Review Article

Changing face of head and neck cancer: Role of human papillomavirus beyond cervical cancer

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ABSTRACT

Human papillomaviruses (HPV) have been an area of interest since last two decades because of its potential role in the pathogenesis of malignant tumors. Approximately 35 years ago a role of human papillomaviruses (HPV) in cervical cancer has been postulated. Today it is well established that this very heterogeneous virus family harbours important human carcinogens, causing not only the vast majority of cervical, but also a substantial proportion of other anogenital and head and neck cancers. This review article has attempted to briefly analyze the present state of linking HPV to human cancers and have discussed some emerging developments. We have emphasized on the fact that HPV positive and negative cancer behave differently and should have separate treatment strategy.

Key words: Cancer, infection, papillomavirus, tobacco

INTRODUCTION

Head and neck squamous cell cancer (HNSCC) constitute tumors of diverse origin involving oral cavity, oropharynx, hypopharynx, larynx, nasopharynx and sinonasal tract. Smoking and alcohol are the two main causative factors accounting for approximately 80% of oral, oropharyngeal and laryngeal carcinomas. The association between human papilloma virus (HPV) and head and neck squamous cell carcinoma (HNSCC) has been under investigation for at least 20 years.[1,2]

The morphological similarity of genital and oral HPV associated lesions was one of the early findings that raised the possibility that HPV might be involved in oral and laryngeal squamous cell carcinomas (SCCs). The oral cavity is lined by a mucous membrane consisting of a stratified squamous epithelium and lamina propria made up of dense connective tissue. The squamous epithelium of the gingiva, hard palate and the dorsum of the tongue are completely keratinized with a superficial horny layer, whereas in the lip, cheek, vestibular fornix, alveolar mucosa, floor of mouth and soft palate, the epithelium is non-keratinized. Thus, the histology of oral mucosa resembles that of the uterine cervix, other lower genital tract or skin, depending on the anatomic site. On the basis of these morphological similarities, one can anticipate the presence of both the mucosal and cutaneous human papillomavirus (HPV) types in different squamous cell lesions of the oral mucosa.[3]

Though smoking and alcohol are established factors responsible for head and neck cancer but role of HPV is of recent interest. Despite the fact that HPV in cervical cancer is well documented fact, its role in H and N cancer is controversial and contentious topic.[4] However, a recent meta-analysis has confirmed HPV as an independent risk factor for oral carcinoma. HPV is the most prevalent infection world wide with several new cases diagnosed every year.[5] HPV is now thought to cause 30–65% of head and neck cancers.[6]

MODE OF ORAL AND OROPHARYNGEAL HPV INFECTION

The infection of HPV 16 is reported in 27% of oral cancer from north India whereas from western part of the country it ranges from 25 to 31%. The reports of HPV prevalence in oral cancer from southern India seems to be highly variable. 34% of invasive laryngeal carcinoma is found to be associated with HPV in India.[8]

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Both oral and oropharyngeal HPV infection and oral and oropharyngeal SCC are associated with the practice of orogenital sex and with the high-risk sexual behaviour of cohabiting with many partners, particularly at a younger age. In a study primarily aimed at vulvogenital HPV infection, tobacco smoking and increasing age were found to be risk factors associated with increased frequency of persistent oral HPV infections in women. This appears to be because tobacco-mediated and age-related local genetic and immune dysregulation renders the tissues more susceptible to HPV infection. Although oral and oropharyngeal HPV infections are primarily sexually acquired, mouth to mouth contact between partners and between family members, autoinoculation, and vertical birth-transmission are also routes whereby HPV infection of oral and oropharyngeal sites can be established.[9-11]

TOPOGRAPHIC REPRESENTATION OF HPV INFECTION IN THE HEAD AND NECK REGION

The proportion of OSCCs that are potentially HPV-related (cancers of the tongue base and tonsil, including lingual tonsil and Waldeyer's ring) increased in the USA from 1973 to 2004, perhaps as a result of changing sexual behaviours.[12] The IARC Multicenter Study estimated that 18% of oral and oro-pharyngeal cancers worldwide are HPV associated.[13,14] There is a general agreement in the current literature as regard the ranking of HPV prevalence according to SCC subsites. HPV infection is most prevalent in OPSCC, followed by Laryngeal SCCs and, finally, by OSCCs, and not detected in tumors from other HN sites.[15] Shiboski *et al*. (2005) showed, with an analysis of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) data from 1973-2001, an annual increase in the incidence of oral tongue, palatine tonsil, and base-of-tongue cancers, by 2.1%, 3.9%, and 1.7%, respectively, in 20- to 44-year-old white patients, while the incidence of HNSCC at other sites declined.[16] Postma and Van Heerden have observed a significant association between cervical and oral carcinoma, suggesting that the oral-genital transmitted HPV infection could induce a neoplastic onset, both synchronous and asynchronous, in different mucosal sites.[17]

MOLECULAR INSIGHT INTO ROLE OF HPV GENOME IN ONCOGENIC MECHANISMS OF H AND N CANCER

Human papillomaviruses (HPV) are epitheliotropic viruses present in the skin and mucosa of several animals. In humans, more than 70 types have been described.[19] According to epidemiological case-control studies, 15 high-risk HPV types have been recognized (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), while 3 types have been nominated as probable high-risk (types 26, 53, and 66) and 12 types have been classified as low-risk [Table 1].[20] Recognized initially as sexually transmitted agents, HPVs are now considered human carcinogens.[21] Functionally high risk HPV infection contributes to carcinogenesis and tumor progression predominantly through the actions of two viral oncogenes, E6 and E7. These oncogenes are consistently expressed in cervical cell lines and in human cancers [Table 2].[22,23] Both of these oncogenes interact with and inhibit the activities of critical components of cell cycle regulatory systems, in particular E6 with p53 and E7 with Rb.[22-24] The E7 protein interacts with pRB and inactivates this cellular protein.[25] As a consequence, E2F transcription factor is released from pRB-E2F complex, leading to transcriptional activation of several genes involved in cell proliferation.[26] Binding of the E6 protein to the p53 promotes the degradation of the latter through a ubiquitin-dependent proteolysis system. Also of significance is that on completion of the degradation of p53 by the ubiquitin-dependent proteolysis system, the E6 protein is free to interact again with remaining p53 molecules, leading to further degradation of the latter.[27] The products of genes E6 and E7 are essential in the process of HPV induced cellular immortalization and transformation.[28,29] The variants are thought to differ in their biological properties and in their contribution to carcinogenesis. The different type of viruses are characterised by genotypic variations in DNA base sequences of E6 and E7. It is this genotypic variation that permits stratification of virus oncogenic phenotype into high, intermediate and low risk types. E.g. E7 protein of HPV 16 is more oncogenic than E7 protein of HPV 6[30] [Figure 1].

Table 1: HPV genotypes and Oncogenic risk[7]

Risk type	HPV type
High	16, 18
Intermediate	31,33,35,39,45,51,52,58
Low	6,11,42,43,44

Table 2: Prevalence of HPV genotypes in Squamous cell carcinoma of oral cavity as determined by Polymerase chain reaction[18]

References	HPV positive	HPV type (s)
Chang *et al.*	11/40 (28)	6,16,18
Shroyer and Green	1/10 (10)	16
Watts *et al.*	8/8 (100)	6,11,16,18
Yeudall and Campo	18/39 (46)	4,16,18
Holladay and Gerald	7/37 (19)	16,18
Woods *et al.*	14/18 (78)	6,11,16,18
Ostwald *et al.*	16/26 (62)	6,11,16,18
Snijders *et al.*	13/63 (21)	16
Premoli *et al.*	30/50 (60)	26,18
Slebos *et al.*	8/36 (22)	16
Chang *et al.*	20/59 (39)	16

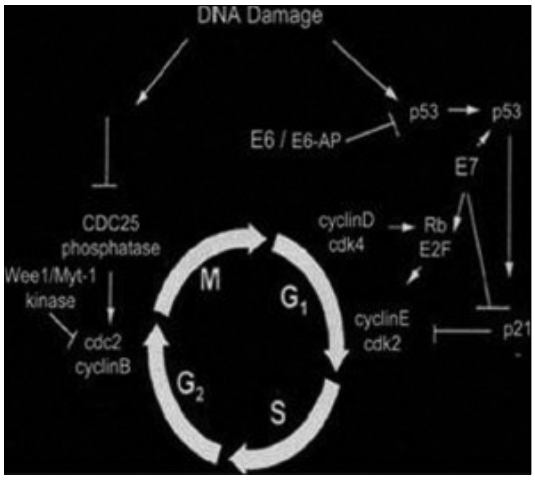

Figure 1: A model explaining the interaction of HPV E6 and E7 with tumor suppressor genes functioning in cell cycle

HPV POSITIVE VERSUS HPV NEGATIVE HEAD AND NECK CANCER

Interestingly, while patients with HPV-associated head and neck cancers commonly present with more advanced disease, they have significantly improved outcomes compared with stage and comorbidity matched HPV-negative patients. Differences in five year overall survival between HPV-positive and HPV-negative patients exceed 30% in a number of retrospective analyses. This difference is one of the largest yet identified for cancers that arise within the same tissues, have very similar patterns of spread, and have overlapping histology. Interestingly, even within patients with HPV-positive HNSCC, those with a history of significant tobacco/alcohol use show significantly worse outcomes than never smokers; but an outcome that remains better than those with HPV-negative disease. Persons with oropharyngeal SCC in which HPV can be detected intracellularly have a better prognosis than persons with HPV-cytonegative oropharyngeal SCC.[6]

Moreover, HPV-positive tumors often present at a higher stage with a small T-size (T1-T2) but frequently there is a large, often cystic, nodal involvement (N+), thus the HPV-positive tumors are often diagnosed in clinical advanced stages, that is, Stages III-IV [Table 3].[31]

DIAGNOSTIC METHODS TO DETECT HPV INFECTION

Until recently, diagnostic laboratory testing for HPV was impossible since the virus does not grow in tissue cultures or in laboratory animals. Currently, with recent technologic advancements in molecular biology techniques for HPV testing, scientists have isolated more than 120 different HPV types.[33-36]

Table 3: Important differences in the Epidemiology, Demographic Background, Molecular etiology and Clinical characteristics of HPV-positive and HPV-negative Head and Neck Squamous cell Carcinoma[32]

	HPV-positive HNSCC	HPV negative SCC
Epidemiology		
Incidence	Increasing	Decreasing
Demographic background		
Age	Younger	Older
Socioeconomic status	Higher	Lower
Risk factors	High-risk sexual practices, marijuana exposure	Tobacco and alcohol exposure
Molecular etiology		
P53 pathway	E6-mediated degradation of cellular p53	TP53 genetic mutation
RB pathway	E7-mediated degradation of Rb	17p LOH, hypermethylation of p16INK4A promoter
P16 expression	Overexpression	Decreased expression
Clinical characteristics		
Location of primary tumor	Oropharynx (palatal and lingual tonsils)	All head and neck sites
Survival	Better	Worse
Response to chemoradiation	Better	Worse
Tumor recurrence	Lower risk	Higher risk

Table 4: Pros and cons of methods used for detection of HPV[17]

Test	Pros	Cons
Southern blot	Specific	sensitivity, requires large amounts of DNA, time intensive
ISH	Specific, performed on FFPE specimens	poor sensitivity
PCR	specific, rapid	false positives
RT-PCR	sensitive and specific, rapid	requires intact RNA
NGS	sensitive and specific, detect multiple HPV types	Cost
p16	perform in clinical labs, correlates with response	not specific for HPV
Serology	Easy to perform	No direct relationship to viral-associated cancer

Light microscopy, Electron microscopy, Non-amplified techniques such as DNA *in situ* hybridisation Southern and dot blot hybridization, Molecular methods e.g. PCR Probe amplification Signal amplification are currently used in detection of HPV [Table 4].

CONCLUSION

However, role of HPV in Head and Neck cancer is controversial and contentious topic which tends to explain the etiology of head and neck cancer besides the traditional tobacco/alcohol factors. We emphasize on the fact that HPV positive cancers behave differently from HPV negative cancer and need separate treatment strategies. So, in future there is a need to run various clinical trials to differentiate HPV positive and negative cancer.

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