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Human Papillomavirus in Head and Neck Carcinoma -How far we have come

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Abstract

Oral cancer otherwise classified as head and neck carcinoma(HNC) and head and neck squamous cell carcinoma(HNSCC) is the sixth to ninth most common malignancy in the world. Some varieties of HPV, transmitted through promiscuous sexual behavior as well as via horizontal, vertical, and other non-sexual modes are known to cause dysplastic changes in the anogenital and oropharyngeal region. Due to the frequent association of HPV with SCC (Squamous cell carcinoma), it has been included under the prognostic criteria of cancer staging by the AJCC. Recently vaccines for HPV infection that are effective against certain subtypes associated with cervical and oropharyngeal cancers have been introduced. While the efficiency of these vaccines is still controversial, some evidence supports the possibility that HPV vaccination may be effective in reducing the incidence of oral cancer. This paper reviews HPV-related pathogenesis in cervical and oral cancer covering HPV structure, classification, modes of spread, effectiveness, and complications of HPV vaccination in case of oral cancer.

Keywords: *cancer; cell; oral; infection; viral; oral mucosa; years age; oral cancer; cervical cancer; hpv infection; hiv 53 access; antiretroviral therapy art; unaids 2017 global; human papilloma virus;45 years age.*

Key messages- This paper reviews HPV-related pathogenesis in cervical and oral cancer covering HPV structure, classification, modes of spread, effectiveness, and complications of HPV vaccination in case of oral cancer.

Introduction

Oral cancer is generally classified as cancer of the head and neck region or head neck squamous cell carcinoma (HNSCC). It is the sixth to ninth most common malignancy in the world. HPV subtypes number more than 150 in the world, and types 16 and 18 are associated with 70% of cervical cancers in the world. Even though alcohol and tobacco remain the principal risk factor for head and neck cancer, HVP has recently become etiologically associated with 20-25% of HNSCC, especially in the oropharynx.

According to ICAR (International Agency of Research of Cancer), there was substantial proof to associate subtype 16 of HPV with oral cancers. Besides in the oral cavity, nearly 24 subtypes of HPV 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 have been associated with benign lesions and 12 subtypes, 2,3,6,11,13,16,18,31,33,35,52 and 57 have been associated with malignant conditions.(24)

Background:

HPV structure and classification: These are DNA viruses that are from a separate Papovaviridae family, including papillomaviridae and polyomaviruses. HPV constitutes a non-enveloped icosahedral capsid along with a circular double-stranded DNA. This small genome consists of 8,000 base pairs together with three distinct regions: the early region(E), upstream regulatory region (URR), also known as the long control region, and late region (L). The URR is found between the E and L regions and has promoter and enhancer DNA sequences. They are critical for regulating viral replication and transcription of both viral and cellular genes 7-9. The URR I is a non-coding region. However, the E and L regions are responsible for coding with open reading frames (ORFs) (24). The E region contains seven to eight genes, the most significant being E6, which degrades p53 oncoproteins, and E7 binds to the Rb oncoprotein. L1 major viral capsid structural protein and L2 minor viral capsid structural protein are located in the L region, which encode structural proteins that are essential for viral capsid formation in the final stages of replication. (24) fig 1.

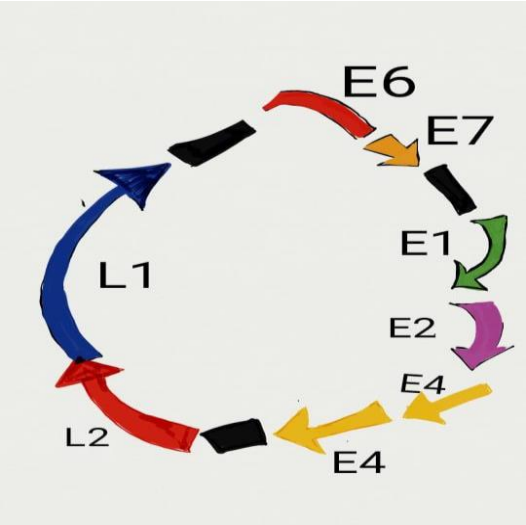

Figure1. Structure of HPV (original)

Incidence: Human Papillomavirus (HPV)

- The HPV infection usually occurs via a breach in the epithelial continuity, tear in oral mucosa, trauma or insult.
- Some studies show evidence of viral spread even via the exchange of body fluids as found in kissing.
- Researchers claim that infection in the healthy, continuous epithelium is unlikely.
- The HPV spreads mainly by sexual contact or direct skin-to-skin contact, as observed in subjects engaging in oral sex or sex without barriers.
- Incidences of vertical or perinatal transmission have been recorded in both males and females. The virus may even spread via the mother's breast milk.
- Besides, incidences of auto or hetero inoculation have been reported.
- According to Ferenczi et al., HPV-DNA positivity in hospitals or surgical instruments was recorded low after being sterilized.
- In clinical setups, transvaginal ultrasound probes and colonoscopes can even transmit the infection.
- Recent studies show a close relationship between smoking and oral sex with the prevalence of HPV infection. It is thought that the damage caused to the oral mucosa by tobacco might be the reason behind the pathogenesis.

Pathogenesis:

- The main pathway of pathogenesis is through entry via a break in the epithelium.
- The virions are released from the stratum corneum and granulosum of the keratinized epithelium, which directly invades the basal cell later by capsid synthesis and late promoter activation.
- The virus enters the epithelium as an extrachromosomal component and undergoes episomal replication during the initial phases. In the initial phase (20-200), copies are present within the host cell, acting as a reservoir. At this stage, the host cells are morphologically indistinguishable from non-infected cells responsible for the latency of the disease.
- The alteration of the keratinocytes by the virus occurs from basal or suprabasal layers containing the alpha integrin. This encourages cell proliferation. (29)
- In the lower epithelial layers, viral plasmid replication occurs, subdivided into amplification and maintenance phases. It is influenced by factors like genome-coded viral proteins and the degree of differentiation of the infected cell.
- The cells that differentiate from the epithelium harbor the vegetative replication of the virus. This stage is linked to viral DNA expression leading to the infective stage of the disease.
- HPV integration occurs on viral DNA rupture and E6 and E7 preservation and transcription, leading to infected cell proliferation, which causes extra aberration production of viral proteins. These proteins, in turn, interact with cellular proteins. (24)

Histopathological Changes:

- When subjected to microscopic evaluation, various histopathological changes have been observed in a virus-altered human cell.
- It included acanthosis, dyskeratosis, keratocyte multinucleation, and koilocytosis (most commonly recorded cytopathologic effect).
- Koilocytosis involves thicker cytoplasm along with morphologically collapsed, atypical stellate nuclei.
- The stratum granulosum and stratum basale have recorded cellular changes such as chromatin peripheralization and the incidence of inclusion bodies.

- HPV-associated carcinogenesis mainly involves E6, E7 expression, which interferes with the P53 gene, thereby inhibiting apoptosis and dysregulation of the cell cycle by binding to pRb protein. (24)

Cytokeratin alteration

- An epithelial tissue's intracytoplasmic cytoskeleton consists of cytokeratin intermediate filaments. They have been classified as HMWCKs & CMWCKs, acidic type (9-23), and primary type (1-8).
- The expression of cytokeratin depends on the type and terminal differentiation status and maturation of the epithelium. (30)
- Healthy or normal oral mucosa contains mainly C5, C5, C13, C14.
- These are also recorded in benign epithelial lesions.
- However, studies of the biopsy taken from oral mucosa revealed that females who were tested positive for HPV were found to express cytokeratin types 19,14,16,17.
- A significant expression of cytokeratin 19 was found in basal cell layers of HPV-positive DNA samples. (24)

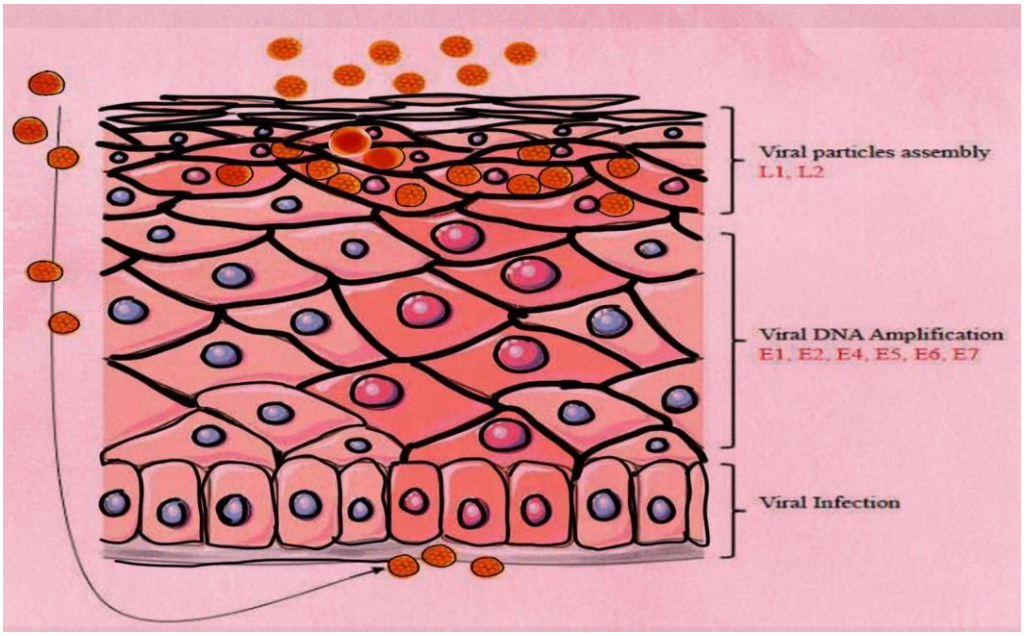

Figure. 2 shows the cellular changes caused by the HPV(original)

Molecular Pathway

- Experiments show that tumor cell viability is decreased when E6 and E7 are inhibited. This indicates that expression of the E6 and E7 oncoproteins is required for tumor maintenance in oropharyngeal cancers, as is seen in cervical cancers (15).
- Besides, E7 is the significant transforming oncogene during the early stages of carcinogenesis in HNSCC compared with E6, which seems to function at a later stage (16).
- When E6, E7, and E6/E7 are expressed under keratin 14 (K14) promoter regulation in transgenic mice, mice tend to develop tumors in their tongue and esophagus. This happened after they added 4-nitroquinoline-N-oxide in their drinking water.
- Tumor genesis in K14E6 mice decreased than in K14E7 mice (22% versus 95%). This was despite the nontransgenic mice having a tumor formation rate of 16%. (31)
- Despite a similar rate of tumor formation as the K14E7 mice, the K14E6E7 mice had an elevated rate of multiple invasive lesions with high-grade cancer. This characteristic hints that E6 and E7 function together to form invasive carcinoma in HNSCC.
- Interactions between E7 and the pRb pocket proteins p107 and p130, as well as the CDK inhibitors p21CIP1 and p27KIP1 (17-19), are described. When these critical regulatory proteins for the cell cycle are arrested, uncontrolled cellular proliferation and carcinogenesis are observed .E6, in agreement with E6AP, influences telomerase activity through activation of hTERT. Cellular immortalization results from the degradation of NFX1 (a transcription repressor of hTERT). fig 2.

Human Papillomavirus in Head and Neck Cancer:

Along with anti-apoptotic effects by degrading p53, E6 directly binds a pro-apoptotic protein Bak with E6AP, contributing to antiapoptosis (20). These transforming effects work in an association such that E6 prevents E7-induced apoptosis by imparting anti-apoptotic effects destroying p53 and Bak. E7 rescues E6 from the inhibition of p16INK4A by directly activating cyclins A and E and inactivating p16INK4A, bypassing its regulation (20,21).

Role of ART (Anti- Retroviral Therapy) In HPV Pathogenesis

- According to the 2016 survey, globally, 36.7 million people were living with the Human Immunodeficiency Virus (HIV), of which 53% had access to antiretroviral therapy (ART) (UNAIDS 2017 Global HIV Statistics)
- However, ART turned out to be a double-edged sword, since, on the one hand, it helped to improve the life span of HIV affected people, it also made them more vulnerable to virus attack especially HPV(Human Papilloma Virus)
- Higher cancer risk in HIV/AIDS patients than the general population results from HIV-related immunosuppression that impairs oncogenic viral infection control. It is also recorded AIDS-defining cancers (ADC) like HPV -induced cervical cancer and non-AIDS-defining cancers (NADC) that include HPV -associated oropharyngeal and anal cancers.
- Various epidemiological investigations depicting diverse cohorts sustain the finding that oral manifestations of HPV infections progressed among HIV-positive subjects on long-term HAART (PI)compared with patients not taking ART. (4,14)
- A study led to investigate HPV vaccine awareness, perspectives, and uptake in first-year college students discovered that a higher number of females(47.3%) were vaccinated instead of males. It was also found that most unvaccinated students were in their early stage of decision-making related to the vaccine. It suggested that students needed required prompt providers along with education concerning the susceptibility to HPV(2)

Treatment and Vaccination:

- A possible correlation was presented in 1983 by Syrjänen et al. between HPV and oral lesions, including non-neoplastic, benign, and malignant lesions by the use of light microscopy as the tool of examination.
- In various squamous cell cancers of the oral epithelium, such as squamous cell papilloma, condyloma, and focal epithelial hyperplasia, HPV subtypes could be anticipated.
- Studies of HPV-induced carcinogenesis in oral mucosa also suggest similar pathogenesis to cervical mucosa targeting the p53 and pRb tumor suppressor pathways, resulting in cell cycle alteration.
- HPV penetration to normal and healthy mucosa is not possible in the absence of microscopic mucosal lesions. Even before HPV vaccination, the first line of defense in preventing oral cancer

should be the maintenance of a healthy oral cavity with clean oral hygiene without precancerous lesions.

- Both in Europe and the USA, the rising incidence of OPSCC, including tonsillar and tongue base cancers, has been attributed to an epidemic of HPV infection(27).
- HPV 16 and 18 account for about 70% of cervical cancer cases worldwide, with relatively small region-specific differences. HPV 16 and 18 are also responsible for more than 90% of HPV-associated non-cervical cancers, with HPV 16 accounting for a large majority of cases (7, 9, 22)
- A decrease in the incidence of cancer at HPV-unrelated sites has been reported in Japan, where about 35% of OPC and 25% of other oral cancers are HPV-positive(27)
- Although vaccine efficacy against oral HPV infection is not yet known in middle-aged adults, vaccination against HPV-positive OSCCs may reduce their prevalence, including tonsil and tongue-based cancers.
- Studies have shown that the qHPV vaccine protects against genital warts and premalignant anal neoplasms in males. (28)
- In an experiment, human kidney cells (293T) or immortalized keratinocytes (HaCaT) were exposed to HPV in the presence of nearly 5,000 biologically active compounds by implication of high-throughput screening. A subset of cell cycle inhibitors (including etoposide, aphidicolin, and 5-fluorouracil) arrests HPV infection. This outcome was also seen at low strengths that have no cell viability. On further examination, it was found that mitosis phase progression is required for HPV infection and early expression of the viral gene. Precisely, the early prophase segment of mitosis is the critical infection period. It is determined by arresting the cell cycle at the G2/M phase using the cyclin-dependent kinase (CDK) 1 inhibitor, purvalanol.
- The latest research shows that if the site of lesion is anywhere except the base of the tongue or tonsil, the vaccine is not needed.
- In most countries, the recommended average vaccination age group for females is 11-26 years, and the adolescent age range for males.
- The current vaccination strategy targeting cervical cancer caused by HPV will provide some amount of protection against oral squamous cell carcinoma.
- The possibility of vaccination against HPV-positive OSCC, including tonsil and tongue-based cancers, was reported to decrease the prevalence of oral HPV infection in middle-aged adults, even though vaccine efficacy against oral HPV infections is presently unknown.

Prevalent Vaccines for the HPV:

- A study of approximately 3,200 women ages 27 to 45 years old found that Gardasil was 88 percent effective in preventing persistent infection, genital warts, vulvar and vaginal precancerous lesions, cervical precancerous lesions, and cervical cancers associated with HPV types covered by the vaccine. (3)
- The FDA,5th Oct 2018, approval of Gardasil 9{Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant} in women 27 -45 years of age is based on these results and findings from the long-term follow-up study.
- Efficacy data for Gardasil 9 in men 27-45 years of age can be inferred from the data described above for women 27-45 years of age and from Gardasil efficacy data in younger men (16-26 years of age) as well as data on immunogenicity from a trial in which 150 men 27-45 years of age received a 3-dose regimen of Gardasil over six months.
- A total of 13,000 men and women were tested for the safety of Gardasil 9. As far as adverse reactions are concerned, pain, swelling, redness, and headaches were reported most frequently.
- A Cochrane review, which included both mono- and bivalent HPV vaccines, indicates that all offered good protection against cervical intraepithelial neoplasia of grade 2 and 3 (CIN2 and CIN3), and in situ adenocarcinomas associated with HPV 16/18 infection among young women who had not been previously infected with hrHPV or HPV 16/18. (1)
- Based on Cobas 4800 testing, Cobas showed a low cross-reactivity with low-risk human papillomavirus (lrHPV), a discordance rate of 3.74% between pre-aliquots and post-aliquots, and failure rates of 4.57% and 1.16%, respectively, after vortexing and swirling. In this study, Cobas test sensitivity, accuracy, and reproducibility were demonstrated for 14 high-risk HPV (hrHPV) genotypes.
- Men, especially those with sex with men, may be able to benefit from a vaccination as it may reduce the population prevalence of HPV and provide direct protection against genital warts and anal and penile cancer. Although the relationship between HPV infection and oral cancer has been well documented, oral cancer has also been linked to different(27)
- Preventive goals should focus on avoiding HPV-related lesions. The current HPV vaccination strategy for cervical cancer will prevent the development of some oral squamous cell cancer, as broadly defined, as well as some anogenital carcinomas, such as anal, penile, and vulvar cancers.

Vaccination and Pregnancy:

Human Papilloma Vaccines are contraindicated during pregnancy and are delayed if a woman is found pregnant after the vaccine series initiation. The rest of the doses are administered after the completion of pregnancy. No extra intervention is needed in case of accidental vaccine administration during pregnancy. This is done to avoid risk to the fetus by administering live, attenuated virus and live bacterial vaccines. (26).In case of HPV infection of a mother, it is advisable to monitor the patient by regular PAP smear and provide immunity to the child by administering the vaccine.

Conclusion:

Several reports claim to find a relation between HPV infection and cancer of the head and neck, especially the oral mucosa. The primary and secondary factors must, however, be considered and categorized to avoid independent results. The results of controlled studies are affected by many factors, such as the study groups, the methods, racial and sexist differences, and particular anatomical sites of the mouth and oral cavity. It is imperative for clinicians treating orofacial carcinoma cases to know about HPV vaccination and be informed of developments in technology for reducing HPV-related infections and cancers. A lot of trials and research is yet to be done to study the effect of vaccines on the HPV-induced HNSCC.

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