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HPV in Oral Squamous Cell Carcinoma-Review Article

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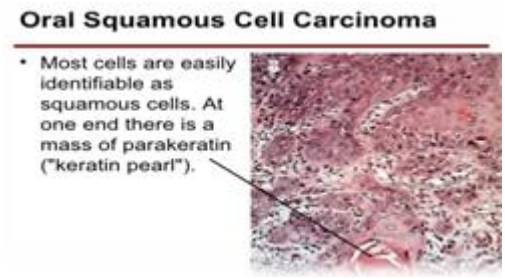
Abstract: ***Aim: The Aim of this study is to demonstrate a possible relation between the oral squamous cell carcinoma and the human papillomavirus (HPV). Objective: The main objective of this article is to get more information and knowledge about Human Papilloma Virus and its types causing the oral cell carcinoma. Background: Growing evidence shows that Human Papillomavirus (HPV) is preferentially associated and has a role with some oral cancer. Human papillomavirus (HPV), the causal agent of cervical cancer, appears to be involved in the etiology of cancer of the oral cavity and oropharynx. Reason: HPV is the leading cause for oropharyngeal cancer (back of the mouth) and front of the mouth, oral cavity cancer. The main reason to study about this is we can prevent oral cell carcinoma if we know about the type of HPV causing it.***

Keywords: Oral squamous cell carcinoma, Human papilloma virus,warts, lesions, koilocytosis

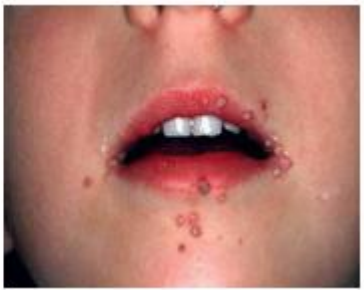
1. Introduction

Human papillomaviruses (HPVs) are a family of small DNA virusesthat infect epithelial cells of the skin and mucosa. Infection results inprimarily benign, self-limiting warts or in epithelial tumors.[1]Among the approximately 100 known types of HPVs, a certain number of so-called high-risk viruses, including notably HPV16 and HPV18, induce lesions with an increased risk of progression to cancer.



Oral cancer is the sixth most common cancer worldwide.[2] More than 90% of all oral cancers are squamous cell carcinoma (SCC) [3,4]. According to data from the International Agency for Research on Cancer (IARC), approximately 263,900 new cases and 128,000 deaths by cancer of the oral cavity are estimated to have occurred in the world[10]. Among the malignant tumors of this anatomic site, more than 90% are oral squamous cell carcinomas (OSCC).The most important risk factors for oral SCC are use of tobacco or betel quid and the regular drinking of alcoholic beverages. However, infection with high-risk human papillomavirus (HPV) genotypes, have also recently been implicated in the aetiopathogenesis of oral SCC [2,5]. To this date, 15 different HPVs have been included in the group of "high- risk" types (HPVs 16, 18,31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), being considered human carcinogens by the InternationalAgency for Cancer Research (IARC)[6,7]. Several studies[8,9]have investigated prevalence of HPV in the oral cancers, butthe prevalence of HPV detection varies broadly, depending onthe population, combination of sub sites, type of specimen, anddetection method. HPV is consistently and more frequently detected in cancers of the oral,oropharynx and tonsil than at otherHead and neck region. However, the specific oncogenesis of these HPV-associated carcinoma entities is still largely unknown.

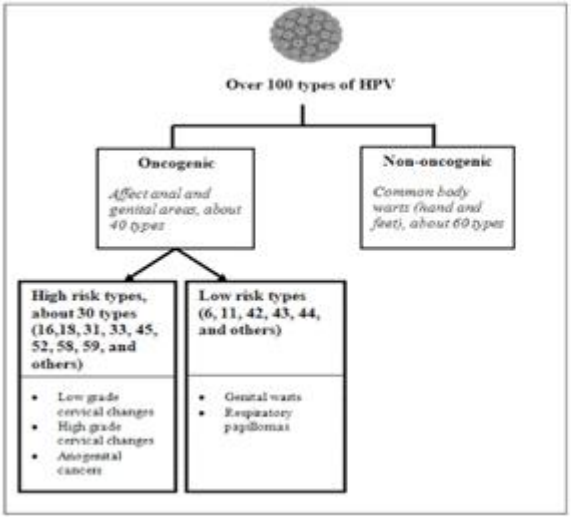
Oral squamous cell carcinomas (OSCC) usually originate from the non-keratinising stratified mucosal epithelium and show morphological similarity to squamous cell carcinomas of other body regions, like those of cervix, anus, or bronchi. It is generally agreed that tobacco, betel quid, and alcohol consumption are the major environmental risk factors for developing OSCC. However, some patients develop OSCC without exposure to these risk factors.Oral SCC more frequently affects men than women (M:F = 1.5:1) most probably because more men than women indulge in high-risk habits. A number of conditions have been associated with an elevated risk of developing oral SCC including Li Fraumeni syndrome, Plummer-Vinson syndrome, Fanconi anaemia, chemotherapy induced immunosuppression of organ transplantation, dyskeratosis congenita, xeroderma pigmentosum and discoid lupus erythematous.[11].



Human papillomavirus (HPV), the causal agentof cervical cancer, appears to be involved in the etiology ofcancer of the oral cavity. The relationship between HPV and OSCC was first suggested in 1983 by Syrjänen et al.[12], when they discovered koilocytotic atypias in malignant oral lesions by optical microscopy. But the presence of viral DNA was only confirmed two years later, by means of in situ hybridisation (ISH)[13]. HPV infection in the oral cavity is associated with risky sexual behaviours, mainly to orogenital sex. However, mouth-to-mouth contact, vertical birthtransmission and auto-inoculation resulting from chewing warts are also transmission modes of this virus to the oral mucosa[14]. Although many studies indicated high frequency of HPV in OSCC specimens, controversy still exists. Therate of HPV detection in OSCC has varied from 0-94%. Thus the ultimate objective of this article is to establish a systematic review over the presence and the role of HPV in oral squamous cell carcinoma based on various studies .

2. Human Papilloma Virus – Types :

HPV lives in the body's epithelial cells. These are flat and thin cells found on the skin's surface and also on the surface of the vagina, anus, vulva, cervix, penis head, mouth, and throat.

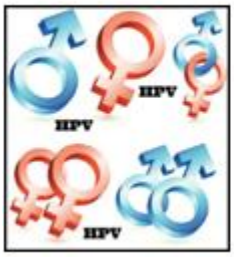


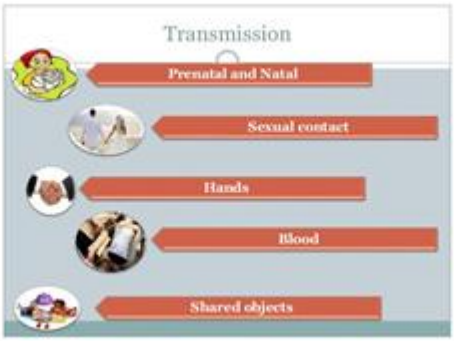
Of the 100 HPV types, about 60 types cause warts on areas such asthe hands or feet. The other 40 or so types of HPV are sexually transmitted and are drawn to the body's mucous membranes, such as the moist layers around the anal and genital areas.HPV is broadly classified into two types high risk, also called as oncogenic and low risk HPVs also called as non oncogenic.Of the 100 known human papilloma viruses, 51 species and three subtypes infect the genital mucosa. 15 are classified as high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), 3 as probable high-risk (26, 53, and 66), and 12 as low-risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108).

Of the HPV family, more than 12 types have been found in oral lesions, including HPVs 1, 2, 4, 6, 7, 11, 13, 16, 18, 30, 32, and 57.[15] HPV-13 and -32 appears to be restricted to oral lesions. Although we found heterogeneity among the various studies , HPV-16 and -18 were detected in 80% of cases, revealing that high-risk HPVviruses were detected 2.8 times more often than the low-risk types in oral carcinomas.

3. Mode of Transmission

These sexually-transmitted HPV viruses are spread through contact with infected genital skin, mucous membranes, or bodily fluids, and can be passed through intercourse and oral sex. Likely requires contact with viable HPV and micro-trauma to skin or mucous membranes to establish infection. It can occur from asymptomatic and sub-clinically infected patients to a uninfected person.Transmission by fomites (inanimate objects such as environmental surfaces andclothing) has never been documented.Rarely, genital HPV infectionwith low-risk types is transmitted from mother tonewborn during delivery and can cause respiratory tract warts in the child, known as juvenile-onset recurrent respiratory papillomatosis (JORRP). Although JORRP rates aresubstantially higher if a woman presentswith genital warts at the time of giving birth, the risk of JORRP in such cases is still less than 1%.



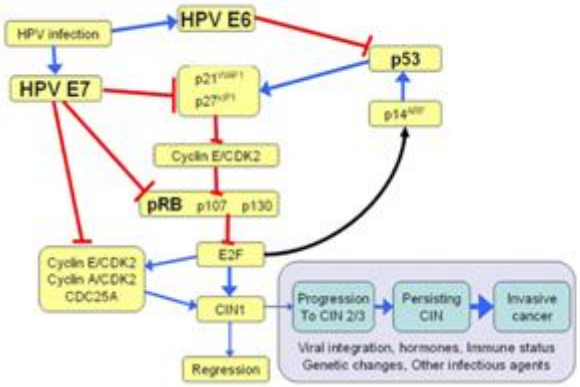


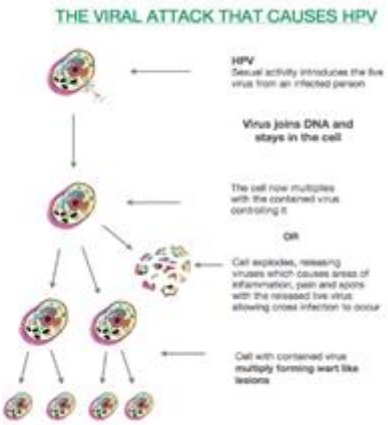
Sharing of possibly contaminated objects may transmit HPV. Although possible, transmission by routes other than sexual intercourse is less common for female genital HPV infection.Fingers-genital contact is a possible way of transmission but unlikely to be a significant source.

Hospital transmission of HPV, especially to surgical staff, has been documented. Surgeons, including urologists and/or anyone in the room is subject to HPV infection by inhalation of noxious viral particles during electrocautery or laser ablation of a condyloma (wart)[16].

4. Pathogenesis :

The HPV genome is comprised of three major regions: the long control region, the early (E1-8) genes and the late (L1-2) genes.High-risk oncogenic subtypes HPV-16, 18, 31,33 and 35 have been shown to be capable oftransforming oral epithelial cells through theviral oncoproteins E6 and E7 [17]. Thevirally encoded E6 binds to a cellular ubiquitin/protein ligase, E6–AP, and simultaneously to the tumour suppressor protein p53, resulting in ubiquitination of p53 and its subsequentproteolytic degradation.E7 binds and destabilizes the tumour suppressor retinoblastoma protein (pRb), preventing it from binding to the E2F transcriptionfactor and thereby promoting cell cycle progression. This functional inactivation of pRb resultsin a reciprocal over expression of p16 tumoursuppressor protein p16INK4A.

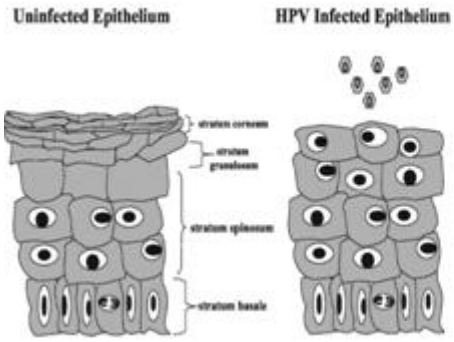


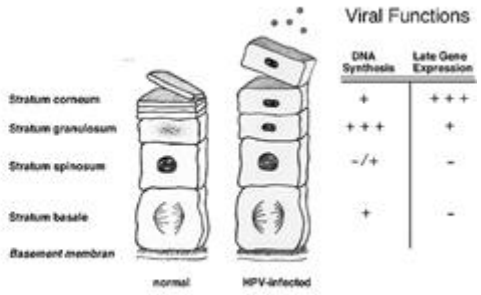


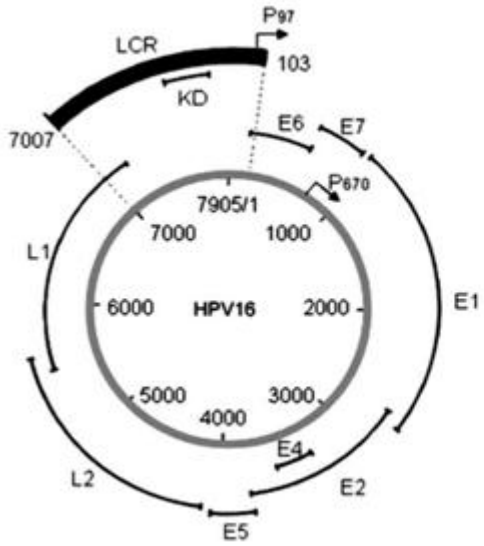
HPVs have been a prime suspect in the etiology of OSCC due to their morphological association with squamous cell carcinomas and their ability to immortalise oral keratinocytes and bring about transformation of epithelial cells[21] . The buccal mucosa, being the site that is most exposed to chemical carcinogens, infections, and trauma, is most vulnerable to carcinogenesis. It has been postulated that abrasions caused due to this continuous exposure might make this mucosal surface more susceptible to HPV by making it easier for the virus to gain entry into the basal cells. [22,23,24]

The proposed mechanism of action of HPV in tumorigenesis includes the following :

- A breakpoint in the E1/ E2 sequence allows integration of HPV into the host genome and significantly increases its tumorigenicity through up regulation of E6 and E7 encoded in the early open reading frame of the virus.
- Expression of E6 and E7 is negatively regulated by E2 protein, which is also encoded in the early open reading frame of the virus.
- By altering host genome functions, HPV E6 and E7 disrupts the p53 and pRb tumour suppressor genes, as well as numerous cellular proteins involved in carcinogenesis. [18]
- Subsequently, infected cells develop defects in gene expression controlling apoptosis, DNA repair, and cell cycle, thus paving the way for cellular transformation.



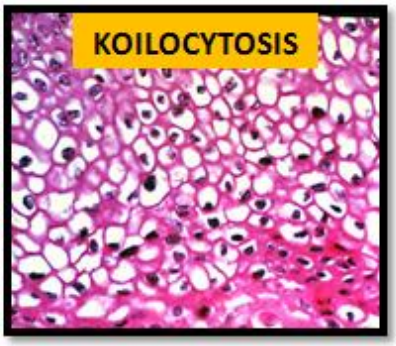


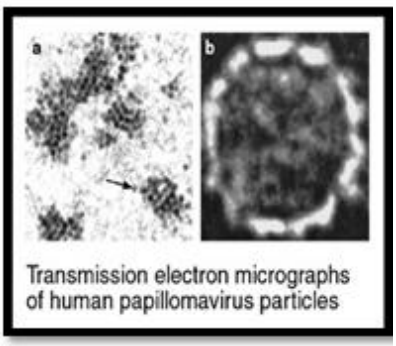


Viral Protein	Functions and Features
E1	It forms a heterodimer complex with E2 and controls viral replication
E2	It regulates early gene promoter and together with E1 viral DNA replication
E4	It may mediate the viral particle realease by destabilizing cytokeratin network
E5	It stimulates mitogenic signals of growth factors
E6	It inactivates many cellular proteins and is one of the major viral oncoproteins
E7	It inactivates many cellular proteins and is one of the major viral oncoproteins
L1	It is the major capsid protein and is the component of the HPV prophylactic vaccine
L2	It is the minor capsid protein

5. Laboratory Diagnosis

HPV has not been cultured by conventional methods. Infection is identified by detection of HPV DNA from clinical samples. Assays for HPV detection differ considerably in their sensitivity and type specificity, and detection is also affected by the anatomic region sampled as well as the method of specimen collection.Several HPV tests have been approved by the Food and Drug Administration(FDA) and detect 13-14 high-risk types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Test results are reported as positive or negative for any of the types; some tests specifically identify HPV 16 and 18.The tests are not clinically indicated nor approved for use in men. The findingsthat confirm HPV participationinthe development of oral squamous carcinomas include the predominant detection of high-risk genotypes (HPV-16/18), the increased prevalence of HPV in dysplasia and squamous carcinomas compared with the normal mucosa, mainly as to high-risk genotypes, indicating HPV as an independent risk factor for the mentioned neoplastic type.[19,20]. It is mostly diagnosed by Pap smear, koilocytosis, PCR.





Evidence Confirming the Role of HPV

As stated by Syrjänen et al.Koch's postulates,[20] at least three conditions necessary to formally confirm the role of HPV as an etiological agent of OSCC have been mentioned as : 1. presence of viral genome in tumourlesions or tumour cells; 2. ability of the virus or viral protein to transform cells in vitro; 3. ability of the virus or viral protein to promote tumour formation in animals. As to the other criteria: 4. viral infection precedes cancer development – in spite of the few prospective studies, we must not forget the work by Lind et al.which some cases of infected leukoplakia progressed to carcinoma within a 10-year period; 5. epidemiologic

association between presence of the virus and development of cancer – although the association has not been proved, several works demonstrate that the prevalence of HPV is higher in pre-neoplastic lesions and carcinomas when compared with the normal mucosa finally, 6. prophylactic HPV vaccination would eliminate OSCC – this effect will only be correctly assessed years after implementation of a vaccine program. If HPV were transient, at least one of the following characteristics should be verified: 1. similar prevalence of HPV among samples of tumour, normal mucosa and pre-neoplastic lesions, including non-tumoral specimens obtained from sites far from the lesions in patients affected by squamous carcinoma; 2. viral prevalence differences in biopsy samples and in oral squamous carcinoma cell lines, due to the potential selectivity of HPV-negative cells during culture; 3.indifferent prevalence of high- and low-risk genotypes in oral cancer samples.

Treatment:

HPV involved squamous cell carcinoma is more radiosensitive[30].Increased radio-sensitivity has been proposed as a possible mechanism. Medical management depends on treatment of the specific clinical manifestation of the infection (such as genital warts or abnormal cervical cell cytology).

A variety of modalities are available for the treatment of oral SCC. These include excision/resection, radio-therapy, systemic cytotoxic chemotherapy and blocking of epithelial growth factor receptor (EGF-R), or a combination of these, either concurrently or in an orderly sequence[25,26] . Surgery is the preferred first line treatment of small, accessible oral SCCs. However, advanced-stage oral SCC is usually treated by a combined treatment program of surgery, chemotherapy, and radiotherapy [27,28] . In cases of recurrent oral SCC, EGF-R inhibitor coupled with chemoradiotherapy, is the first line of treatment [29] . Also in chemoradiation therapy the response rate was 84% vs. 57%, for HPV-positive and HPV-negative patients, respectively[31]. The response is significantly more in HPV positive patients. Moreover when HPV is identified inthe DNA, the patients are called for frequent followup to check for recurrence.

Vaccination

There are currently 3 vaccines which protect against both HPV 16 and 18, which are known to cause at least 70% of oral cancers. Cervarix (produced by GlaxoSmith Kline,Brentford, UK) is a vaccine against HPV-16and HPV-18.Each 0.5-mL dose of HPV4 contains 20 micrograms HPV 6 L1 protein, 40 micrograms HPV 11 L1 protein, 40 micrograms HPV 16 L1 protein, and 20 micrograms HPV 18 L1 protein. The vaccine antigen is adsorbed on alum adjuvant. The vaccine also includes sodium chloride, L-histidine, polysorbate 80, and sodium borate. HPV4 does not contain a preservative or antibiotic. The vaccine is supplied in single-dose vials and syringes. A 9-valent vaccine (Merck) was approved by the FDA in December 2014.

Gardasil (produced by SanofiPasteur MSD Lyon, France) is a quadrivalentvaccine protecting against the oncogenic HPV-16 and HPV-18, but also HPV-6 and HPV-11,which are capable of inducing genital condylomas. The vaccine is approved for females 9 through 25 years of age. HPV2 is not approved for males. The L1 antigen is adsorbed onto aluminium hydroxide. The unique adjuvant system, AS04, is composed of 3-O-desacyl-4'-monophosphoryl lipid A (MPL) adsorbed onto aluminum hydroxide. Each 0.5-mL dose contains 20 micrograms of HPV type 16 L1 protein and 20 micrograms of HPV type 18 L1 protein. HPV2 does not contain a preservative or antibiotic. It is available in 2 types of pre-filled syringes.The vaccines are now part of the publicvaccination programme in several countries andare offered to girls from the age of 12 years orprior to sexual debut. The vaccines may also have some cross-protection against other less common HPV types which cause cervical cancer. One of the vaccines also protects against HPV types 6 and 11 which cause anogenital warts.

Clinical trial results show that both vaccines are safe and very effective in preventing infection with HPV 16 and 18.Both vaccines work best if administered prior to exposure to HPV. Therefore, it is preferable to administer them before first sexual activity.

A severe allergic reaction (e.g., anaphylaxis) to a vaccine component or following a prior dose of HPV vaccine is a contraindication to receipt of HPV vaccine. Anaphylactic allergy to latex is a contraindication to bivalent HPV vaccine in a pre-filled syringe since the tip cap contains natural rubber latex. HPV vaccine is not recommended for use during pregnancy. The vaccine has not been causally associated with adverse pregnancy outcomes or with adverse effects on the developing fetus, but data on vaccination during pregnancyare limited.

6. Conclusion

The relationship between HPV and oral carcinomas have been investigated for three decades, and as previously stated, in spite of the conflicting findings, there is a mass of evidence confirming the involvement of this virus in a percentage OSCC, which may reach a little more than a quarter of OSCC. There has been a rising international recognition of the role of HPV as an etiologic agent in a subset of oral cancers.

The HPV detection rate of 20-50% in oral carcinomas is among the highest of any extra-genital human malignancy. Given this high rate of positivity, HPV may berecognised as a tumorigenic factor for the development of oral cancers.

HPV association has been linked with better overall survival of these patients. It therefore becomes essential to consider cytological screening of patients who may harbor latent high-risk HPV in their oral mucosa. This knowledge would be helpful in certain situations; for example, the detection of HPV in a patient with dysplastic oral will be of great help in guiding decision making. Also, treatment modalities are different for HPV-associated OSCCs vs non-HPV-associated OSCCs.

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