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HPV In Malignant and Potentially Malignant Lesions – A Brief Review

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Abstract

Oral Squamous Cell Carcinoma (OSCC) presents as the most common form of oral cancer. Many etiological factors have been attributed to cause the disease, of which tobacco and alcohol consumption are well established. Currently, there is considerable indication that Human Papilloma Virus (HPV) positive oral cancers are on the rise. Oral HPV infection can be acquired mainly by high risk sexual behaviour observed typically in younger individuals. High risk type HPV 16 has shown to play a role in the carcinogenesis of oral and oropharyngeal SCC. This article aims to briefly review hpv in malignant & potentially malignant lesions.

Introduction

Cancer is a silent killer and one possess a major threat to public health in the world. Cancer is the 2nd most common cause of death in the developed world. Research in the field of cancer possess a challenge to medical professionals [1,2,3]. Incidence of Head & neck squamous cell carcinoma is higher in India (5%) when compared with other parts of the body. Head & neck cancer commonly arise from oral cavity & pharynx. [4,5]. The head and neck cancers form the 6th most common type of cancer accounting for 3% of malignancies world-wide [6]. OSCC is the most common form of oral cancer [7]. These are usually preceded by potentially malignant disorders (PMD). Malignant transformation of PMD are not seen in all cases. Some OSCC can develop in lesions without epithelial dysplasia [8,9].

Oral cancer is multifactorial in etiology. Several extrinsic and intrinsic factors play a role in the oral carcinogenesis, such as smoked or smokeless tobacco, alcohol consumption, viruses, hormones, UV radiation, tumor suppression genes, oncogenes, enzymatic mechanisms and immunosuppression [10,11]. Currently, human papillomavirus (HPV) infection has been recognized as an etiologic agent [12].

HPV Association With Malignant And Potentially Malignant Disorders

High-risk HPV-16 and 18 has been linked with malignant and potentially malignant disorders. HPV-16 and 18 is linked with OSCC and HPV-16 with oral leukoplakia

Table 1: Brief Review of the literature

Author	Year	Type of lesion	Percentage of age detection and hpv type
Lee et al [16]	2010	25 controls & 36 oscc	36%oscc(hpv 16-85%),4% control
Jalouli et al [17]	2010	12 osmf and 62 oscc	91% osmf,24% oscc
Saghravanian et al[18]	2011	21 vc,20 ol and 18 controls	14.3% vc (16 and 18),0% ol,0% control
Mathew et al [19]	2011	45 oscc and 20 ol	73.3% hpv-16,71.1% hpv -18 and 57.7% for hpv-16,18
Palmieri et al[20]	2011	278 oscc	1.79% hpv -16,1.79% hpv-11,and 0.36% hpv-6
Pannone et al [21]	2011	38 oscc	10.5% oscc
Elango et al [22]	2011	60 oscc and 46 controls	80% oscc (hpv-16),0% control
Lin et al[23]	2011	48 controls	0% vc
Hwang et al [24]	2012	53 verrucous lesions	58.8% in malignant and 13.9% in benign lesions
Stokes et al [25]	2012	20 % verrucous lesions	0% by ish and 30% by pcr
Mattila et al [26]	2012	82 olp	15.9% olp
Goot-heah et al [27]	2012	30 controls,16 opmds and 14 oscc	3.3% in opmds and oscc,0% in control
Jalouli et al [28]	2012	155 oscc	35% oscc
Ariracharan et al [29]	2013	37 olp	2.7% olp
Gonzalez - ramirez et al [30]	2013	80 oscc and 320 control	5 % oscc(hpv 16 and 18),2.5% in control
Akhter et al [31]	2013	34 oscc	0%
Babiker et al [32]	2013	100 oscc and 100 control	66.7 % oscc(hpv 16-50%,hpv 18-34%,hpv 31-8% and hpv 33-8%),33.3% control
Braakhuis et al [33]	2013	31 oscc	3% (hpv-16)
Sikka and sikka et al [34]	2014	91 ol and 100 control	45% in ol,23% in control
Mccord et al [35]	2014	28 typical papillary lesions and 14 malignant papillary lesions	22.7% (low risk)
Nasrollah saghravanian et al [36]	2015	114 sccs, 21 vcs, 20 lps and 18 controls	0% in normal mucosa and lp lesions, in vc 14.3%,13.1% in oscc
A. Pierangeli et al [37]	2016	54 controls and 62 lesion group	33/62, 53.2% hpv positive in 62 lesion group and (19/54, 34.5%) in control group
Cao j et al [38]	2016	91 olp,28 oscc	Hpv in olp 12.12%, in olk 2.59% and in oscc 7.14%
Jesinda p et al[39]	2016	206 oscc	Hpv16 igg 197 (95.6%) oscc,hpv16-specific igm in 42 (20.4%) oscc

PCR: Polymerase chain reaction, OL: Oral leukoplakia, ISH: In situ hybridization, OLP: Oral lichen planus, VC: Verrucous carcinoma, OSMF: Oral submucous fibrosis, OSCC: oral squamous cell carcinoma, HPV: Human papilloma virus, OPMD: Oral potentially malignant disorders

(OL) [13,14]. HPV shows a wide variation in its prevalence (4-80%) that can be attributed to small sample size, differences in the lesions, differences in sampling methods, different detection methods, and epidemiological characteristics of the population under study [15]. Table I shows a brief review of literature of HPV prevalence.

1. HUMAN PAPILLOMA VIRUS GENOME

HPV is nonenveloped, small, circular DNA virus. It measures 52–55 nm in diameter. Cellular histones bind the double-stranded DNA molecule in a protein capsid without envelope [42]. They are categorized into early, late and long control region (LCR or noncoding region [NCR]) [43]. They encode 6 "early region" and 2 "late region" proteins [44].

Table II: Important roles of high risk HPV expressed proteins [44]

Protein	Role in the virus life cycle
E1	Genome replication: ATP-dependent DNA helicase
E2	Responsible for genome replication, segregation, encapsidation, and transcription. Cell cycle and apoptosis regulation. Regulation of cellular gene expression.
E4	It remodels cytokeratin network. Irion assembly Cell cycle arrest.
E5	This Controls of cell growth, cell differentiation and Immune modulation.
E6	Oncoprotein. Inhibits apoptosis and differentiation. Regulates cell shape, mobility polarity, and signaling
E7	Controls centrosome duplication. Cell cycle control.
L1	IT is a Major capsid protein
L2	Minor capsid protein. Virus assembly. Recruits L1

DNA base sequences of E6 and E7 show genotypic variations that characterizes the different HPV types. HPV are classified as high-risk type (HPV-16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59) and low-risk type (HPV 6, 11, 42, 43, 44) based on their oncogenic potential [42].

Table III: Pathways of transmission of HPV Infection:

Most common pathway	Horizontal transmission consequent to sexual activity [45]
Less common pathway	Autoinfection, Perinatal transmission of the neonate via infected birth canal of the mother, open mouth kissing, [41] fomites and skin contact. [45]

HPV infection of the oral cavity at subclinical levels in not uncommon. The oral epithelium could aid as a virus reservoir. Activation of the virus could play a role in HPV positive oral SCC [46].

Relationship of HPV To Oral Squamous Cell Carcinoma

International Agency of Research of Cancer (IARC) IN 2012 stated that there was adequate evidence to associate HPV 16 with oral cancers. HPV positive and HPV negative oral cancers behave differently with respect to prognosis and overall survival rates. 24 types of HPV has shown association with benign lesions (1, 2, 3, 4, 6, 7, 10, 11, 13, 16, 18, 30, 31, 32, 33, 35, 45, 52, 55, 57, 59, 69, 72, and 73) and 12 types with malignant lesions (2, 3, 6, 11, 13, 16, 18, 31, 33, 35, 52, and 57). Majority of the HPV infection in HNSCC are associated with high-risk types 16, 18, 31, or 33. However, HPV 16 seems to be the most common [15].

Table IV: HPV negative vs HPV Positive cancers [47]

	HPV positive	HPV Negative
Global Incidence	Increasing	Decreasing
Age	Younger	Older
Risk Factors	Sexual behaviour	Tobacco, Alcohol
Molecular genetics	P16 increased P53 wild type Rb decreased	P16 decreased P53 Mutated Rb increased

Established etiological role of HPV in cervical Squamous cell carcinoma, detection of HPV genotypes in cases of OSCC, epithelial tropism of HPV, Similarity between oral and genital epithelia can be attributed to the role of HPV in oral carcinogenesis [48]. Degradation of the tumor suppressors p53 and pRB is implied to tumorigenesis of HPV oncoproteins E6 and E7.

Overexpression of p16 protein and lack of p53 mutations is a hallmark feature of HPV related HNSCC. during early tumorigenesis there is loss of transcriptional repression that occurs as a response to upstream signals [49].

The possible mechanism in tumorigenesis of HPV could be explained as follows [50].

- HPV gets integrated in the host genome when a breakpoint is noticed in the E1/E2 sequence leading to increase in tumorigenicity. This occurs due to the upregulation of E6 and E7 that is encoded in the early open reading frame of the virus.
- E2 protein negatively regulates the expression of E6 and E7. This is encoded in the early open reading frame.
- HPV E6 and E7 disrupts the cellular proteins and tumor suppressor genes (p53 and pRb) that is involved in carcinogenesis by altering host genome.
- This causes defects in the gene expression of infected cells that controls DNA repair, apoptosis, and cell cycle leading to cellular transformation

Diagnostic Methods: [48,51]

HPV can be detected either by cytology or biopsy samples. The cytological features are grouped into major criteria and minor criteria. Table V

Based on sensitivity & specificity diagnostic methods are classified as low sensitivity, moderate sensitivity and high sensitivity. Low sensitivity tests like In situ hybridization and immunohistochemistry detects virus when present more than ten copies of viral DNA/ cell. Moderate sensitivity test like dot blot, southern blot, and reverse dot hybridizations detects virus when present in one to ten copies of viral DNA/cell. High Sensitivity test like reverse transcriptase polymerase chain reaction (RT- PCR) and polymerase chain reaction (PCR) detects less than one copy of viral DNA/cell.

HPV Vaccine

Gardasil, Cervarix and a 9-valent vaccine (Merck) are FDA-approved vaccines. They are highly immunogenic and produce neutralizing antibodies to prevent infection with HPV 16 and 18 but its efficacy in reducing oral HPV infection questionable. The vaccines usefulness in reducing the incidence of HPV positive OSCC has not been documented [52]. Gardasil is a quadrivalent vaccine (qHPV) that is available in two types of pre-filled syringes and Cervarix is a bivalent vaccine(biHPV) that is supplied as single dose vials and syringes [53, 50].

Inactivation of the HPV before infecting the host cell thus stimulating humoral immunity is the modus operandi of these prophylactic vaccine [54]. HPV vaccination has been introduced into the national immunization programs in many countries. A three-dose series of qHPV vaccine or biHPV vaccine is recommended in females aged 11 to 26 years in many countries. a three-dose series of qHPV vaccine is recommended for adolescent males in several countries [15].

The adverse effects of biHPV and qHPV includes fever, exanthema or erythema, local reaction, headache, menstruation problems, and malaise. Anaphylactic reaction to vaccine component or to latex present in the tip cap of a pre-filled syringe in bivalent HPV vaccine is a contraindication [50, 15].

Conclusion

HPV has been gaining attention as an etiologic factor in OSCC and OPMD. HPV infection in oral leukoplakia could play a pivotal role in carcinogenesis. HPV positive

oral cancers has become an important global problem. It has been foreseen that by 2020 HPV positive oral cancers can exceed cervical cancer [55]. HPV positive tumours show better survival and prognosis. It may be prudent to consider screening patients who may harbour latent high-risk HPV cytologically.

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