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HUMAN PAPILLOMA VIRUS AND ORAL CANCER

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ABSTRACT
Oral Squamous Cell Carcinoma (OSCC) constitutes one of the most common malignant tumors worldwide. In India its incidence remains high and major cause of morbidity and mortality. The rising incidence of oropharyngeal carcinoma in the absence of risk factors like smoking and alcohol consumption suggests that genetic predisposition, diet, nontraditional behavioral and oncogenic virus are driving the attention. The link between Human Papilloma virus and oropharyngeal carcinoma is trending in recent decades. HPV type 16 and 18 have been considered as high risk types since studies have proved their association with head and neck carcinomas. Since HPV infection has been associated with more favourable disease outcome., early diagnosis and prompt treatment is obligatory to promote the prognosis of oral cancer.

KEYWORDS: Human papilloma virus, Oral squamous cell carcinoma, Koilocytes. HPV DNA.

INTRODUCTION

Oral Squamous Cell Carcinoma (OSCC) constitutes one of the most common malignant tumors worldwide. In India its incidence remains high and major cause of morbidity and mortality.[1]

Etiology of OSCC is multifactorial. However, oral habits, such as tobacco, areca nut chewing and alcohol are widely believed to be major preventable risk factors responsible for the causation of OSCC. But in some instance OSCC is seen associated with additional factors, such as genetic pre-disposition, diet or oncogenic viruses.[2.3]

The role of oncogenic viruses in human cancer is an evolving area of research. Viruses are proficient of hijacking host cellular genome and modifying DNA and the chromosomal structures as well as inducing proliferative changes in the cells. Human papillomavirus (HPV) is one of the most common oncogenic viruses which has been recognized as a causative agent for oral carcinoma.[4]

First evidence of HPV in the etiology of OSCC was seen in 1977. Numerous studies have also been conducted in this regard supporting the role of HPV in carcinogenesis.[5] The HPV oncogenesis was first recognized in the uterine cervix.[6] Similarities in the morphological features between cervical and oral HPV-associated lesions incited to indicate that HPV might be involved in oropharyngeal carcinogenesis as well.[7]

The oncogenic potential of HPV in oral carcinogenesis was first proposed in 1983 by Syrjanen et al and supported by several other authors.[8]

PREVALENCE

Since the detection rates of HPV DNA have been highly variable, the oncogenic role of HPV has been controversial.[9-12] Initially the estimated prevalence rates of HPV associated OSCC was around 20–30%, but is now considered to be as high as 50%. The association is strongest in the tonsil and base of tongue.[13-14]

According to a meta-analytical study, HPV is associated with approximately 26% of all head and neck squamous cell carcinomas. The data linking HPV to oropharyngeal cancers is even stronger, with various published series showing detection of HPV in 50% or more of cases.[15]

PATHOGENESIS

HPV belongs to a heterogeneous group of "Papillomaviridae" family. It comprises of a double stranded closed circular DNA genome with diameter of 50 µm and is covered by an icosahedral capsid comprising of 72 capsomeres.[8, 16.17]

According to epidemiological studies 15 high risk (oncogenic) HPV types have been acknowledged (type 16,18,31,33,35,39,45,51,52,56,58,59,68,73 & 82), while 3 types as probable high risk (type 26, 53, 66) and 12 types have been classified as low risk types. Of these 15 high risk types HPV 16 and 18 are the most common strains associated with head and neck squamous cell carcinoma.[18]

The HPV genome is divided into about eight open reading frames (ORFs). In a functional point of view, the HPV genome is divided into three regions. The first is long control region (LCR) which is required for replication and transcription of viral DNA. The second is an early region (E); it is required for replication, cell transformation and control of viral transcription and third is late region (L): it encodes structural proteins like L1 and L2.

The early region consists of six ORFs: E1, E2, E4, E5, E6, and E7 involved in viral replication and oncogenesis. E5 stimulates proliferation and inhibits apoptosis, while E7 and E6 act as oncoproteins.[19, 20 21] These oncoproteins lead to unregulated cell proliferation, with subsequent immortality of the keratinocyte. This is due to the integration and expression of the viral genome into the host cell. Inhibition of tumor suppressor factors (p21, p53 and pRb) brings about chromosome aberrations and excessive production of viral DNA.[22, 23]

HPV has a tropism for immature basal cell of the epithelium and is thought to reach these cells through microabrasion or cracks within the epithelium. Viral replication is strongly related to the differentiation stage of the virally infected cells. Replication of the HPV genome is controlled by cellular mechanisms within the basal cells, so that the viral DNA replicates within the host genome.[24]

KOILOCYTOSIS

Viral infection stage comprises of production of large numbers of complete viral genomes and packaging with the capsid proteins into infectious virions. HPV infected squamous cells show characteristic cytologic changes like nuclear enlargement, nuclear hyperchromasia, irregular nuclear outlines and multinucleation and perinuclear halos. Squamous epithelial cells demonstrating these cytopathic features are referred to as *koilocytes*, a word derived from the Greek *koilos*, which means *hole*.[25,26] These koilocytes are viral infected squamous epithelial cells that contain an acentric, hyperchromatic nucleus that is displaced by a large perinuclear vacuole.[27]

HPV DETECTION TECHNIQUES

HPV viral load is a measure of the amount of HPV DNA in the biopsy specimen alone or in conjunction with well-characterized HPV serological assays.[28]

The diagnosis of human papillomavirus infection can be inferred from morphological, serological and clinical findings.

In most cases accurate identification of HPV relies on molecular biology techniques since it cannot be propagated in tissue culture.

Initially, hybridization techniques such as in situ, Southern blotting and dot-blot used radio-labeled nucleic acid assays to detect HPV infection. Though these techniques provided high-quality information, the disadvantages of these probes include the need for relatively large amounts of purified DNA, low sensitivity, and time consuming procedures.[29]

Nucleic acid-amplification methods

With a DNA genome of about 8,000 base pairs in length and a well-known physical structure and gene organization, tests of choice for detecting HPV from clinical specimens are based on nucleic acid probe technology.[30]

Polymerase chain reaction (PCR)

The PCR techniques are highly sensitive, specific, and widely used. The PCR can generate one billion copies from a single double-stranded DNA molecule after 30 cycles of amplification. In a conventional PCR, the thermostable DNA polymerase recognizes and extends a pair of oligonucleotide primers that flank the region of interest.[29.30]

Microarray analysis

This method uses probe amplification, the PCR product is hybridized onto a chip and hybridized signals are visualized with a DNA chip scanner.

The advantage of this microarray-based automated techniques allow for parallel analysis of multiple DNA samples. DNA microarray analysis can be coupled with PCR for detection and genotyping of the HPV. [31]

Signal amplification assays

This method based on the hybridization of the target HPV-DNA to labeled RNA probes in solution. This assay distinguishes between high risk and low risk groups, but was not designed for genotyping single HPV.[32]

PROGNOSIS AND TREATMENT

In addition to having distinct histopathologic and molecular characteristics, HPV-positive oral cancer carries a better prognosis than HPV-negative one. Numerous studies have publicized that patients with HPV-positive oropharyngeal cancer are more responsive

to treatment and have better disease-specific survival rates than those with HPV-negative oropharyngeal cancer.[33, 34]

According to Fakhry et al. 2008, the overall two-year survival rate for patients with HPV-positive tumors was 95% as compared with HPV-negative tumors whose survival rate was 62%. In addition, they found that patients with HPV-positive tumors had shown a better response to induction chemotherapy.[35]

A meta-analysis of 37 studies, conducted by Ragin and Taioli (2007) which conclude that patients with HPV positive oral cancer had a lower risk of death (HR = 0.85 target; 95% CI, 0.7-1.0) and lower risk of recurrence than in HPV negative cases.[36]

A retrospective study conducted by Lassen *et al* showed that among 1,294 Danish patients with advanced stage OSCC, HPV 16 positivity was significantly higher in oropharyngeal than non-oropharyngeal squamous cell carcinoma. (P < 0.0001). HPV positive patients presented a statistically significant improvement with primary radiotherapy.[37]

CONCLUSION

The mounting incidence of HPV positive OSCC is a significant concern. HPV association has been linked with better overall survival of the patients. Hence early detection, prompt treatment and follow up is necessary in HPV induced oral squamous cell carcinoma to improve the survival rates and quality of life.

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