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REVIEW

Human Papilloma Virus and oral cancer: Narrative review of the literature.

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Abstract: The Human Papilloma Virus (HPV) infection is now more common sexually transmitted diseases, with an incidence of 5.5 million worldwide, with 85% of the carrier of this virus adult population. Their oncogenic potential and increased oral lesions associated with oral HPV infection have led us to make a narrative review of the literature on the role of HPV in oral cancer, especially types 16 and 18. Here we refer to the possible routes of infection, oncogenic mechanisms, both benign and potentially malignant oral lesions associated with the infection, different methods used for detection, prediction and prevention of infection. We stress the importance of the role of the dentist to identify individuals considered high risk and ease of performing detection in the oral cavity, through a quick and easy method as exfoliative cytology.

Keywords: *Oral cavity, squamous cell carcinoma, HPV 16, HPV 18.*

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INTRODUCTION.

The Human Papilloma Virus (HPV) is the most common sexually transmitted infection in the world. It has an incidence of 5.5 million people worldwide[1] and 85% of the adult population would be carrier of this virus. However, this does not necessarily mean they have some kind of injury.

HPV consists of a double-stranded DNA containing 8,000 pairs of bases covered by a non-enveloped capsid in which three regions are identified. The first one is called "EarlyRegion". It corresponds to 45% of the viral genome and E1, E2, E4, E5, E6 and E7 genes[2], which are responsible for cellular regulation and transformation, can be found in it[3]. The second one is called "Late Region". It corresponds to 40% of the viral DNA and L1 and L2 genes, which encode viral capsid proteins, are found in it. The latter, called "Third Region LCR" or "Long Control Region" is responsible for regulating cell functions[2] (Table 1). This virus has a variation in the E6 and E7 genes and this allows to identify more than 120 subtypes of HPV[3], which are classified according to their oncogenic potential (Table 2)[1].

These various subtypes of HPV can cause benign, potentially malignant and malignant injuries in the skin, the anogenital area, the oral cavity and especially in the oropharyngeal area. In 1907, HPV infection was associated to benign lesions for the first time. Then, in 1976, ZurHausen proposed that HPV has a causal role in cervical cancer and, in 1983, Syrjanen *et al.* proposed it has a role in head and neck cancers[4]. Among the benign lesions, there are the papilloma, vulgar wart and the condylomata acuminatum[3]. Dysplastic and neoplastic lesions were mainly associated with HPV subtype 16. From among these lesions, the squamous cell carcinoma (SCC) of the oropharynx is mainly highlighted[5]. This is based primarily on the epitheliotropic characteristics of HPV, because of the morphological resemblance between the genital and oropharyngeal epithelium and the etiologic role this virus has in cervical cancer[4].

The importance of determining the presence and type of HPV in oral and pharyngeal samples of SCC is based on existing epidemiological, histopathological, molecular

Table 1. Viral genome and protein functions[1].

FUNCTION
E1 Initiation of DNA replication and transcription.
E2 Control of DNA replication and transcription.
E4 Cytoskeleton disruption.
E5 Interaction with cellular proteins.
E6 Degraded p53.
E7 Rb protein binding.
L1 It encodes viral capsid proteins for the production of new virus.
L2 It encodes viral capsid proteins for the production of new virus.

Table 2. Human Papilloma virus genotype and its oncogenic risk[1].

TYPE OF ONCOGENIC RISK	TYPES OF HUMAN PAPILLOMA VIRUS
High	16, 18
Intermediate	31, 33, 35, 39, 45, 51, 52, 58
Low	6, 11, 42, 43, 44

Table 3. Difference between HPV positive and HPV negative oropharyngeal cancer[1].

AGE	HPV POSITIVE 30-50 YEARS OLD	HPV NEGATIVE 50-80 YEARS OLD
Risk factor	Number of sexual partners, history of sexually transmitted disease.	Cigarettes and alcohol.
Incidence	Increasing	Decreasing .
Location	Base of tongue, tonsil.	Oral mucosa .
Field cancerization	No.	Yes.
Histology	Basaloid, poor differentiation.	Different degrees of differentiation.
Biomarker	p16 overexpression, p16 and pRb inactivation.	p16 loss, pRb mutation, overexpression of epidermal growth factor.
Chromosome Mutation	Less frequent.	Frequent .
Prognosis	Very good, good response to chemotherapy and radiotherapy.	Variable.
Metastasis	Rare	Frequent.
5-year survival rate	60-90%	20-70%

Table 4. HPV associated oral lesions diagram [3,12].

BENIGN LESIONS	POTENTIALLY MALIGNANT LESIONS	MALIGNANT LESIONS
Squamous papilloma	Leukoplakia	Spinous cell carcinoma
Verruca vulgaris		
Condyloma acuminatum		
Focal epithelial hyperplasia		

and even post treatment evolution differences between different samples or SCC which are or not associated with HPV infection. These differences can be observed in Table 3[1]. According to the above, it can be inferred that SCC samples associated with HPV have a less aggressive biological behavior.

The increase in HPV-associated oral lesions and their consequent oncogenic potential has led to make a narrative literature review regarding HPV and its role in oral cancer. Below, it talks about the possible routes of infection, oncogenic mechanisms, oral lesions associated with the infection (benign potentially malignant and malignant), different methods used for its detection, prognosis and prevention, highlighting the role dentists plays. Finally, there will be authors' comments on the issue.

HPV FEATURES.

Transmission.

The mode of transmission of HPV to the oral mucosa is not clearly known yet. The infection usually starts early in life and it has been demonstrated the presence of this virus in 6% of children, 13% of adolescents and 23% of adults[2]. It can be spread vertically and/or horizontally. The first one is a perinatal transmission of cervical origin. The second one, which is considered as the primary means of transmission, is sexual and is caused through oro-genital contact producing micro traumas in the mucosal when in contact with the virus[3].

Recently, HPV has been detected in histopathology sections of most patients diagnosed with oral cancer and who have a sexual history linked to more than one sexual partner, coupled with oro-genital contact, compared with histopathology sections of patients who have also been diagnosed with oral cancer but have not participated in these kind of practices. Therefore, this could be considered as important data in the virus transmission[6].

HPV infects squamous cells because it has an affinity for the epithelium[7], which is where virus replication takes place. This depends on the proteins encoded by the viral

genome and the differentiation degree of the infected cell[3]. First, HPV infects the basal epithelium cells, but there is a limited expression of viral genes in these cells and additional genes of the virus start expressing as epithelial cells differentiate[7-8]. Mature virions are produced in the granular layer, resulting in perinuclear vacuolization which is a characteristic of the epithelial cells called koilocytes, which are finally released into the stratum corneum[7].

Oncogenic mechanism.

HPV infection was first associated with cervical cancer and it has been found that the Papilloma Virus 16 and 18 are mainly involved[9].

The possibility for the Human Papilloma Virus becoming involved in carcinogenic mechanism depends on the type of virus which infects the epithelial cell, the synergistic action with different agents (physical, chemical and/or biological), genetic constitution and the host response immune[3].

High oncogenic risk viruses insert their viral genome into the host keratinocytes. The integrated part of the viral genome into the cell corresponds to E1, E6 and E7 regions, while E2, E3, E4 and E5 regions get lost (Table 1). The loss of E2 region during the integration process results in loss of control of the E6 and E7 regions, which are directly related with the cell cycle, by inhibiting the normal functions of the p53 and pRB proteins, respectively. These two proteins regulate normal cell division. The first produces transcription factors required for progression through the cell cycle. This denotes that RB prevents the cell from dividing until enough proteins have been isolated for cell division. E2F is the protein which produces Rb, making it a suppressor gene which prevents the cell cycle from continuing. When HPV infects a cell, E7 gene binds to Rb so that it releases E2F gene, being an advance signal for the cell cycle. So, as long as E7 gene remains stationary to Rb, the cell cycle continues in an uncontrolled way, which is a characteristic of malignancy[8]. Furthermore, when the DNA of a cell is damaged, p53 stops cellular division and repairs DNA. If this is not possible, this protein induces apoptosis, ensuring that the damaged cell dies and is not reproduced. The viral protein E6 can bind to p53 and inactivate it. This allows the virus to replicate in the cell, since p53 gene, inhibited by the virus, cannot stop it or start the process of cell death[8-9].

The role of the immune response against HPV is unclear[3]. This response is cellular and humoral. The first one is characterized by the involvement of natural killers, CD4 lymphocyte inducing an adaptive immune cytotoxic response mainly directed to the early E6 and E7 proteins[10]. Regarding the humoral response, IgA, IgM or IgG antibodies reach their maximum values 6 to 12 months after being infected[3-11]. Antibodies are raised against the viral capsid proteins and early viral proteins including the E6 and E7 oncogenic proteins[7-11]. The presentation of viral antigens mediated by cells is so minimal that the infection can be maintained for months or years without being detected clinically. Therefore, the absence of clinical evidence is not synonymous of the virus absence[12].

Oral manifestations associated with human papilloma virus infection.

The presence of HPV in the oral mucosa is associated with benign, potentially malignant and malignant lesions. Table 4[3-12].

BENIGN LESIONS.

Squamous papilloma.

It corresponds to a papillary growth of the squamous epithelium[13] and is mainly associated with HPV types 6, 11[13-14] and HPV 18[13].

It presents an estimated prevalence of 1 in 250 adults[13]. This injury is more common in children and has the same frequency in men and women. It is preferably found in the soft palate, tongue and lips. However, other areas of the oral mucosa can be affected as well.

Clinically, an increased soft exophytic mass with numerous verrucoid projections, pedunculated, normal color, white or slightly red, asymptomatic and approximately 0.5 cm diameter is observed.

Histopathologically, an intense proliferation of squa-

mous epithelium in papillary growth with projections surrounding connective tissue is seen. Generally, the basal epithelial layer has hyperplasia, mitotic activity which may involve higher strata. Also, sometimes koilocytes can be observed in the spinosum stratum, corresponding to clear epithelial cells with pyknotic nuclei altered by viral infection[15].

Verruca vulgaris.

Common wart is the most prevalent injury of different HPV-associated lesions and affects both the skin and the oral mucosa. The most affected areas in the oral mucosa are keratinized, i.e., the hard palate and gingiva and this is because of their histological similarity to the skin. HPV types which are more closely associated with oral mucosal warts are 2, 4 and 57[16].

Clinically, a papule or nodule with papillary projections is observed. It may be sessile or pedunculated. Most of them are white but they can also be pink.

Histologic features include intense epithelial proliferation with papilliform projections on the connective tissue, hypergranulosis and koilocytes in the spinous layer[16].

Condyloma acuminate.

It is a warty lesion associated with infection due to HPV 6 and 11 and occurs in the oral and anogenital mucosa. In adults, it is sexually transmitted and can be passed on through contaminated objects in children under two years old[5].

The oral lesions are usually in the labial mucosa, soft palate and lingual frenulum. It is seen as a well-defined exophytic mass. It is sessile, pink and tends to be larger than the common wart (1 to 1.5 cm).

Histopalogic features include intense epithelial proliferation with papillary projections and crypts of keratin between them. Koilocytes are observed in the surface layers and these are less prominent than in genital lesions[15].

Focal epithelial hyperplasia.

This lesion was first described as multiple nodules in the oral mucosa in 1965 by Archar *et al.* It is more prevalent in children in India (37%) and has been associated with HPV types 13 and 32.

It affects the labial mucosa, buccal and lingual and multiple rounded nodular lesions with flat surface and pale pink are observed.

Histopathologically, it can be observe a hyperplasia of stratified squamous epithelium, thick and elongated ridges, koilocytes in the surface layer and sometimes nuclei of the keratinocyte are altered resembling mitotic figures[15-16].

POTENTIALLY MALIGNANT LESIONS (CANZERISABLE).

The presence of HPV in potentially malignant lesions is important because it suggests the possibility of playing an important role in malignant transformation, which highlights the non-homogeneous leukoplakia. It is estimated that the prevalence of this virus in these lesions ranges from 0 to 85% and is mainly associated with virus type 16 and 18[2-17]. This wide variation in the range may be related to demographic variables, differences in the categorization of the studied lesions, differences in sampling, as well as the sensitivity of the technique employed for molecular detection[2].

The role this virus plays in oral leukoplakia, as well as in its pathogenesis and malignant transformation, is unclear. But this mechanism can be explained through the action of HPV E6 and E7 proteins which promote keratinocyte to recommence the S phase of the cell cycle resulting in altered epithelial proliferation and maturation[2,3,12,18,19].

The most frequent morphologic features in HPV associated with dysplasia are the presence of eosinophilic cells distributed throughout the thickness of the epithelium, due to the presence of apoptosis and cytological changes such as hyperchromatism[20].

MALIGNANT LESIONS.

The presence of intraoral SCC associated with HPV is specially set up at the base of the tongue[2,6,17,19]. Nevertheless, when considering the larynx and oropharynx, it is more frequent in the last one. When determining the pre-

valence of HPV associated with these different areas with presence of SCC, it is statistically significantly higher in the oropharynx (48.5%) than in the oral cavity (32.5%) and larynx (30%). When comparing its presence in relation to different geographical areas, it has been reported that Asia has a prevalence of 49.1%, Europe 25.6% and America 23.8%[21].

By observing these data, it can be inferred that there is a high incidence of HPV infection in patients with SCC, suggesting it has a relevant role in its etiology. The largest association of HPV infection in the oropharynx can be understood by the morphological difference with the epithelium of the oral cavity and its similarity with the epithelial and lymphoid tissue in the uterine endocervix. Furthermore, the differences registered in location can be attributed to different ethnic groups, the environment, lifestyle and health conditions. In Europe and America, it is primarily associated with sexual activity and number of partners[21].

According to an analysis by the International Agency for Research on Cancer (IARC), there is an increased incidence of cancer in the world's poorest regions: Africa, Southeast Asia, India and Latin America. Also, there are divisions among their socioeconomic levels in each country, showing that men from most vulnerable groups have a greater risk of developing and dying from oropharyngeal cancer and the most vulnerable women are at higher risk of contracting and dying from esophageal cancer[22].

The main types of virus associated with the genesis of SCC are high risk, especially types 16 and 18[23] and less frequently types 8, 31, 38 and 66. Regarding the presence of HPV specifically types 16 and 18, in the study by Kreimer *et al.*, it was found that out of 2642 biopsies of SCC of head and neck, 16% were positive for HPV16 and 3.9% at 18 and 23.5% was associated with SCC specifically in the oral cavity and the oropharynx 36.5%[6-24].

Patients with oropharyngeal cancer associated with HPV are characterized by being younger (5-10 years) than patients with carcinomas not associated with HPV. They are usually not smokers or alcohol drinkers and the risk of developing it is equal in men and women[23].

DETECTION METHODS.

There is no standard method for the detection of HPV in the oral cavity. However, currently, virological laboratories provide a kit containing a sterile cytology brush and a tube for transportation. Then, the oral mucosa is brushed and it is possible to obtain epithelial cells where viral DNA is detected through chain reaction (PCR). It is important to highlight the quality of the nucleic acids in formalin-fixed paraffin-embedded samples is low. Therefore, it is not recommended to obtain viral DNA from these samples[25].

Other molecular techniques, such as in situ hybridization and Southern Blott, are known for detecting nuclear DNA. But,from among these different types of methods, it is preferably to use PCR, since it has been seen that the other types of procedures mentioned detected a loweramount of viral DNA[6].

PROGNOSIS.

SCC associated with the presence of HPV has a better prognosis[11,24,26] and a lower mortality rate than the one which is not associated with HPV[13]. The reason for this is unclear. However, this might be explained by the ability of HPV positive cancer cells to produce apoptosis in response to DNA damage. Another reason could be the inability to induce neoplastic transformation in uninfected cells into cancer cells. Thus, it is easy to understand why a HPV-positive SCC does not induce multifocal lesions[11].

PREVENTION.

Prevention of HPV infection has recently been achieved by developing vaccines based on the use of virus-like particles (VLP). VLP are obtained by synthesis and autoassembly in vitro of the main proteins of major capsid of HPV virus. These are morphologically identical to HPV virions but do not contain viral DNA and this means that they cannot transmit the virus or cause disease, but do induce the generation of neutralizing antibodies and

confer protection against HPV.

There are two types of prophylactic vaccines: Bivalente Cervarix, which protects against types 16 and 18 and Quadrivalent Gardasil, which protects against types 6, 11, 16 and 18. These vaccines are administered intramuscularly in three doses, at two and six months respectively after the initial dose and are effective for 3 to 5 years[2].

Depending on the natural history of HPV infection and mainly cervical neoplasia, it seems logical that vaccination would be before initiation of sexual activity. The Advisory Commite on Immunization Practice (ACIP) recommends that primary vaccination is done between 11-12 years old, but there is also a range between 9 to 26 years approved by the Food and Drug Administration (FDA)[27].

Herrero *et al.* reported that vaccination against high-risk subtypes (16 and 18) decreases the prevalence of the oral infection. It is estimated that the efficacy of vaccination would be about 93% (95% CI 62.2% to 99.7%). The author also suggested that the vaccine is effective when given to patients who have not been exposed to HPV[28].

It must be considered that these vaccines are not a treatment for infections. Instead, they provide a benefit if the person receives it before being sexually active[13].

Routine vaccination programs have been implemented in several countries with satisfactory results. Australia showed that a routine program for men and women is effective and successful, proving a reduction of 77% of genital warts for women in the age range of 12-17 years old and a reduction of 44% is observed in men. The same results were observed in Rwanda, Africa. It has been observed that vaccination against HPV-16 to prevent the infection of the uterine cervix would also have an effect on the infection by HPV-16 at oral level. However, further studies are needed to confirm this theory[29].

FINAL COMMENT.

The relationship between HPV infection and cervical cancer has been well established and its presence has been observed in 90% of intraepithelial neoplasias. This has increased interest in discovering whether there is a positive association between HPV infection and oral cancer. Despite several studies on this subject, the results are not conclusive to date. For example, Kreimet *et al.* found a prevalence of 24% of HPV presence in SCC, while other studies have found that the prevalence of HPV-associated oropharyngeal cancer is 35%. Näsman *et al.* observed an increased incidence among tonsillar cancer associated with the presence of HPV, 23% in 1970 to 93% in 2007[24]. A study by Lopes *et al.* attempted to establish the prevalence and relationship between the research of HPV and HPV 16-18 in oral carcinomasby using PCR and Q-PRC. This study suggested that HPV, as anoncogenic factor, is uncommon and only high viral load numbers would have a causal relationship[30].

In Chile, both in SciELO Chile and the Health Ministry database, there are no available epidemiological data on oral lesions associated with HPV. So, we are working on keratinized mucous detection in both groups with and without factors risk. However, in data obtained from the IARC about incidence and mortality of the oral cavity cancer in South America, it is observed that the incidence for men is 2.5% while the mortality rate is 1.8%. The incidence for women is 1.4%, and the death rate is 0.9%[31].

It is noteworthy that this year the vaccine against HPV will be incorporated as part of the national immunization program, benefiting all girls aged 9. It will be administered in schools and then be reinforced in a year in order to protect from cervical and oropharyngeal cancer. Although the development of genital lesions associated with HPV is more important in women, vaccinating men could also be promoted since indicators of oral health show some increase in oral SCC and HPV involvement.

Considering and highlighting the major route of virus inoculation is sexual and it is asymptomatic, it would require significant health policies and appropriate preventive efforts which involve both the medical and dental profession. Therefore, a correct history and clinical examination by the dentist in order to identify individuals considered high risk, such as those who start their sexual history early, have promiscuous sexual behavior,

oral-genital contact, and history of warty lesions in other anatomic areas, is important.

Because of the association of this virus with the development of potentially malignant lesions and oral carcinomas, it is recommended to primarily search throughout verrucoide like injuries, as this virus tends to produce epithelial proliferation and malignancy and in every malignant lesion of epithelial nature. This can be done quickly and easily in the clinic by a general dentist using a kit with a cytology brush provided by laboratories which then confirms its presence through PCR tests.

Finally, the importance of promoting sex education campaigns and prevention with the vaccine against the virus can be highlighted. It has been noted in literature that the creation of public policies on education and awareness about HPV are primary preventive measures which have a large social impact, are effective and simple to develop. In the gynecological area, prevention of HPV infection is widely described in literature, but not in the dental area[29].

Virus Papiloma Humano y cáncer oral: Revisión narrativa de la literatura.

Resumen: El Virus Papiloma Humano (VPH) en la actualidad constituye la infección por transmisión sexual más frecuente, presentando una incidencia de 5,5 millones en el mundo, siendo un 85% de la población adulta portadora de este virus. Su potencial oncogénico y el aumento de lesiones orales asociadas a infección oral por VPH nos han llevado a realizar una narración de la literatura referente al rol del VPH en el cáncer oral, especialmente de los subtipos 16 y 18. Nos referiremos a sus posibles vías de contagio, mecanismos oncogénicos, lesiones orales tanto benignas como potencialmente malignas asociadas a su infección, diferentes métodos utilizados para su detección, pronóstico y prevención de contagio. Destacamos la importancia del rol del odontólogopara identificar individuos considerados de alto riesgo y la facilidad de realizar sudetección en la cavidad oral, a través de un método rápido y sencillo como es la citología exfoliativa.

Palabras clave: *cavidad bucal, carcinoma espinocelular, VPH 16, VPH 18.*

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