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Virus del papiloma humano y el cáncer de cabeza y cuello: revisión de la literatura desde México y Colombia

Human Papillomavirus and Upper Aerodigestive Tract Neoplasm: A Review Literature from Mexico and Colombia

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RESUMEN
Antecedentes: Los papilovirus o virus del papiloma son considerados el grupo más prevalente de virus que causa tumores de cabeza y cuello asociados a la infección con virus del papiloma humano (VPH). *Objetivo:* Realizar una revisión sistemática de literatura acerca del VPH como agente causal del cáncer de vías aéreas y digestivas superiores (VADS), según información epidemiológica y clínica. *Métodos:* La búsqueda de literatura biomédica fue efectuada en varias bases de datos, como Medline, Proquest, Science Direct, Ovid y Cochrane, así como información disponible en páginas en internet de revistas y organizaciones nacionales. *Resultados:* Según revisiones sistemáticas sin hallazgos en Colombia, la prevalencia de VPH en el proceso de malignización de lesiones de VADS es 35,6% en orofaringe, 23,5% en cavidad oral y 24% en laringe. En el mundo, la prevalencia de cáncer de cabeza y cuello producido por VPH de alto riesgo, como el VPH 16, es aproximadamente del 30,9% en orofaringe, 16% en cavidad oral y 16,6% en laringe. Esta revisión destaca los genotipos de VPH de bajo riesgo (VPH 31, 45, 6 y 11). Se muestra la efectividad del método PCR-RFLP como punto de partida para monitorear la infección y su progresión a cáncer, comprender su virulencia y contribuir a la disminución de las tasas de incidencia a causa de las imprecisiones de diagnóstico clínico por metodologías convencionales que dificultan la detección precoz del CVADS.

PALABRAS CLAVE
Cabeza y cuello, cáncer, detección temprana, papilomavirus, PCR-RFLP.

ÁREAS TEMÁTICAS
Diagnóstico, epidemiología, medicina oral, oncología.

ABSTRACT
Background: Papillomavirus or papilovirus is considered the most prevalent group of viruses that cause tumors of head and neck associated with infection with human papilloma virus (HPV). *Purpose:* Carry out a systematic review of literature on HPV as causal agent of upper aerodigestive tract neoplasm (UADTN), according to epidemiological and clinical data. *Methods:* Pertinent biomedical literature was searched in several databases such as Medline, Proquest, Science Direct, Ovid and Cochrane, as well as available information from websites of national journals and organizations. *Results:* According to systematic reviews that did not show findings in Colombia, the prevalence of HPV in the process of malignant lesions of UADTN is 35.6%, in the oropharynx, 23.5%, in oral cavity, and 24% in larynx. Worldwide, the prevalence of head and neck cancer produced by high-risk HPV, such as HPV 16, is approximately 30.9% in oropharynx, 16% in oral cavity and 16.6% in larynx. This review also highlights that the genotypes of low-risk HPV are HPV 31, 45, 6 and 11. It emphasizes the effectiveness of the PCR-RFLP method as the starting point to monitor the infection and progression into cancer, to understand its virulence, and to contribute to reduce incidence rates because of the inaccuracies of clinical diagnosis by conventional methods that hinder the early detection of UADTN.

KEY WORDS
Early detection, head and neck, neoplasm, papillomavirus, PCR-RFLP.

THEMATIC FIELDS
Diagnostics, epidemiology, oncology, oral medicine.

Artículo de revisión de la literatura que hace parte de trabajo de colaboración de los autores en Colombia y México.

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INTRODUCTION

Papilovirus or papiloma viruses are involved in the etiology of various forms of epithelial neoplasms in humans. They are considered the most prevalent groups of neck and head tumor causing viruses associated to the infection of human papilloma virus (HPV) (1).

According to systematic reviews based on studies in 26 countries of the world, with no findings in Colombia, the prevalence of VPH in the process of malignant lesions of the upper aerodigestive tract in oropharynx UAT is 35.6%, 23.5% in oral cavity and 24% in larynx. Worldwide, the prevalence of head and neck cancer produced by high risk VPH such as VPH16, is approximately 30.9% in oropharynx, 16% en oral cavity and 16,.6% in larynx. The low risk VPH genotypes are VPH 31, 45, 6 y 11, which, according to reports, induce precancerous lesions outcome (2).

A large number of reports support the hypothesis that specific types of human papilloma virus exist which play a central role in the pathogenesis of precursory UATN lesions and even exist VPH type variations at inter population level; so for science it is relevant to clarify the VPH types related to this malignant transformation sequence by means of molecular typing. Furthermore, to add to this purpose, the clinical diagnose imprecision done by conventional methodologies that difficult the early detection of cancer of upper aerodigestive tract. Nevertheless, multidisciplinary studies with PCR-RFLP, molecular diagnosis done by geneticists, dentists and clinicians, are so strong that contribute to the decision making of prevention and control of one of the most aggressive and lethal malignancies, with multiple etiologic factors, high metastatic potential and with the feature of being cumulative over time (3,4). Therefore, it's necessary this systematic review about human papillomavirus (HPV) as causal agent of upper aerodigestive tract neoplasm according to epidemiological and clinical information.

UPPER AERODIGESTIVE TRACT NEOPLASM

Cancer is the second leading cause of mortality in developed countries and is a health problem of indisputable importance. The head and neck cancer (HNC) accounts for 5-10% of all malignancies (5,6). Squamous Cell Carcinoma of the Head and Neck affects 550,000 new patients worldwide annually (7). The head and neck cancer (HNC) accounts for 5-10% of all malignancies in Colombia (6,8). In countries like Mexico, the prevalence of head and neck cancer ranges from 3-9%, according to a recent 24 years follow-up study (9). If it revises the localization of upper aerodigestive tract as oral cavity, the estimated lethality is 36.8% (10).

The head and neck cancer includes some anatomical regions and that because of their location and lymphatic spread have very different treatment. It represents 5-6% of all tumors. It is more common in men than in women and has its highest incidence in the fifth and sixth decades of life. It affects such important functions such as speech and swallowing. It includes the following locations: nasal cavity and paranasal sinuses, nasopharynx or nasopharyngeal, oral cavity, oropharynx, larynx, hypopharynx and salivary glands. The most common histological type is squamous cell carcinoma. There are premalignant lesions such as dysplasia and frequent occurrence of second tumors (11). It can stay subclinically for a long time and symptoms may appear when the disease has reached and advanced stage. Its main feature is the easy dissemination to cervical lymph nodes, metastasis is rare, being, when it occurs more frequently in the lung (12).

The frequency of head and neck cancer varies with the specific anatomical location, oral cancer is the most frequent with 40.6%, tongue 21%, gums 5%, floor of the mouth 2%, lips 2.5%, other oral mucosal locations 14.1%, in salivary glands is 15.3%; pharyngeal cancer accounts for 15% (5.7% oropharynx, 4.7% nasopharynx, 4.8% laryngopharynx) and unspecified sites cover the other 24.8%. The head and neck cancer includes some anatomical regions that because of their location and lymphatic dissemination have very different treatment. It is more frequent in men than in women and has its highest incidence in the fifth and sixth decade of life (13).

HUMAN PAPILLOMAVIRUS (HPV)

The human papilloma viruses (HPV) are a diverse group of DNA viruses that infect the skin and mucous membranes of humans and a variety of animals. There are more than 100 different types of HPV. Some types of HPV can cause warts while others subclinical infections resulting in precancerous lesions. All HPVs are transmitted by skin to skin contact. These are viruses that do not have very stable membrane envelope. They withstand adverse environmental conditions and are highly infectious (14).

Between 30 and 40 HPV are typically transmitted through sexual contact and infect the anogenital region. However, there have also been reported oropharyngeal infections

and tonsillitis caused by them. Within papilloma viruses that can affect humans, there are some with or without oncogenic effect, which can be classified as high and low risk, some of the sexually transmitted types (types 6 and 11), can cause genital warts. While others may infect the genitals and cause no appreciable signs of infection (15-17).

Persistent infection by the sub-group known as *high risk*, which includes about 13 types of sexually transmitted HPV virus, we find the types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 (18), which are different from those that cause warts. They may promote the development of: (a) CIN (cervical intraepithelial neoplasia); (b) VIN (vulvar intraepithelial neoplasia); (c) PIN (penile intraepithelial neoplasia); or (d) AIN (anal intraepithelial neoplasia) (19). These are precancerous lesions and can progress to invasive cancer. An HPV infection is a necessary factor in the development of nearly all cervical cancers and some head and neck (20).

Genotypic differences between the types of papilloma virus are marked by the different amino acids that form the L1 protein (structural protein of the virus that also has antigenic effect.) The properties of this protein allow the virus to be treated as "low or high risk" and therefore their specific genotype is used to classify these viruses. According to the genotype of the L1 protein, we can classify the virus as type 16 L1, L1 HPV type 18 or type 16, HPV type 18. The HPV life cycle program strictly follows the differentiation of the keratinocyte host cell. It is thought that HPV virion infects epithelial tissues by microabrasion, where the virion is associated with putative receptors such as alpha integrins and laminins, entering the virions into basal epithelial cells through clathrin-mediated endocytosis and / or endocytosis caveolin-mediated, depending on the type of HPV. At that point, the viral genome is transported to the nucleus by unknown mechanisms and it sets (settles?) with a number of copies between 10-200 viral genomes per cell (21).

Then to divide the host keratinocyte and increase differentiation in the upper layers of the epithelium, a complex cascade-mechanism of transcription occurs. It is thought that viral oncogenes E6 and E7 alter cell cycle, keeping the differentiated keratinocyte in a friendly state for the amplification of viral genome, replication and subsequent late gene expression. In the upper layers of the epithelium of the host, the latest genes L1 and L2 are transcribed / translated and serve as structural proteins that are encapsulated for the amplified viral genomes. The virions can then be released in the dead skin flakes of the host epithelium and the viral life cycle continues. This disease currently has no cure, but in general the body eliminates (restrains, controls), it over time. It is believed that knowing if a man has or has had HPV at some point in life, it is not very important to the health of a man, unlike the case of a woman, as the chances of developing cancer are higher (22).

About a dozen types of HPV (including types 16, 18, 31, 45) are called *high risk* types because they can trigger cervical or upper aereodigestive tract cancer given the similarity? Or also anal cancer, vulvar cancer, cancer of penis. Several types of HPV, particularly type 16, have been found associated with oropharyngeal squamous cell carcinoma, a form of head and neck neoplasm. HPV-induced cancers often have viral sequences integrated into cellular DNA. Some of the "early" genes of HPV, E6 and E7, are known to act as oncogenes that promote tumor growth and malignant transformation (23).

The p53 protein prevents cell growth in the presence of damaged DNA primarily through the X protein domain associated with BCL-2 (BAX) (which blocks the effects of antiapoptosis BCL-2 receptor, mitochondrial. In addition, p53 also regulates p21 protein, blocking the formation of the cyclin D/Cdk4 complex, thereby preventing phosphorylation of RB and, in turn, causing hesitation cell cycle progression by preventing the activation of E2F. In short, p53 is a suppressor gene tumor that arrests cell cycle when DNA is damaged. E6 and E7 proteins work by inhibiting the tumor suppressor genes, in such a process: E6 inhibits p53, while E7 inhibits p53, p21, and RB (24).

A history of infection with one or more types of high-risk HPV is believed to be a prerequisite for the development of cancer (the vast majority of HPV infections are not of high risk). The sexually transmitted HPV can also cause a greater fraction of anal cancer and approximately 25% of cancers of the mouth and throat (oropharynx) (25). The latter is common in the area of the tonsils, and HPV is linked to the increase in oral cancer in nonsmokers. The contact of anal sex or oral sex with an HPV infected partner may increase the risk of developing these cancers (26).

HPV IN UPPER AERODIGESTIVE TRACT

In a study, Schwartz and colleagues examined samples of oral cavity mucosa and serum to diagnose HPV 16 in patients without lesions compared with patients with

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tumors of the oral cavity, and their results suggested a close relationship between HPV and cancer (26% in tumors and 9% in patients without lesions, seropositivity in 35% of the controls and 75.5% in HVP plus tumor). They also found that alcohol and cigarette consumption increases the risk of oral cancers associated with HPV type 16. On the other hand, recent studies examine the association between HPV along with p53 mutations or the suppressor gene of retinoblastoma (Rb) and suggest the association between HPV and squamous cell carcinoma of head and neck (27).

Some studies conducted in different populations of patients with head and neck cancer have identified HPV DNA in diagnosed tumors. And they suggest that there is enough evidence for the important role of HPV infection in the pathogenesis of some types of head and neck carcinomas, mainly in oral cavity and oropharynx (28).

In a study conducted at the Hospital de Niños "JM de Los Ríos" in Caracas, 53% of the processed samples in youngsters, HPV types, 4 of the type VPH 6 and 4 of the HPV type 11, were determined. In relation to the prevalence of asymptomatic infection in the oral cavity in adults it is estimated to be between 5% to 11% depending on the sample and the diagnostic procedure performed. HPV types both low and high risk are found in similar frequency. HPV infection is associated with the upper digestive tract in benign lesions, including focal hyperplasia, sinus inverted papilloma, juvenile and adult papillomatosis especially in the respiratory tract. These lesions are usually associated with low risk HPV infection, that is to say 6 and 11. Malignant transformation of injuries associated with low-risk HPV is rare, but cases have been reported especially with all inverted papillomas (29).

In a study of molecular typing of HPV in oral cavity, found a relationship between smoking habits, consumption alcohol and positive for HPV16 in the tissue, because 75% of cases was consistent with moderate and poorly differentiated tumors. Likewise, the authors recommend further study of the relationship between injury affected by the virus, concomitant genital disease to establish whether these patients, if the mode of transmission is oral or genital, and vaccine development prevention in asymptomatic individuals infected by HPV at risk of developing tumors in the oral cavity (30).

Of the nearly 100 genotypes of HPV detected as infectious to humans, the 15 genotypes considered as high risk, are the necessary cause for cervical cancer and have been implicated as carcinogens in the vulva, vagina, penis, anus and oropharyngeal cavity Among the most important are HPV 16 and 18. For their part, HPV 6 and 11, considered as low risk for cervical cancer, are responsible for 90% of genital warts (condylomata) and recurrent respiratory papillomatosis RRP and suggest that molecular typing is necessary for HPV infectives for the prevention and management of populations at risk of developing cancer in any of the aforementioned anatomical locations (31).

HPV infections similar to those anogenital, suggest that HPV 6 and 11 are the most common types associated with benign lesions of Squamous cells in the oral cavity, pharynx and sino-nasal mucosa, while HPV 16 and 18 have been found in premalignant lesions and squamous cell cancer (32). The number of copies of HPV DNA is low in head and neck carcinomas, except in tonsillar carcinoma, indicating that there is a clonal association of these tumors. The HPV detection rate of 51% in tonsillar carcinomas is the highest among human malignant tumors. Out of the known and emerging HPV lesions tonsillar carcinomas have special characteristics (33).

Some recent epidemiological studies, multicentered and case-control studies, have confirmed that HPV is a risk factor for developing oral cancer, with an OR (odd ratios) between 3.7 and 5.4. By 2002, 4768 oral carcinomas were analyzed for HPV infection and 22% reported to contain HPV DNA by any of the detection techniques. Of all the non-genital cancers, carcinomas of the tonsils, seem to have the highest prevalence of HPV. Towards the end of 2002, 422 cases of carcinoma of the tonsils were analyzed for HPV DNA, found a detection rate of 51%. HPV 16 is the most prevalent type found in 84% of tumors positive for HPV DNA (34). The HPV detection rates reported in head and neck cancer do not give a detailed overview of the association of HPV in different conditions and even less detailed at anatomical location level. For its part, the role of HPV in laryngeal carcinomatosis remains controversial. Therefore, future studies that lead to explain the molecular mechanisms associated with head and neck carcinogenesis associated with HPV are needed, but not before securing the data from molecular epidemiology (35).

MECHANISM OF INFECTION HPV

The HPV life cycle strictly follows the process of differentiation of the host cell. The HPV virion infects epithelial tissues by microabrasion, where it associates with receptors such as alpha integrins and laminins.

Virions enter the basal epithelial cells through clathrin-mediated endocytosis and / or caveolin-mediated endocytosis, depending on the HPV type. At this point, the viral genome is transported to the nucleus by still unknown mechanisms and is settles with a number of copies, between 10-200 viral genomes per cell. Then occurs a complex cascade mechanism of transcription, the dividing host cell, increases the differentiation in the upper layers of the epithelium (36).

As a result of the multiplication, the viral genome enters the host cell and then activates genes of early expression of its genome or so-called genome E. The oncogenic role of E6 and E7 genes should highlighted, which alter the cell cycle by their ability to inactivate p53 and pRB (retinoblastoma protein), respectively, and induce alterations in cell cycle by deregulation of tumor suppressor genes. In the upper layers of the epithelium of the host, the L1 and L2 genes are translated into structural proteins that encapsulate the multiplied viral genomes. The virions can then be peeled off in the dead epithelial host flakes and continuing with the viral life cycle (37).

For its part, as normal p53 protein prevents cell growth in the presence of DNA damage primarily through protein domains associated with BCL-2 (BAX) which blocks the effects of antiapoptosis of the mitochondrial BCL-2 receptor. Furthermore, the protein p53 over-regulates protein p21 and blocks the formation of cyclin D/Cdk4, and so prevents phosphorylation of pRB, and the normal cell cycle progression by inhibiting the activation of E2F. To sum up, p53 is a tumor suppressor gene that blocks the cell cycle when DNA is damaged. Proteins E6 and E7 work by inhibiting the tumor suppressor genes in this process: E6 inhibits p53, while E7 inhibits p53, p21, and RB (38,39).

HPV AND CANCER DEVELOPMENT

HPV transmission is currently through sexual relations; it is estimated that between the infection and the onset of injury, there may be a period ranging from three months to several years, there have been even reported cases where there is the presence of the virus but without any injury. Another form of infection is by vertical transmission from mother to child when the pregnant mother, carrier of HPV, transmits it to the fetus or newborn during the time of delivery (40,41).

A high-risk HPV infection is considered as a final condition for the development of cancer. The sexually transmitted HPV can also cause a greater fraction of anal cancer and approximately 25% of cancer in mouth and throat (oropharynx). The latter is commonly present in the area of the tonsils (42,43). The contact of anal or oral sex with an HPV infected partner may increase the risk of developing these cancers. HPVs are associated with all early cancers, 20% to 30% of head and neck cancer and other. Because the head and neck cancer are also in HPV-negative people, this kind of cancer generates interest in defining cancer similarities and differences between HPV-positive and HPV negative ones in the same tissue. In this sense, in a study that examined the expression profile of 84 patients with metastatic head and neck cancer, cervical cancer and samples of normal epithelial cells by capturing with laser microdissection revealed that HPV + head neck cancer and cervical cancer differ their patterns of gene expression and show many changes compared to those HPV-patients. It also showed the important role played by the E6 and E7 genes in the activation of oncogenes and cell cycle deregulation of host cells. This involves a new association of HPV oncogenes with specific expression profiles (44).

The squamous cell carcinoma of head and neck (HNSCC) has rates that vary widely in incidence and mortality worldwide, with the highest rates mainly in Southeast Asia and East Europe. The main risk factors for developing squamous cell cancer of head and neck are the consumption of cigarettes, chewing gum and alcohol (45). For 15 years, HPV infection is the necessary cause of cervical cancer. Among biopsies of patients with squamous cell cancer of head and neck, the true prevalence of HPV DNA remains unclear, some studies have estimated that over 60% of these cancers may be positive for HPV. The detection of HPV in tumor biopsies is not sufficient evidence of causing them, molecular biology studies have helped identify a subset of these cancers that could be caused by HPV infection, out of which, a subset has been found in the oropharynx . Of the 40 types known to infect the mucosal surfaces of the genital tract, 14 are detected in almost all biopsies from patients with invasive cervical cancer and, for that reason, they have been considered of oncogenic high risk. Some of these high-risk types (HPV 16, 18) have been found in the oral cavity and oropharynx of patients without cancer and in biopsies of patients with squamous cell carcinoma of head and neck (46-48).

The term *Head and Neck Cancer* includes injuries to several anatomical sites such as lips, oral cavity, nose, sinuses, nasopharynx, oropharynx, hypopharynx,

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larynx, esophagus, salivary glands and other soft tissues neck and ear (49).

DIAGNOSTIC METHODS

Virus Diagnostic Techniques Human Papillomavirus

1. Clinical examination.
2. Biopsy.
3. Cytology (Pap smear).
4. In situ hybridization using biotinylated probes (HIS).
5. Polymerase Chain Reaction (PCR).
6. Analysis of Immunohistochemistry IHC (50).

The most important method of detection of Virus Human Papillomavirus is:

Exfoliative Cytology

It is a simple technique, non-invasive, relatively painless and well accepted by patients, so it might be useful in early diagnosis of oral cancer. However, the use of oral exfoliative cytology for the diagnosis of epithelial atypia and especially of oral squamous cell carcinoma has become less important, especially because of its low sensitivity represented by the high number of false negatives. In terms of sampling the use of cytobrush appears to increase the number of cells collected per sample, and allows a better distribution of them on a slide, which may increase the sensitivity of the technique (51,52).

PCR-RFLP Typing

PCR-RFLP is used for the analysis of microsatellite markers, which are small repeated sequences of DNA but also has demonstrated effectiveness in the assessment of causative agents related to cancer development. Exfoliative cytology has been used in studies of molecular analysis for the assessment of genomic component of patients who have shown tumor development. Probably the molecular analysis becomes an essential technique in the diagnosis and management of oral cancer, which will be useful in carrying out preventive programs (53).

DNA markers have several advantages at the time of diagnosing and typing as they are not affected by environmental or process variation, they show the very basis of the variation of the specimens, they allow selecting specific regions within the DNA molecule for these kinds of studies. The number of polymorphisms detected is theoretically unlimited, it allows to analyze both the expressed as the non-expressed information and nowadays there have been developed a number of appropriate techniques for the diagnosis of diseases, among them, the PCR-RFLP's which allows the analysis of the genetic variability of the virus through different molecular patterns of their DNA. They represent changes along the DNA in specific-site cutting restriction enzymes for sequence changes (CFSCAN, 2003) (54). One of the molecular markers most widely used for studying and typing of Human Papillomavirus are E6 and E7 genes, which can be amplified by the forward primers GTTACCACAGTTATGCACAG and a first reverse TCATATACCTCACGTCGCAG for HPV 16 and ACCGCATGCATGCCATA and TGTGTCTCCATACACAGAGT and GP5/GP6 genes, ß-interferon and ß-interferon. This molecular approach has had a major impact on the diagnosis of the causative agents such as viruses in particular as regards the study of cancer development, to establish criteria for early diagnosis and treatment effectiveness (55).

DNA Extraction

During this stage, the molecular information needed for the analysis and typing of HPV is carried out. The methodology to extract DNA has specificities according to the virus species as well as all other process for obtaining molecular information. The most appropriate tissue is chosen in accord with the lesion and proceeds to macerate in a lysis buffer (1.0 M NaCl, 0.2 sucrose, 0.1 M Tris - HCl, pH 9.0) with 0.5 M EDTA and Sodium Dudocil Sulfate (SDS), it is centrifuged to homogenize the sample before incubating the mixture between 60 ˚C and 65 ºC for no longer than 30 min. It is subsequently added to the mixture, potassium acetate (KAc), this step should be performed on a bed of ice and left this for 15-30 min, then centrifuged at 12,000 rpm for 15 min. Supernatant is removed and placed in another tube with ET-OH 100%, immediately centrifuged at 12,000 rpm for 15 min. The supernatant is removed and added ET-OH 70% and again centrifuged at 12,000 rpm for 5 min. Finally removed the supernatant and the pellet is resuspended in TE containing RNase (5 µg/ml) (56).

Analysis PCR-RFLP

The RFLP'S is a technique by which two DNA sequences can be differentiated by analysis of different molecular patterns of this genetic material, which represents changes in the length of DNA between the cleavage sites of restriction enzymes specific for sequence changes, so if two DNA sequences differ from the distance of the cleavage sites of a particular endonuclease, the length of the restriction fragments generated for each of the DNA will be different, so the generated patterns allow, in this case, differentiate, for example, among

different types of Human Papilloma Virus (CFSCAN, 2003). The RFLP's technique is the combination of the in vitro amplification system of specific DNA segments and the cutting with restriction enzymes in order to increase the detectable level of molecular variation (57,58).

CONCLUSION

It is necessary to establish at an interpopulation level the typing of HPV in head and neck, especially in upper aerodigestive tract. Typing of HPV is the starting point in the monitoring of the infection and progression to cancer, to help improve the patients (54) quality of life and reduced incidence rates, which are unknown in many regions.

There are still uncertainties in clinical diagnosis due to conventional methods that hinder the early detection of cancer. Thus, molecular diagnosis with PCR-RFLP promises to be crucial in the decision making of prevention and control of the upper aerodigestive tract malignancies, as one of the most aggressive and lethal cancers, with multiple etiologic factors, with a high metastatic potential and with the property of being cumulative over time. Added to this, there is insufficient information about the variation of HPV types associated with precursor and malignant lesions in UADT in some populations, let alone multidisciplinary studies among geneticists, dentists and physicians toward that direction.

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