polymerase Chain Reaction (PCR) based detection of HPV and In Situ Hybridizations useful for HPV detection. PCR based assays have higher sensitivity with lower specificity, due to transcriptionally inactive viral DNA or cross contamination that may give false positive results. Immunoexpression of p16 has been shown to be a surrogate marker for high risk HPV. Studies suggest that p16 expression by immunohistochemisty as an excellent surrogate marker that reflects the functional effects of HPV E7 induced inactivation of pRB. A Meta analysis conducted on more than 5,000 cases of squamous cell cancers, 2,642 oral cancers, 969 oropharyngeal cancers and 1,435 laryngeal cancers, from 26 different countries and 60 studies that used PCR methodology showed HPV prevalence of 35.6 % in oropharyngeal cancers, 23.5 % in oral cancers and 24.0 % in laryngeal cancers. The overall prevalence of HPV in HNSCC was found to be 26 % [10]. A Meta analysis on studies using Formalin-Fixed, Paraffin-Embedded samples reported a pooled HPV prevalence of 34.5 % from SCCs originating from oral, oropharyngeal and laryngeal cavities alone. Several studies have shown high levels of agreement of p16 IHC and HPV ISH scoring. A study on tonsillar carcinomas showed combined p16 IHC and HPV ISH positivity for HPV infection to be lower than that of combination of p16 IHC and HPV PCR, therefore suggested for a three tiered, staged algorithm of p16 IHC/HPV ISH/HPV PCR in conjunction with the HPV ISH reports giving a less equivocal molecular classification [11].

Changing Trends in Epidemiology of HPV Associated HNSCCs

The epidemiology of HNSCC has shown a dramatic change over the past two decades. A study conducted in banked oropharyngeal tumor samples for HPV evaluation for several decades showed an increase in HPV incidence from 23 % in tonsillar cancers in 1970s to 28 % in 1980s and 57 % of all oropharyngeal cancers by 1990s. In the past decade during 2000–02, 2003–05, 2006–07, the trend has increased to 68 %, 77 %, 93 % respectively [12] . Only 16 % of U.S. oropharyngeal cases had HPV detected in 1984–1989 compared to 73 % during 2000–2004, a four-fold increase in only two decades [13]. This change does not appear to be related to the integrity of the tumor samples and appears instead to reflect an actual change in the etiology of this disease.

Developed countries have shown a decrease in the incidence of tobacco associated HPV unrelated HNSCC [14, 15], however, the incidence of HPV associated oropharyngeal cancers have been shown to be increasing [16, 17]. Studies show that despite the decrease in the tobacco use,

the traditionally known important risk factor, the incidence of oropharyngeal cancer rates continue to increase [18].

Not much data is available regarding the incidence of HPV-induced head and neck cancers from India, 33.6 % of oral cancer patients were HPV positive in Eastern India as compared with 67 % in South India and 15 % in Western India [19, 20]. In a study of 110 oral cancer patients from Eastern India, out of 37 patients who were HPV positive, HPV-16 was the most frequently involved type (22.7 %), followed by HPV-18 (14.5 %) and HPV-16/18 co-infection (10 %) [21]

Interestingly, the incidence of both HPV-associated and HPV-unassociated HNSCC is more than two-fold higher among men than women [14]. The reason for the higher incidence in men than women is not clear. A higher incidence of heavy smoking and alcohol related and HPV unrelated HNSCC in men can be attributed to their habits. Previous evidence show that extended field cancerization occurring in upper aero digestive tract due carcinogenic insult of alcohol, tobacco and related carcinogens can get accentuated, amplified and intensified by HPV infection further. These integrated processes develop into a condemned mucosa syndrome described due to HPV viral infection and associated cellular and genetic alterations [22].

HPV as Risk Factor

Epidemiological studies on HPV-associated cervical cancer have clearly demonstrated that HPVs are transmitted by sexual contact and today there are several studies suggesting that HPV-positive HNSCCs are also sexually transmitted [23–25]. It is assumed that HPV infection precedes the development of HPV positive head and neck cancers, and the presence of high-risk HPV infection on the oral mucosa and seropositivity increase the risk of development of HNSCCs [26, 27]. A case control study also [28] reported that oral HPV infection is sexually transmitted. A high of 26 or more number of life time vaginal sex partners and 6 or more lifetime oral sex partners were associated with an increased risk of HNSCC with an OR of 3.4 and 3.1 respectively.

Understanding what is driving the increasing incidence of HPV-associated HNSCC is of interest, and changes in sexual behaviors have been speculated as a possible reason. As HPV infection usually takes more than 10 years to progress from infection to malignancy, a temporal change in sexual behavior could explain the increased incidence observed in these cancers one and two decades later [23–25]

Among all the high risk HPVs, HPV 16 in HPV positive HNSCC (85–95 %) is greater than cervical cancer (50–60 %) totally worldwide. Meta-analyses have shown that the HPV subtypes associated with HNSCC are broadly similar but not identical with those seen in cervical cancers [10, 11] This is more dependent on the HPV subtypes particularly HPV 16 that are able to transform and immortalize cells in vitro. The heterogeneity and multiple pathways to carcinogenesis are very likely in head and neck cancers. Though HPV 16 is the most dominant form, both its integrated and episomal forms are seen in several studies. HPV 16 DNA is found to be integrated in 48 % and episomal in 35 % and found as mixed populations of both episomal and integrated forms in 17 % of head and neck tumours [29]. Tonsillar carcinomas have the highest HPV prevalence rate [30] and interestingly studies have shown exclusively episomal forms of HPV DNA in these tumours.

Two genetic routes of multistep head and neck carcinogenesis have been suggested [31]. The first route is characterized without HPV with losses of whole or large parts of chromosome arms 3p, 9p, and 17 p and the second route could be associated with HPV infection with lower level of chromosomal loss at these hot spots.

Whether tobacco and alcohol increase the risk of HPV associated tumours is not clear, whereas some studies have found no association while others have found that their use increases the risk. But there appears to be distinct tumor site differences in the combined exposure risks, suggesting that different molecular pathways are involved. Thus, as has been discussed above, four risk factors have been found to be significantly associated with an increase in HPV detection, i.e., male sex, oropharyngeal tumors, less frequent tobacco usage, and history of oro-genital sex.

Molecular Biology of HPV Infection

HPV is a small epitheliotropic DNA double stranded virus. All HPV transformed cells show abnormal chromosomal abnormalities like breakage, condensation, dicentric and acentric chromosomes. HPV has an unusual life cycle by synthesizing new virions in cells which have undergone mitosis and one of the daughter cells has completed differentiation as well. They infect the cells in the basal layer of the stratified squamous epithelium. These cells are the only proliferating cells of the normal epithelium as they become exposed to small micro wounds. The differentiated cells are present in the supra basal cells and they exit the cell cycle. Following infection, HPV genomes establish as episomes and carry on their life cycle, using the host cell machinery. During HPV infection, the supra basal cells remain active in cell cycle even as they undergo differentiation. The HPV E6 onco protein forms a complex with E3 ubiquitin ligase, E6 – AP and ubiquitinates p53 leading to its degradation. p53 degradation, results in deregulation of both G1/S and G2/M cell cycle checkpoints upon DNA damage and cellular stress leading to genomic instability. The HPV E7 protein binds to cullin 2 ubiquitin ligase complex and ubiquitinates RB

tumour suppressor protein. Degradation of pRB leads to uncontrolled G1/S phase of cell cycle. Inhibition of HPV E6 and HPV E7 leads to apoptosis, decreased cell viability, indicating that HPV E6 and E7 are required for the tumour maintenance of oropharyngeal cancers. Figure 1 shows the roles of HPV E6 and E7 and their interactions with p53 and RB deregulating the normal course of cell cycle.

The proliferative capacity of these HPV infected cells is uncoupled from differentiation and they are controlled by various cellular factors, the prominent of which are members of the RB family of proteins consisting of pRB, p107, p130. The combined actions of high risk E6 and E7 proteins help to maintain the S phase competence in differentiating cells resulting in abrogation of many cell cycle regulators [32].

HPV as a Prognostic Factor

HPV status is the most important prognostic variable in multivariate analyses taking into account the other prognostic factors such as tumor stage, smoking status, age and performance status. In a meta-analysis of 37 studies, patients diagnosed with HPV positive HNSCC had a lower risk of mortality (Hazard ratio [HR] 0.85; 95 % CI: 0.7–1.0) and of recurrence (HR: 0.62; 95 % CI: 0.5–0.8) as compared with patients with HPV-negative tumors. In a subset analysis that included only patients with oropharyngeal cancer, subjects with HPV-associated tumors had a 28 % reduced risk of overall death (HR: 0.72; 95 % CI: 0.5–1.0) and disease free survival (HR: 0.51; 95 % CI: 0.4–0.7) as compared with those with HPV-negative tumors [33]. More recent studies have addressed some of these issues and found a similar survival advantage in HPV-positive cases of oropharyngeal cancer [34–38].

The recent analysis of the TAX 324 study, showed a markedly improved survival of the HPV positive patients in both arms (when compared to HPV negative) and this was attributed to improved loco regional control [39].

Aspects of Biological Differences Between HPV Positive and HPV Negative Tumours

Table 1 shows the key differences in HPV positive and HPV negative tumours. HPV positive tumors are more radiosensitive and this could be mediated by intact p53 gene and an intact adaptive response [40]. Studies have shown low level EGFR expression and gene copy number in HPV positive tumours [41]. There seems to be a variation in HPV viral copy numbers as well. Studies have shown that higher viral load is associated with a favorable outcome [42]. Evidences from earlier studies also show that median copy number of E6 DNA was about 80,000 fold higher in tonsillar cancers compared to non-tonsillar head and neck cancers. The tumours with episomal DNA were found to be larger

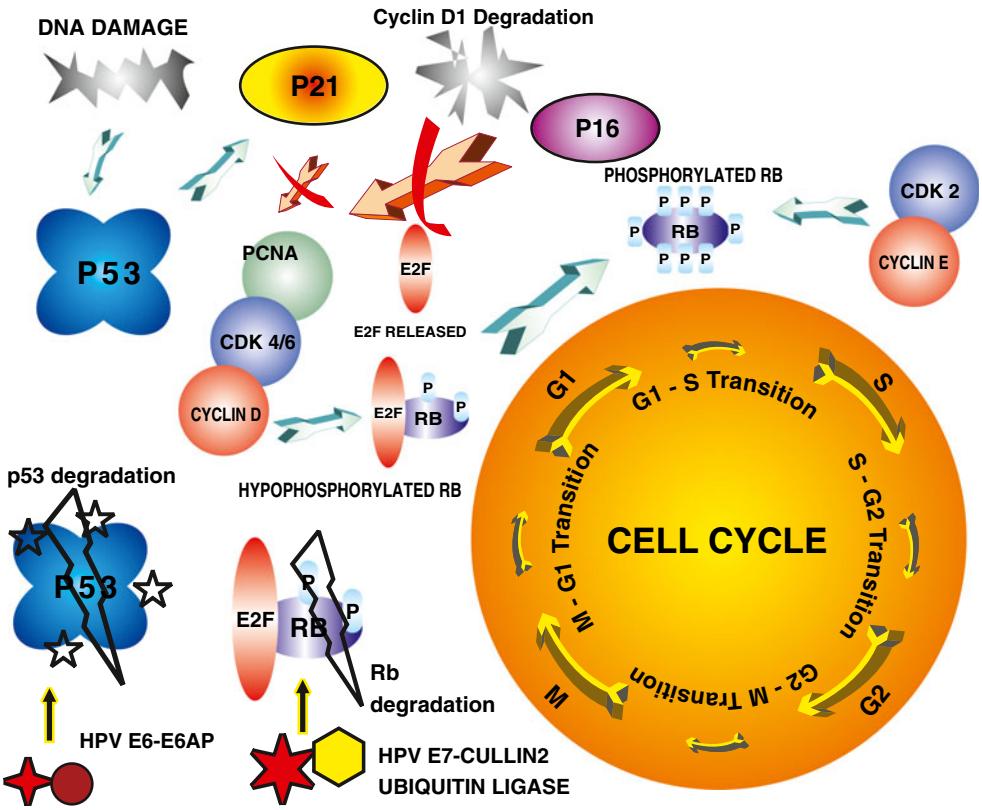

Fig. 1 The figure shows the phases of cell cycle elaborating the normal role of p53 and Rb protein. Normal p53 sensing DNA damage activates p21 which in turn can inhibit CyclinD1/CDK4. Under normal circumstances, phosphorylation of RB protein by Cyclin D1/CDK4 releases E2F activating the cells into the S phase which is in turn inhibited by p16. HPV oncoproteins E6 and E7 alter cell cycle functions. HPV E6 along with host cellular E6-AP binds to p53 leading to p53 ubiquitination and degradation. HPV E7 along with Cullin 2 ubiquitin ligase binds to RB protein leading to RB ubiquitination and degradation. Loss of both the crucial players p53 and Rb leads to deregulation of cell cycle

Table 1 Differential aspects of HPV Positive and Negative HNSCC

	HPV positive HNSCC	HPV negative HNSCC
Incidence	Increasing	Decreasing
Age	Lower	Higher
Socioeconomic status	High	Low
High Risk sexual Behaviour	Present	Absent
Tobacco/alcohol exposure	Low	High
Marijuana exposure	High	Low
Tumour Size	Mostly Smaller primary tumours with large cystic nodes	Larger size
P53 pathway	Cellular p53 degradation	Tp53 genetic mutations, 17pLOH
RB pathway	Degradation of RB	RB intact
P16 expression	Over expression	Decreased expression due to promoter methylation, 9p loss
EGFR	Lesser copy numbers	Increased gene copy numbers
Predilection to Oropharynx	Present	Not present
Response to chemo radiation	Better	Comparatively less
Locoregional control and recurrence	Better with fewer recurrences and lower rates of second primaries	Poorer outcome
Disease free survival	Better	Worse
Overall Survival	Better	Worse

compared to the mixed and integrated forms of viral DNA. Probably HPV DNA in episomal form is able to induce more growth with the expression of its viral oncogenes. Several studies have also shown p16 nuclear or cytoplasmic expression to be a surrogate marker for presence of HPV. Studies have shown smoking related HNSCC harboring a methylated p16 promoter compared to HPV positive HNSCC harboring an unmethylated promoter.

Therefore based on the viral load and p16 expression, HNSCC can be classified into 3 classes, HPV negative and p16 low, HPV positive and p16 low, HPV positive and P16 over expressed. It is this last category of tumours that show significantly better overall 5 year survival and increased disease free survival rate and decreased local recurrence rate when compared to the tumours of the first two categories. Their HPV viral load is also considerably higher with 46 copies compared to 0 copies and 3.6 copies in the first two categories [43].

Patients with HPV-positive tumours in the oropharynx show an improved survival regardless of treatment strategy. The debate today is whether the intense therapy is too aggressive in this group of patients since they show a superior survival regardless of treatment strategies. Strengthening this theory, a recent published study [35] showed no significant difference in overall survival between a concomitant boost accelerated fraction regimen of radiotherapy and a standard fractionation regimen when combined with concurrent high-dose cisplatin for HPV-positive patients. Further three clinical trials are currently investigating the potential for de-escalation of radiation therapy in HPV-HNSCC in the setting of various regimens of chemo radiotherapy. (NCT01084083/ECOGE1308, NCT01088802/J0988 and NCT01221753)

It is currently not advisable to change management for either HPV-positive or HPV-negative oropharyngeal cancers as high-quality evidence to support such an approach is lacking. More high quality randomized controlled trials are required to assess the efficacy of the different treatment modalities currently available for both HPV-positive and HPV-negative oropharyngeal cancers [44]. There is however a need to classify HNSCC into HPV negative classical tumors that is less responsive to conventional cancer therapy and HPV positive HNSCC that show low risk of death and recurrence and different management options like immunomodulating strategies or targeted therapy can be tried. Biomarkers are therefore necessary to develop diagnostic tools and thus contributing to therapeutics as a predictor of choice for the correct clinical management. In addition, studies are also necessary to prove whether HPV alone will be a factor determining the prognosis.

However there is a subset of HPV positive tumors with worse outcomes when compared to other HPV positive patients and that have resemblance to clinical course of HPV negative patients. But this subset is supposed to have extensive smoking histories, p53 mutations, higher EGFR,

BCL-xl expressions suggesting that HPV status alone may not be sufficient to segregate these tumors [45, 46].

Prophylactic Vaccines and HPV in HNSCC

Currently two prophylactic vaccines are commercially available, the bivalent (HPV 16, 18), Cervarix (GSK) and a quadrivalent vaccine (HPV16, 18, 6, 11) Gardasil (MERCK). With a global license, these vaccines have been shown to prevent infections and tumors induced by the vaccine HPV types [47].

There has been no clinical trial to investigate the efficacy of these vaccines in preventing oropharyngeal cancer, but, in theory, they are promising since they have been found to elicit systemic high titers of neutralizing antibodies against HPV-16 and may reduce the burden of HPV infection within the population. If proved, they may contribute a major breakthrough providing the missing link in the chain of evidence that shows HPV is involved in etiology of HNSCC. Therapeutic vaccines are also currently under investigation for HPV-associated carcinomas. DNA vaccines, viral vector vaccines, peptide vaccines, bacterial vector vaccines, and cell-based vaccines are some of those that are actively being studied [48]. Most therapeutic vaccine trials to date have been early phase and have demonstrated safety and feasibility.

Conclusion

HPV positive HNSCCs are a distinct clinical entity compared to the HPV negative counterparts. Epidemiologic evidence suggests that the incidence of HPV-associated oropharyngeal cancers has been on the rise over the past four decades. HPV-associated HNSCC tends to affect younger patients who have had less exposure to tobacco and alcohol use, but who may have had more marijuana exposure and/or higher numbers of sexual partners. They affect a patient population with defined risk factors, have a genetic expression pattern more similar to cervical squamous cell carcinoma than non-HPV-associated HNSCC and may warrant divergent clinical management compared with HNSCC associated with traditional risk factors. The natural history of HPV-infection in HNSCCs is not yet fully understood. HPV status is an independent prognostic factor for treatment response as well as progression-free and overall survival. There is a therefore an urgent need for a better understanding of the tumor biology and for identification of additional clinically useful biomarkers to combine with HPV-status for appropriate risk stratification in future clinical trials. Clinical testing for HPV status within tumors should be routinely performed since HPV status provides prognostic information as well as identifies patients who may be eligible for clinical trials aimed at developing tailored therapies for this patient population. Clinical studies such as de-escalation of chemo radiation treatment, HPV vaccine therapies, and other targeted approaches are being evaluated in this patient population. HPV tumor status may provide more than just prognostic information; it may be used to personalize treatment plans for each individual HNSCC patient in the near future.

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