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# Role of Oncogenic Viruses in Oral Squamous Cell Carcinoma

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## ABSTRACT

Oral Squamous cell carcinoma (OSCC) is the most common oral malignancy which consistently ranks as one of the sixth most common cancer with significant morbidity and mortality. Oncogenic viruses, particularly Human Papilloma Virus (HPV) and Herpes simplex Virus (HSV) play an important role in the pathogenesis of OSCC. These viruses promote cell transformation and prompt uncontrollable cell generation, resulting in the formation of malignant tumors. The role of oncogenic viruses HPV, HSV in OSCC is presented.

**KEYWORDS:** Oncogenic virus, Herpes Simplex Virus, Human Papilloma Virus, Oral Squamous cell carcinoma

## INTRODUCTION

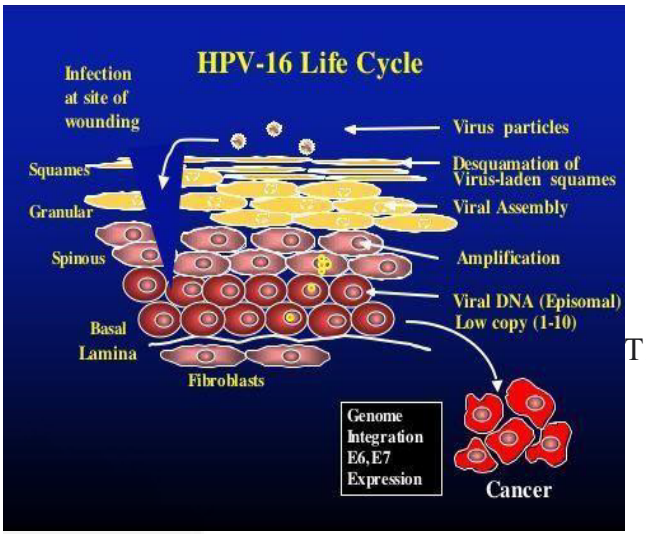
Oncogenic viruses (tumor viruses) which are responsible for producing cancer comprises of both Deoxyribo nucleic acid (DNA) and Ribo nucleic acid (RNA) viruses. DNA tumor virus oncogenes encode viral proteins necessary for viral replication. RNA tumor viruses carry variants of normal host cell genes, which are not necessary for viral replication.1 During the viral replication process, the oncogenic viruses can affect the genes of the host cells and cause malignant transformation.2 Human Papilloma Virus, Herpes Simplex Virus, Epstein Barr Virus, , Human Herpes Virus 8, Hepatitis B virus, Human T-cell leukemia virus-1, Hepatitis C virus and Merkel cell polyoma virus are the oncogenic viruses.3,4 Among these, Human Papilloma Virus and Herpes Simplex Virus are commonly associated with Oral squamous cell carcinoma. Initiation and progression of cancer is attributed to the viral manipulation of the host cellular signalling, DNA damage responses, host immunity and microRNA targets.5 An update on the life cycle, pathogenesis, oncogenic mechanisms and the role of HPV and HSV in oral squamous cell carcinoma is given.

Rapid development in the field of communication technology ensures growth in sectors like-agriculture, education, healthcare etc. However a users located in rural area are unable to take the advantages of the communication revolution on account of lack of technical information. According to the UNESCO report, population of such people in the globe is 64% who are unable to use the technology due to language and technology barrier.

## HUMAN PAPILLOMA VIRUS

Human Papilloma viruses are oncogenic DNA viruses of Papillomaviridiae family. HPV is associated with many benign and malignant lesions of skin and oral epithelium. These viruses are also implicated in carcinomas of pharyngeal tonsil, larynx, oesophagus, uterine cervix, uvula and penis. HPV positivity has been reported to be higher in tumors of the oral cavity (59%), pharynx (43%) and larynx (33%).6

## LIFE CYCLE OF HPV: LIFE CYCLE OF HPV




The viral replication cycle is a highly regulated process, depending both on viral proteins coded by the viral genome and the degree of differentiation of the infected cell. Infection usually starts in the basal and para-basal cells of squamous epithelium.7 The changes in keratinocytes from the basal layer to the surface of the epithelium provide a suitable micro- environment for productive cell replication, responsible for the malignant transformation (Figure 1).[8]

SUB TYPES OF HPV:

Around 120 subtypes of HPV have been identified. De Villiers et al categorised HPVs by their genotypes into high risk or low risk.9

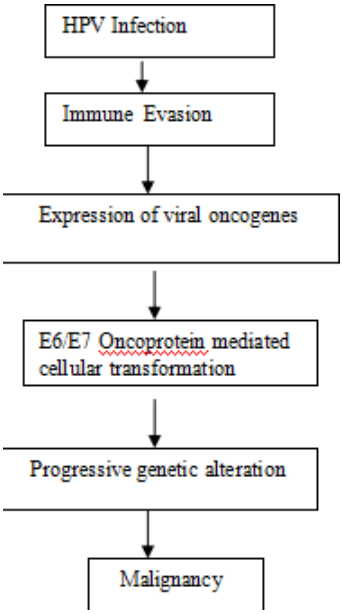
LOW RISK HPVs:

HPV subtypes 6, 11, 40, 42, 43, 44, 54, 61 and 70 are low risk groups. They have lower affinity for tumor suppressor genes and have lesser oncogenic potential. The infections are self limited and are mainly associated with benign lesions.10

HIGH RISK HPVs

HPV subtypes 16, 18, 31,33,35,39, 45, 51, 52 and 56 are high risk groups and are mainly associated with cervical cancer. Munoz et al in his studies has shown that HPV subtypes 16, 18, 31 and 33 are also most commonly associated with oral squamous cell carcinoma.11 HPV 16 is the most potent sub type accounting for the majority of oropharyngeal tumors. It was detected in 16 % of oral squamous cell carcinomas among 70 % of HPV positive cases. HPV 18 is the next most common oncogenic HPV type detected in 8 % of oral squamous cell carcinoma.12
HPV AND ORAL CARCINOGENESIS: 13

HPV genome encodes eight non structural proteins such as E1 E2 E3 E4 E5 E6 E7 and E8 which are involved in replication and structural proteins such as L1 and L2.14 Two viral oncoproteins E6 and E7 inactivate the tumor suppressor genes p53 and pRb which results in cellular proliferation, loss of cell cycle regulation, impaired cellular differentiation, induced mutations and chromosomal instability.15




- HPV involvement in oral carcinogenesis was first proposed in 1983 by Syrjanen et al based on:16
- The epithelial tropism of HPV
- The ability of HPV to immortalize human oral keratinocytes in vitro
- Detection of HR HPV genotypes in samples of oral squamous cell carcinoma
- The special tropism for squamous epithelial cell

Yabe Y, Sadakane H and Isono H emphasized that HPV associated oral squamous cell carcinomas show equal risk for men and women, whereas non HPV associated carcinomas are more frequent in men.

Smith EM, Ritchie JM, Summersgill KF, suggested that HPV positive oropharyngeal cancer is distinct

with p53 degradation, Retinoblastoma pathway inactivation and p16 upregulation .Whereas HPV negative oral squamous cell carcinoma are characterised by p53 mutation and down regulation of p16.

HPV related squamous cell carcinomas presents with more advanced clinical stage and high nodal category, with early lymph node metastasis, different tendencies for extra capsular spread and perineural invasion compared to non HPV related squamous cell carcinomas.13

## HERPES SIMPLEX VIRUS:

Herpes simplex viruses (HSV) are DNA viruses belonging to the Hepesviridiae family. The Human Herpes Virus (HHV) includes;

- HHV 1 - HSV1 (oral herpes )
- HHV 2 - HSV2 (genital herpes )
- HHV 3 -Varicella Zoster Virus (VZV)
- HHV 4 - Epstein Barr Virus (EBV )
- HHV 5 - Cytomegalovirus (CMV)
- HHV 6 - Human B cell Lymphotropic virus
- HHV 7 - Associated with HHV type 6
- HHV 8 - Kaposi Sarcoma Virus ( KSV )

These viruses affect the skin, mucous membranes, and less frequently, the esophagus and brain. HSV evades the immune system through interference with

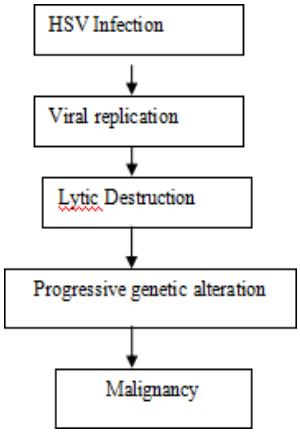
MHC class I antigen presentation on the cell surface.17 They produce primary infections in the initial period and later produce periodic episodes of recurrent infections in tissues derived from ectoderm. The significant characteristic of herpes simplex virus is the affinity to reside latently in regional autonomic sensory ganglionic neurons.18

## TYPES OF HSV:

Two major types of HSV are recognised: HSV 1 and HSV 2. HSV-1 is predominant in oropharyngeal infections. HSV-2 has a strong predilection for anogenital sites. HSV type-2 is more virulent than type-I and it has been significantly associated with carcinoma of the uterine cervix.19

HSV INFECTION AND CARCINOGENESIS:

Herpes simplex infection generally occurs in two phases: the initial, primary infection, followed by secondary, recurrent disease. In the first phase, the virus spreads by close person to-person contact with lesions or mucosal secretions (e.g., saliva or cervical discharge) as well as via respiratory droplets.20 Once the virus is transmitted, incubation period is around 10 days; the virus then spreads to regional lymph nodes, causing lymphadenopathy.




HSV virus infection includes oral or perioral lesions, ocular infections, congenital skin lesions, genital, skin or mucous membrane lesions, and serious systemic illnesses such as encephalitis and neonatal disease. Oral herpetic infections are caused more frequently by HSV-1 than HSV-2.21

Genetic studies reveal that the viral replication cycle results in lytic destruction, progressive genetic alterations like chromosomal aberrations, mutations and selective DNA amplifications which lead to malignancy.22

## HSV AND ORAL CANCER

HSV nucleic acids have been detected in the saliva of oral squamous cell carcinoma patients, the antibody levels to HSV-1 and HSV-2 is higher in the saliva of these patients when compared to controls.23

The integration of DNA from herpes simplex virus into the human genome is associated with the expression of oncogenes and the down regulation of tumor suppressor genes in OSCC patients.24

The inherent cytotoxicity of the HSV -1, its large genomic size, ability to infect cells with a high degree of efficiency and presence of inherent replication

controlling mechanism makes it a potential etiological factor for OSCC.25

## CONCLUSION

It is known that the oncogenic viruses are commonly associated with benign oral lesions such as condylomas, focal epithelial hyperplasias and squamous papillomas. The role of HPV has been conclusively established as an etiologic agent in oral squamous cell carcinomas. HSV is known to cause Oro labial herpes (HSV-1) and genital (HSV-2) herpes. Oncogenic potential of HSV and its implication in OSCC is currently explored. Understanding the oncogenic mechanisms of Human Papilloma virus and Herpes simplex virus and their role in oral squamous cell carcinoma is essential and future studies at molecular level may prove beneficial in revealing novel drug targets for treatment of viral malignancies.

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