Human Papillomavirus and Its Role in Oral and Oropharyngeal Carcinoma

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ABSTRACT

Human papillomavirus (HPV) consists of a large group of double-stranded DNA viruses, belonging, to the family Papillomaviridae. HPV shows an affinity for squamous epithelium and may infect skin or mucosa. Mucosal infection by HPV may arise in various sites of its inoculation namely, the anogenital tract, urethra, skin, larynx, tracheobronchial and oral mucosa. It has been hypothesized that HPV may have a role in malignant potential of oral squamous cell carcinoma owing to its high frequency. This review aimed at highlighting the possible mechanism of infection of HPV, its possible role in oral and oropharyngeal carcinoma along with other features associated with the virus.

Key words: Human papillomavirus, oral squamous cell carcinoma, oropharyngeal carcinoma.

ÖZET

İnsan papilloma virüsü (HPV), Papillomaviridae ailesine dahil olan, çift sarmal DNA virüsleri grubundan oluşmaktadır. HPV, skuamöz epitel için afinite gösterir ve cildi veya mukozayı enfekte edebilir. HPV'nin mukoza enfeksiyonu, inokülasyon yaptığı bölgelere göre, anogenital sistem, uretra, deri, larenks, trakeobronşijal ve oral mukozada ortaya çıkabilir. HPV'nin oral skuamöz hücreli karsinomadaki yüksek frekansına bağlı olarak, bu hastalığın malign potansiyelinde rol oynadığı düşünülmektedir. Bu derleme, HPV enfeksiyonunun olası mekanizmasını, bunun virüsle ilişkili diğer özelliklerle birlikte oral ve orofaringeal karsinomadaki muhtemel rolünü aydınlatmayı amaçlamaktadır.

Anahtar kelimeler: İnsan papilloma virüsü, oral skuamöz hücreli karsinom, orofaringeal karsinom.
Introduction

As the number of cancers increase, the viral etiology has emerged as a crucial factor associated with them, with around twenty percent of them closely linked to viral presence. Oral cavity cancer is the sixth most common cancer around the world, and among various etiological agents tobacco, alcohol and high-risk genomes of human papillomavirus (HPV) comprise of the main factors in its occurrence. In addition to being the usual cause for infections of sexual origin, HPV’s role as being carcinogenic has been broadly accepted by numerous studies.

The decisive part of HPV in the development of carcinoma of the oral cavity is still under dispute regardless of its firmly-established role in the overwhelmingly increasing number of carcinoma involving cervix. Head and neck carcinoma (HNSCC), conventionally credited to tobacco and alcohol intake has seen a decline during the past 30 years. However, one of its subtypes involving oropharynx occurs in a significant proportion. The involvement of HPV in oral squamous cell carcinoma (OSCC) was reported in 1983, and existence of its DNA in OSCC was confirmed after two years through immunohistochemistry. The aim of this article is to review general characteristics of HPV and its possible mechanisms in oral and oro-pharyngeal carcinoma.

Structure of Human Papillomavirus

HPV is a deoxyribonucleic acid (DNA) virus, circular in shape, nonenveloped, having a size of 55nm, from the group of papillomaviridae viruses and consists of 5500 nucleotide base pairs. The recent recommendations by International Committee on Taxonomy of Viruses (ICTV) puts total number of genera of HPV at 30, with 189 papillomavirus types which include 120 types isolated from humans.

Approximately eight open reading frames (ORFs) are encoded by DNA of HPV, and each ORF is subdivided into the early (E) region-comprising of forty-five percent of the genetic material, the late (L) region-comprising of forty-percent of genetic material and a long control region (LCR). Early ORFs encode for E1, E2, E4, E5, E6, and E7 proteins, and this encoding is vital for HPV to replicate, help in its cellular transformation and viral transcription, E1 and E2 maintaining DNA of virus in the form of an episome and simplify the separation of the genetic material of virus during cellular division. The cell cycle progression is stimulated by E6 and E7 during productive infection, whereas E1, E2, E4, and E5 express themselves during...
amplification of DNA virus, occurring in cells of superior layers of epithelium. L region encodes capsid proteins that take part in virion assembly. LCR is vital for the replication of DNA and its transcription. Stratification of HPV into various risk categories is permitted by its disparities in the DNA base arrangements of E6 and E7. Based on this genotypic variations HPV is categorized into high-risk, intermediate-risk, and low-risk virus types (Table 1).

Table 1. Different strains of HPV and their associated levels of risk

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Risk Type</th>
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<tbody>
<tr>
<td>16,18</td>
<td>High</td>
</tr>
<tr>
<td>31,33,35,39,45,51,52,58,59,68</td>
<td>Intermediate</td>
</tr>
<tr>
<td>6,11,42,43,44</td>
<td>Low</td>
</tr>
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Transmission

The main sites where HPV harbors in humans include epithelium of anal canal, vulva, vagina, penis, cervix, perianal region, oropharynx and tonsillar crypts. HPV is seen in the normal mucosa of around 0.6 to 81% of individuals. Oral HPV infection is related to aggressive sexual activity, indicated by many oral or vaginal sexual partners during one’s lifetime. The transmission of oral HPV has been seen to be more related to the multiple current oral sex and open kissing partners as compared to the variable number of mates indulging in normal sexual practices. Smoking and increased age was shown to act as predisposing component for persistent oral HPV infections in women because tissues become more susceptible to tobacco and age-dependent indigenous genetic and immune disruption.

Carcinogenesis and HPV

Although there is a clear relationship between HPV and cancer of the cervix, and to demonstrate a similar association of HPV and oral squamous cell carcinoma (OSCC) there should be an indication that HPV infected oral mucosa will develop OSCC in time. The numerous factors that could dictate the possibility of HPV budding towards malignancy include the type of HPV, the genetic framework, the interaction with various biological, physical, and chemical agents, and immunologic status of the host, which altogether can alter the progression of HPV. HPV types 16 and 18 considered to be high-risk ones increase the risk of cancer development by inducing precancerous lesions, and furthermore, incorporation of DNA virus in genetic framework of the host appears to precede any shift from dysplastic features to aggressive malignancy. Under favorable conditions, the genome of the high-risk
HPV combines with the genetic framework of the host, and such integration is vital for keratinocytes to become immortal. At the time of this integration, genome of virus breakdowns at E1 and E2 locations and E2 loss during this reaction leads to forfeiture of E6 and E7 regulation. The arrangements of E6 and E7 plays a direct part in cell cycle through impeding the normal functions of p53 and pRb, respectively. The E6 protein interacts with a cellular protein, E6 associated protein (E6AP) deteriorating p53, and furthermore, p53 tumor suppressor gene regulates apoptosis and arrest of growth following DNA damage. As a result, mutation of p53 gene leads to dysregulation of its role causing abnormal cellular proliferation, a build-up of injured DNA, in the development of cells with DNA errors with extended persistence of cells. E6 additionally prevents apoptosis by snooping with proteins favouring apoptosis, like Bak and procaspase 8. Under the influence of mitogenic potential, p53 actions facilitate cell proliferation, arresting cell cycle at G1 check point subsequent to DNA injury, thus allowing DNA repair prior to the entry of cell into synthetic phase of the DNA, and arbitrate initiation of apoptosis in cells, that have been injured beyond repair.

Numerous studies over the previous decade have shown telomerase and similar elements as source of target for E6 and such an integration has a capacity to cause cellular transformation. Telomerase is not present in normal somatic cells with its actions limited to embryonic cells only. In its absence, the continuous division of cells result in progressive shortening of telomeres eventually resulting in cellular senescence. HPV encourages stimulation of telomerase preventing them to be shortened leading to an extension of the lifetime of cells infested with HPV.

The product of retinoblastoma tumor suppressor gene, pRb, and its other associates, p107 and p130, have been seen to be the target of the E7 protein of HPV. pRb and its other family proteins in their hypophosphorylated state, can combine with various factors of transcription like E2F family members, and suppress the progression of the cellular cycle by stalling the transcription of particular genes. E7 disrupts binding of pRb-E2F complexes by being able to combine with hypophosphorylated pRb and thus cells are induced to enter S phase prematurely. Because E7 can attach to unphosphorylated pRb, it could irresponsibly cause cells to go into the S phase by unsettling pRb– combinations. The action of the E7 protein of HPV helps the virus to replicate in the upper epithelial areas, where normal descendant cells usually differentiate, leaving cell cycle completely. Overexpression of P16INK4a—which prevents phosphorylation of pRb, occurs when pRb is disabled by the E7 protein belonging to...
HPV, and furthermore, this overexpression of P16INK4a can be utilized as an important biomarker during the assessment of HPV pathogenicity. E6 and E7 show a vital part in HPV reliant malignant conversion and lead to impairment of control of cell cycle control and cell maturation.

**HPV in Oral and Oropharyngeal Carcinoma**

The role of human papillomavirus (HPV) in oral and oropharyngeal carcinogenesis was first suggested in 1983. Ever since, numerous studies have shown conflicting results concerning the detection of HPV in oral carcinomatus change, with varying reports about the incidence of HPV-associated such changes, liable on the people studied, on the site of the carcinomatus lesion, on the nature of sample, and on various methods of virus detection. The viral DNA of HPV can be seen in conditions like oral squamous papilloma, focal epithelial hyperplasia (Heck Disease), Common warts, oral condyloma acuminatum, oral leukoplakia, oral lichen planus and 20% cases of oral squamous cell carcinoma(OSCC). HPV DNA has been reported to vary from 0 to 100% in head and neck squamous cell carcinoma (HNSCC). HPV was seen to harbor OSCC involving oropharynx and the tonsil as compared to other head and neck regions. The various findings favoring suggestion regarding role of HPV in OSCC, include existence of high-risk HPV genomic arrangements with appearance of transcriptionally active E6 & E7 proteins in nucleus of malignant cells, their associated metastases; integration of HPV DNA into the genome of cells; and the presence of considerable reproductions of viral DNA.

In Europe, oral HPV incidence ranges from 0 to 18% among men, however owing to lack of well-established studies in the region, such a range of HPV prevalence should be considered with caution. Due to continuously evolving reports, of a relationship among HPV and HNSCC, the prevalence of HPV infection attains considerable significance when it involves oropharyngeal region. An international study was conducted to quantify HNSCC based on the incidence of HPV-DNA, and results showed, HPV-associated cancers of oropharynx constituting 22.4%, of oral cavity about 4.4% and that of larynx constituting 3.5% of cancers were associated with HPV-DNA, thereby confirming the importance of HPV in carcinoma of oropharynx.

The incidence of HPV-positive cancers of the tonsillar area was seen to have increased drastically in Swedish men from 23% in 1970 to 93% in 2007. The researchers suggest numerous factors for extreme disparity in reporting of HPV-associated oral and oropharyngeal...
carcinoma, ranging from lack of enough sample numbers; putting together of different lesions; variances in the sampling techniques; different ethnic and geographic backgrounds of samples examined; and to differences in the methods applied for the isolation of the virus\textsuperscript{27,40,41}.

Despite variable results in detection of HPV-associated carcinomas, it is widely acknowledged that around 26\% of specimens are positive for HPV DNA when biopsies of SCC of head and neck region are carried out\textsuperscript{27,41}. It has also been seen that in HNSCC, the HPV-positive neoplasms show more prevalence in tonsil area when comparison with other sites of the region is made\textsuperscript{27,39,41,42}. A review carried out on 50 studies, conducted to detect HPV in several oral lesions, showed HPV-positive OSCC in the range of 0\% to 80\% with HPV 16 and 18 being the most prevalent types in OSCC than other types of HPV\textsuperscript{2}. HPV infection in the tonsillar area was shown to have a strong correlation with tonsil related cancers in Montreal, and recently there has been an upsurge in HPV-linked OSCC in US population; similar to a trend observed in other developed countries\textsuperscript{43}.

As there is a strong link between antibodies to HPV-16 capsid protein L1 and oral and oropharyngeal SCC, and furthermore these antibodies infer a chronic contact to HPV 16, it is highly likely that exposure to HPV-16 occurs before the development of oropharyngeal SCC by several years\textsuperscript{27,30,44}. This finding, however, should be carefully assessed because HPV infections, like warts, surge HPV antibody titers, and could be confounding with observations associated with serum HPV antibody levels and oral and oropharyngeal SCC\textsuperscript{44}.

### Risk Factors

Sexual behavior has been seen to carry an increased risk of HPV infection\textsuperscript{2}. Higher incidence of this infection is reported among adolescent men who have increasing number of open-mouth kissing partners in the past year, and in people having variable number of open-mouth kissing partners during life time, in addition to increased frequency of oral HPV infection in men with a genital HPV positive sexual partner\textsuperscript{45}.

The correlation between tobacco and alcohol and HPV if any is not clear regarding any synergistic effect between these components in the etiology of OSCC\textsuperscript{46}. However, there was no such synergistic effect seen in one of the recent case-controlled studies conducted for any correlation between tobacco/alcohol and HPV and oral-oropharyngeal carcinoma\textsuperscript{46}.
Molecular Factors and Prognosis

There is a noted molecular difference seen between HPV-positive OSCC and HPV-negative cancer, with p16, overly expressed in most of the HPV-positive tumors. There is no association of bcl-2 and p53 with HPV-positive OSCC and any mutations in p53 are scarcely seen in HPV-positive tumors in comparison to HPV-negative tumors. OSCC associated with HPV-positive infection occurs mostly in younger patients, presenting at a higher stage along with bulky metastatic lymph nodes. HPV-positive carcinoma has been seen to have a better prognosis as compared to HPV-negative carcinoma, and this improved prognosis does not depend on the treatment provided. HPV-positive patients with overexpression of p16 also show better prognosis.

Diagnosis

The various methods for analyzing HPV include viral DNA detection with polymerase chain reaction (PCR) or In Situ Hybridization and p16 detection by immunohistochemistry. Genotyping and detection of HPV are mostly done by amplification of target DNA sequences by PCR followed by hybridization with dedicated probes. Although few studies have shown HPV in saliva and desquamated cells of the mouth, HPV role if any is still not clear owing to low sensitivity and specificity of such detection in saliva.

Vaccination

There were 3 types of HPV vaccines available before 2017 in the United States: bivalent(2vHPV)-Ceravix, quadrivalent (4vHPV) -Gardasil, and 9-valent(9vHPV)-Gardasil 9, and all the three protect against HPV types 16 and 18, that lead to 63% of HPV-linked cancers in the United States. 4vHPV and 9vHPV also protect from HPV Types 6 and 1, that result in ninety percent of genital warts. 9-valent(9vHPV) vaccine, additionally protects against 31, 33, 45, 52, 58 types of HPV. 9-valent(9vHPV) vaccine is the only vaccine used against HPV in the United States nowadays.

Conclusion

The rate of cancers attributed to Human papilloma virus (HPV) is rising. HPV infection is associated more with oropharyngeal SCC as compared to oral SCC. Both the oral and oropharyngeal HPV infection and tumors associated with it usually occur in persons exhibiting
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Diagnostic HPV infection is critical for the tumors associated with it as HPV-positive malignancy differs from HPV-negative malignancies and thus can have an impact while managing such cases.

References


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