Chapter 9

The Role of Human Papillomavirus in Pre-Cancerous Lesions and Oral Cancers

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1. Introduction

The head and neck squamous cell carcinomas (HNSCC) are the sixth most frequent malignancy worldwide. It is properly established as heterogeneous solid tumor, composed by cells with different phenotypic features with malignant potential. Oral squamous cell carcinoma (OSCC) is a significant subset of the worldwide burden of HNSCCs. It is essential the understanding of the OSCC biology and biological behavior of pre-cancerous conditions and pre-cancerous lesions that may be responsible for malignant transformation. Heterogeneity in prevalence and anatomic distribution are associated to demographic differences in the habits of exposure tobacco and alcohol. The use of tobacco and alcohol are often established as risk factors for OSCC, but this phenomenon could also emerge in individuals not exposed to them. As OSCC, the pre-cancerous lesions also present a strict connection to tobacco consumption. However, a relationship between alcohol carcinogenic effect and pre-cancer lesions are not clear. These populations that develop the pre-cancer lesions or OSCC in the absence of prior contact with risk factors suggest that others factors can play a role in head and neck carcinogenesis. There is a longstanding analysis, over the past 2 decades, whether the human papilloma virus (HPV) infection could have a role in the OSCC carcinogenesis. HPV were first established as cancer development agent in cervical cancer, succeeding reports established the HPV infection in mucosal tissues of the oral cavity upper gastrointestinal tract, anogenital tract. In cervical cancer the categorization subdivided the HPV types into low-risk high-risk types, only the types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 58 are consistently grouped as high risk. The high-

risk types 16 and 18, as in the cervical and anogenital cancer, are the most common entities detected in pre-cancerous and HNSCC lesions. Miller & Johnstone [1] describe that likelihood of detecting HPV, comparing pre-cancerous lesions and HNSCC to normal epithelium, was three times higher in pre-cancerous lesions and four a five times higher in HNSCC. In despite of large number of studies, the accurate role of HPV in the HNSCC development and progression has been controversial so as in OSCC. HPVs are a circular virion enclosed in a small capsid. The carcinogenic process occurs through the HPV-DNA integration into host cell. Usually, the viral oncoproteins codified by HPV-DNA, leads a functional alteration in p53 and pRb pathways, and consequently genomic instability. However, the oncoproteins expression alone is not sufficient to induce neoplastic transformation suggesting the requirement of supplementary genetic modifications. Increased understanding of the role of HPV antigens in neoplastic pathogenesis confirms the HPV as an etiological agent for cancers and, the knowledge of HPV cancer biology consequently will provide the development of preventive vaccines and antiviral treatment. The HPV vaccines have been formulated as a result of core technologies implementation that is able to construct virus-like particles (VLPs) equivalent to natural virions but, at the same time, are not capable to induce an infectious process. In addition, in this chapter we will discuss the HPV relationship with the pre-cancerous lesions and OSCC. The present data summarize the knowledge regarding the epidemiology, behavior, biology, malignant transformation mechanisms, and prognosis of HPV infection.

2. A brief history of papillomavirus and cancer

Human Papillomavirus infection was firstly identified from the embalmed body of a 12th century B.C. ancient Egyptian worker [2]. During the mummy necropsy procedure Scientists observed a wart on the sole of his foot. This evidences demonstrated that HPV infection occurred [3]. Medical literary tidings regard skin and genital warts were described in classical Greek and Roman literature [2]. However, association between viral origin of warts and sexual transmission was only confirmed in 19th century [2]. Rigoni-Stern (1842) hypothesized that cervical cancer could be promoted through sexual contacts. The Italian physician postulated this conception through the observation of high rates on cervical cancer in sexually active women, in comparison with non-sexually active women. [4]. Essays to establish relationship between cervical cancer and HPV-infections were initiated in 1972, this hypothesis was supported by a rare description of condylomata acuminate malignant transformation into squamous cell carcinomas highlighting the carcinogenic potential of hpv [4]. Harald zur Hausen, in 1975 [5], published that HPV could have a pivotal role in human cervix carcinogenesis. Eight year after, Hausen et al. identified the subtypes HPV16 and 18 on cervix cancer.

HPV infection was well established as etiologic factor of almost 100% of cervical malignancies [6]. After this appointment, several studies have addressed to find presence and prevalence of HPV infection in different tumor sites, including skin, urethra, nasal cavity, paranasal sinus, larynx, tracheobronchial mucosa and oral cavity [7]. In 1983, a series of studies presented by Syrjänen et al. [8] highlighted the possible correlation between HPV and oral lesions (non-neoplastic, benignant and malignant lesions). At the same year, a light microcopy study

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provided by Syrjänen et al. [9-11] firstly suggested a link among HPV infection, HNSCC and OSCC, through the examination of 40 biopsy specimens. These authors described morphological alterations caused by HPV infection in 16 cases; this observation gives supports to HPV involvement in the development of OSCC. However, the confirmatory evidence of HPV-DNA in the oral lesions was presented only in 1985 [6,12]. Although the presence of HPV DNA has been suggested as a possible etiologic factor of oral pre-cancer and cancer, this association has not been as reliable as in cervical cancers.

3. HPV biology: General considerations

HPV represent a group of DNA viruses that was recently recognized to form their own family, Papillomaviridae that initially, together with polyomaviruses, was grouped in the Papovaviridae family [13]. They are an ancient family of pathogens and are known to infect epithelial tissues of amphibians, reptiles, birds and mammals [14]. The virus is formed by a non-enveloped icosahedral capsid with circular double-stranded DNA [15-16]. The genome is small, comprising to 8.000 base pairs, but it is complex, composed of three distinct regions: early region (E), late region (L) and upstream regulatory region (URR) or long region control (LCR).

The E region contains from seven to eight genes (E1, E2, E3, E4, E5, E6, E7 and E8), of which E1 is related with viral replication, E2 with viral transcription and DNA replication, E4 with maturation and alteration of extracellular matrix cell and E5, E6 and E7 are involved in cellular transformation. The E3 and E8 genes have been recently described only in a few HPV types but their function is unknown [16-18].The L region containing two genes, L1 and L2, which encode structural proteins necessary for viral capsid formation in the final stages of replication. Both E and L are coding region therefore called open reading frames (ORF), however the region URR does not fit in this description because it is a non-coding region. The URR region is found between E and L region and contain promoter and enhancer DNA sequences critical to regulate viral replication and transcription by both viral and cellular genes [19].

Based on phylogenetic analysis, the HPV is classified into genera (alpha, beta, gamma, mu and nu), species and types [15]. The classification of HPV types is based mainly on analyses of the L1 gene, which is the most conserved gene in all known papillomaviruses. When the DNA sequence of the L1 ORF differs by more than 10% from the closest known virus type, a new papillomavirus is recognized. Differences between 2% and 10% homology define a subtype and less than 2% a variant. A viral variant can differ between 2% in coding regions and 5% in non-coding regions [13,15]. Currently, approximately 150 different types are recognized and 120 HPV types are fully sequenced [18]. Types classified as members of the same species with approximately 80-90% of similarities trend to share biological properties such as the tissue tropism, disease manifestation, and pathogenicity [14].

According to their tropism, the HPV also can be classified as cutaneous and mucosal type. The cutaneous type are associated with skin lesions, being HPVs 1, 2 and 4 the most prevalent in common and plantar warts, and the types 5, 8, 9, 12, 14, 15, 17, 19-25, 36, 46 and 47 the most

frequent in epidermodysplasia verruciforme. HPV-5 and -8 are associated with skin carcinoma [20-21]. HPV with mucous tropism infects the anogenital tract, upper aero digestive tract, other head and neck mucosa and are generally subdivided into high-risk and low-risk type based on their oncogenical potential. The most relevant low-risk type are HPV-6 and 11, however the types 40, 42, 43, 44, 54, 61, 70, 72 can be observed in genital benign lesions. Among the high-risk types, the HPV 16 and 18 are most common; especially type 16, which can be found in various cancers such as cervical, oropharyngeal and penile carcinomas. Types 31, 33, 35, 52, 58 and 67 belong to a category of moderate to high-risk [20,22-24].

HPV life cycle is closely linked to the differentiation program of infected epithelial cells, more specifically the keratinocytes. Infection is initiated through microlesions in the epithelium, which allow virions come in contact with the basal cell layer by direct HPV receptor connection to surface host cell ligands. The receptors involved are not fully identified, but some data revealed a role for $\alpha 6$ integrin and heparin sulfate. Following infection, the virus probably maintains its genome as a low copy number episome in the basal cells of the epithelium, providing a reservoir of viral DNA for further use in cell divisions. When infected basal cells begin to divide, viral DNA is distributed among the daughter cells with a massive upregulation of expression of all early genes mainly the E6 and E7. After mitosis some daughter cells may persist in the basal layers, whereas other move toward the upper layers of the epithelium and begin to differentiate. During this differentiation process there is viral DNA replication that amplifies the amount of virus at least 1000 copies per cell, and finally expression of the coat proteins L1 and L2 followed by assembly of infectious virus [25-28].

The mechanism of viral-induced cell growth is analogous to other tumors viruses that deregulate the cell cycle. Cancer appearance in lesions with persistent HPV is related to the overexpression of E6 and E7 proteins. E6 interfere with the function of p53 whereas E7 with the function of Rb protein, leading to abnormal cells growth by promoting inhibition of apoptosis and dysregulation of cell cycle, respectively. [28]. Basically, HPV infection occurs through sexual contact, non-sexual contact and maternal contact. In healthy individuals most (around 80%) HPV infections clear spontaneously but in some cases, HPV infection persist, leading to cancer development [26,29]. A series of events allows the viral persistence: differentiation-specific organization of the virus life cycle, mechanisms to maintain genome copy-number in undifferentiated cells, angiogenesis promotion, and strategies to evade both innate and adaptive immune surveillance [28].

4. HPV and head and neck sites

Twenty-five percent of HNSCC are associated with HPV [30]. There is increasing evidences that sexual practices are the means by which HPV-Positive HNSCC patients are exposed to virus. Therefore, changes in sexual practices (young people with their first sexual experience at an earlier age, numbers of sexual partners and higher probability of engaging in oral sex compared to individuals from earlier decades) may be associated with HPV-infection prevalence [31].

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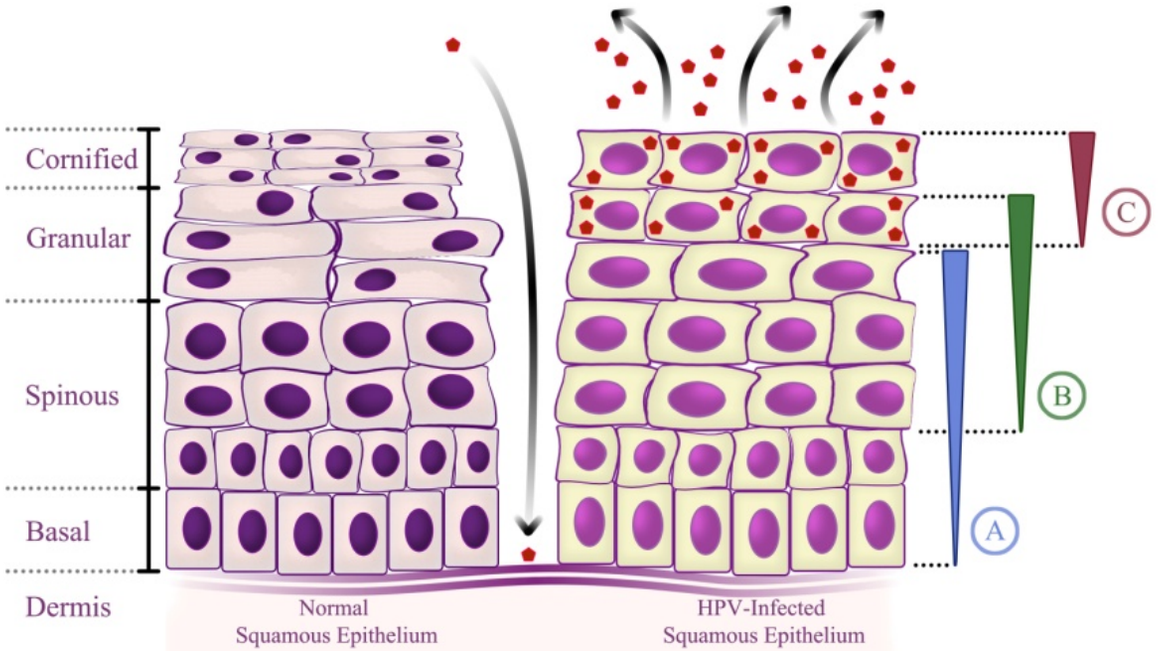

Figure 1. Human Papillomavirus Life Cycle: A: Early gene expression E1, E2, E6 and E7; B: Viral genome amplification; C: Virion assembly and release (Adapted from Moody & Laimins 2010).

Recently, a specific correlation between HPV-positive patients and sexual behavior has been established in HNSCC [32]. This study shown, in patients with HNSCC, that high-risk HPV-16 was correlated with vaginal/oral sex partners, casual sex habits and infrequent users of barriers during vaginal/oral sex. Heck et al. [31] presents association between HNSCC subtypes and sexual behavior. In Oropharynx Cancer the prevalence of HPV infection is close to 36% [30] and this entity was associated with the number of sexual partners and lifetime oral sex partners [31]. A similar result was described by D'Souza et al. [33], which presented an association between HPV-16 measurements and presence of oral HPV-infection. The authors has also found HPV-16–positive oropharyngeal cancer correlated with oral-sex or vaginal-sex partners, engagement in casual sex, early age at first intercourse, and infrequent use of condoms. In tonsillar cancers, Hemminki et al. [34] demonstrated that women with cervical lesions present an increased risk of tonsillar cancer. In addition, increased risk was also found among husbands of women with invasive cervical malignancies. Heck et al., [31] has also found correlation among tonsillar cancers, number of oral sex partners, and earlier age at sexual debut. At the same study, another subtype of HNSCC (Cancer of the Base of the Tongue) was associated with sexual behavior; it was related with oral sex among women, number of sexual partners, and among men presenting history of same-sex sexual contact.

The sexual behavior has been associated with oral HPV-infection. Univariate analysis showed that oral HPV-infection was significantly increased with the lifetime number of oral/vaginal sex partners. Multivariate analysis demonstrated that oral HPV-infection was significantly elevated among individuals who reported having either 10 oral or 25 vaginal sex partners during their life [35]. In addition, a curious fact was demonstrated: the open-

mouthed kissing was associated with oral HPV-infections and could contribute to HPV-infection among individuals who might not otherwise be exposed. To summarize, all these findings suggests that HPV- infection sexually transmitted could play an important role in HNSCC carcinogenesis [35].

5. Oral premalignant lesions

The transformation of normal oral mucosa in OSCC entities can be linked to the emergence of Pre-Cancerous lesion [36]. This association with several oral mucosa disorders such as oral leukoplakia, oral erythroplakia, oral lichen planus, nicotine stomatitis, tobacco pouch keratosis and oral submucous fibrosis (Table1) could be seen. However, that kind of disorders presents a varied spectrum of malignant transformation potential [37]. Reviewing the clinical features of oral Pre-Cancerous lesions and OSCC, the literature emphatically agrees that the early detection is the most important strategy for diagnosis and prevention of OSCC [37]. Applying this diagnosis strategy the OSCC-patients reduces the treatment in advanced stages, thereby increasing the chances of cure [36]. One of the extensive efforts in the clinical management of patients diagnosed with Pre-Cancerous lesions is to delineate clinical outcome, since it is difficult to separate lesions that follow a benign transformation from the entities that are predisposed to malignant course [38]. However, can be observed only a subset of Pre-Cancerous lesions following the malignant course blowing in OSCC.

Disease Name	Malignant Potential
Proliferative Verrucous Leukoplakia (PVl)	6
Nicotine Palatinus in Reverse Smokers	5
Erythroplakia	5
Oral Submucous Fibrosis	5
Erythroleukoplakia	4
Granular Leukoplakia	4
Laryngeal Keratosis	3
Actinic Cheilosis	3
Smooth. Thick leukoplakia	2
Smooth. Red Tongue of Plummer-Vinson Syndrome	2
Smokeless Tobacco Keratosis	1
Lichen Planus (erosive forms)	1
Smooth Thin Leukoplakia	+/-

Table 1. Malignant transformation Potential of *Precancerous Lesions* (adapted from Neville et al. 2009).

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The role of HPV in cancer has been exhausted discuss during the recent years. However, HPV in Pre-Cancerous lesions malignant transformation remains under study. Currently, some of the most studied Pre-Cancerous lesions in the literature are: Oral leukoplakia, Oral erythroplakia, Oral lichen planus Oral submucous fibrosis and Smokeless tobacco keratosis. Aimed to understand the malignant potential of theses lesions some author have attempted to relate the disorder progression with HPV malignant mechanism. Even so, the complete knowledge of viral infection and malignant transformation still remains obscure and controversial.

5.1. Oral leukoplakia and HPV

Oral leukoplakia (OL) is considered an uncommon potentially malignant lesion of the oral mucosa. In 1978, Kramer and colleagues defined Oral leukoplakia as ''a white patch or plaque that cannot be characterized clinically or histopathologically, as any other disease'' [39]. Observing only oral Pre-Cancerous Lesions, OL is the most frequent potentially malignant lesion of this mucosa, represents 85% of oral Pre-Cancerous Lesions presenting a predilection to male gender [40-42]. However, additional reports found no differences among gender [43]. OL affects 3% of white adults [42] with age distribution in the developed countries between the fourth and seventh decades of life, whilst in the developing countries might occur up to 5-10 years earlier [41].

Clinically, OL can be separated in homogeneous and non-homogeneous leukoplakias entities. The first group (homogeneous) was classified into flat, corrugated, wrinkled and pumice-like, and the latter group of leukoplakias (non-homogeneous) was classified into verrucous, nodular, ulcerated and erythroleukoplakia. The authors has also describes that a non-homogeneous leukoplakias presents an increased malignant potential when compared to homogeneous entities [44]. OL can be microscopically characterized by a hyperkeratosis of squamous epithelium. This hyperkeratosis consists of hyperparakeratosis or hyperorthokeratosis; however, a combination between hyperparakeratosis and hyperorthokeratosis also can be seen. In spite of hyperkeratosis, the underlying epithelium layer can show atrophy or thinning. However, spinous layer can presents acanthosis process and the subjacent connective tissue can present a chronic inflammatory infiltrate, ranging from spread foci of inflammatory cells presented in smooth leukoplakia to the numerous foci observed on speckled leukoplakia [42].

Through the years, OL increases the tendency to malignant transformation [45]. The causes of OL remain unclear, in spite of that tobacco intake is considered the most common risk factor for oral leukoplakia development [41-42]. This relation seems to be universal; it appears both in the developing and developed world [41,46]. HPV-infection was well established as etiologic factor of almost 100% of cervical malignancies [6]. Through this establishment, several studies have addressed to find presence and prevalence of HPV-infection in different tumor sites. In the oral cavity, benign lesions have been associated with 24 types of HPV (1, 2, 3, 4, 6, 7, 10, 11, 13, 16, 18, 30, 31, 32, 33, 35, 45, 52, 55, 57, 59, 69, 72 and 73) and malignant entities have been associated with HPV types 2, 3, 6, 11, 13, 16, 18, 31, 33, 35, 52 and 57 [47-48].

Presence of HPV-DNA was more frequent in pre-cancerous lesions and OSCC when compared with control samples. However, only pre-cancerous lesions reach a statistical significance ($P = 0.0216$) [49]. Comparing OSCC and control samples with pre-cancerous lesions pre-cancerous

lesions the authors also found a significant prevalence of Low- risk HPV in pre-cancerous lesions. Significant prevalence of Low-risk HPV in pre-cancerous lesions has also observed by Miller & Johnstone [1] meta-analysis. They reported that low-risk HPV DNA was more prevalent in OL and; on the contrary, observed that high-risk HPVs was 2.8 times more frequent in OSCC.

The presence of HPV has been analyzed in potentially malignant lesions, and HPV DNA has been found in different proportions. Sugiyama et al. [50] detected HPV-16 and -18 in normal, dysplastic, and malignant oral epithelium and found statistical significance between the HPV-16 detection in epithelial dysplasia group and OSCC group. A study comparing normal oral mucosa, OL and OSCC was coordinated by Llamas-Martinez et al. [51], aiming to determinate the HPV genome as an independent clinicopathological factor and detect different HPV-genotypes. The data do not show relationship between HPV-genotypes and clinicopathological factors. However, the presence of HPV-16 was increased in OL and OSCC (14/35 cases 40%, 11/33 cases 33.3% (p=0,0005); respectively). These results suggest that HPV-16 is related with OL and OSCC pathogenesis. Campisi et al. [52] investigating the relation among High-Risk HPV infection, apoptosis (bcl-2 and survivin) and proliferation biomarkers (PCNA) observed HPV-DNA in 38.1% of samples. HPV infection was associated with survivin and PCNA suggesting the interference of HPV on epithelial maturation. A year before, Lo Muzio et al. [53] showed increased rates of HPV-positive OL related with a survivin expression and suggested an unfavorable clinical outcome to these lesions. This unfavorable behavior was induced by influence of survivin on apoptosis process.

In conclusion, the correlation between OL malignant transformation and HPV infection were not totally understood. However, these data suggests that HPV-infection could play an important role in oral carcinogenesis leading to OL malignant transformation.

5.2. Oral erythroplakia and HPV

The expression 'erythroplasia' initially was used to describe a reddish precancerous lesion that develops on the glans of penis [55]. Due to clinical and histopathological similarities with genital process, the reddish precancerous oral lesion has also named erythroplakia. The *Oral erythroplakia* (OE) is presented like an unknown-causes lesion. However, it is assumed the same association with OSCC [42]. The authors has also describes that OE presents an increased malignant potential when compared with others pre-cancerous entities [42,55], Older men are predominantly affected by OE with peak prevalence in the sixth decade of life (65 to 74 years). Floor of mouth, tongue, and soft palate are the most common sites of involvement [42].

Clinically, OE may be associated with leukoplakia (erythroleukoplakia) and OSCC [56]. Usually, the lesions do not present symptoms but, is not uncommon some patients reporting a burning sensation and/or sore. The altered mucosa can present a well-demarcated erythematous macule or plaque with a soft, velvety texture [55]. Microscopically, reddish color of erythroplakia can be explained by a combination of features. Red color is presented by underlying microvasculature, and additionally, this color can be due to low keratinization and epithelial thinness [42]. Generally, OE can be associated to severe epithelial dysplasia and, at the time of biopsy, may presents 'carcinoma in situ' or 'invasive carcinoma' [55].

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Information about the role of HPV infection in OE is limited. Reichart & Philipsen (2004) discussed the role of hpv infection in OE together with p53 alterations [56]. Nielsen et al. [57] immunohistochemically detected hpv-infection (by situ hybridisation and PCR) in potentially malignant oral lesions. Fifty percent of OE studied cases were HPV-positive. The authors suggest that HPV may be an etiologic co-factor involved in development of oral cancer. However, we can not assume that HPV is the major etiologic factor involved in malignant transformation of OE

5.3. Oral lichen planus and HPV

In 1869, Dr. Erasmus Wilson provided the first medical report about the chronic derrnatologic disorder *lichen planus*. The British physician appointed the disorder "*lichen planus*" because the skin lesions appear to be quite similar to the symbiotic algae and fungi relationship (*lichen*) [42]. *Oral lichen planus* (OLP) is a chronic mucocutaneous disorder presenting a potentially premalignant behavior. However, less than 1% of OLP progress to malignancy state [58]. This injury is most common in middle-aged adults within preponderance for female gender (3:2 ratio) [42]. Mattila et al. [58] characterized the OLP in 6 variants: reticular, papular, plaque-type, atrophic, erosive and bullous. Clinically, Neville et al. [42] mentioned reticular and erosive forms as the most common variants presented in the oral mucosa. Although, not common as reticular and erosive, the bullous form was considered a rare oral disorder [59]. Three most common oral mucosa sites involved in OLP are: buccal mucosa, gingivae and lateral borders of the tongue. Additionally, its can be originated in any site of oral mucosa and frequently, is seen as bilateral lesions [59].

Microscopically, the OLP is presented like a non-specific lesion. Moreover, some oral disorders may also demonstrate a similar histopathologic pattern to the OLP-lesions. The injured epithelium may present orthokeratosis and parakeratosis. A spinous cells layer thickness can be observed in different degrees. The rete ridges may be presented as a classically "saw toothed" shape. Due to hydropic degeneration is evident a destruction of the epithelium basal cell layer and, subjacent to epithelium an intense T lymphocytes band-like infiltrate can be observed [42].

Some authors attempt to elucidate the correlation between HPV-infection and malignant transformation of OLP; however, results from pertinent literature are conflicting. The High-risk HPV-16 was described in 26.3% of OLP, with significant statistical difference between High-risk HPV-16 prevalence and OLP when compared to control samples [60]. A study performed by Sand et al. [61] demonstrated the High-Risk HPV-18 in approximately 27% of lichen planus cases but do not found statistical difference between HPV infection and oral lesions suggesting the unclear pathologic correlation between HPV and OLP. On the other hand, Campisi et al. [62] demonstrated the presence of HPV-DNA in 19.7% (n = 14/71) of patients with OLP, with significant statistical difference in comparison with controls cases (5/90; 5.6%) (P = 0.005). In the present study, the High-risk HPV-18 was the most frequent genotype found, it was present in 71.4% (10/14) of samples. In a second analysis, all of cases were pooled in 2 clinical groups: (1) atrophic-erosive (AE) (atrophic, erosive, bullous, and mixed AE variants); and (2) nonatrophic-erosive (non-AE) (reticular, plaque-like, popular, and

mixed non-AE variants) to evaluate the association between OLP variants and HPV-infection. However, this analysis failed to find particular correlation between OLP variants and HPV-infection. Analyzing 82 patients diagnosed with atrophic OLP, Mattila et al. [58] found that HPV-infection was present in 15,9% of lesions and was related with High-risk HPV-16. In addition, the HPV-positive cases presented a higher proliferation index and overexpression of Topoisomerase IIa (protein responsible for removal of DNA positive supercoils) in supra-basal layers in comparison with HPV-negative cases.

Ostwald et al. [63] studying prevalence and influence of Low-risk Hpv 6/11 and high-risk Hpv16/18 in benign oral lesions and OSCC detected the HPV-infection in 15.4% of OLP cases. Low-risk HPV presented the higher prevalence in OLP, whereas the High-Risk HPV presented the higher prevalence in OSCC. These interesting results demonstrated that High-risk HPV infection was successively increased from low-level premalignant lesion to OSCC, suggesting a correlation between High-Risk HPV and malignant potential [64]. The conflicting results of studies involving HPV-infection and malignant transformation of OLP lesions may occur due to differences in sample size of patients, associated comorbidities, and other external factors.

5.4. Oral submucous fibrosis and HPV

The name "*Oral submucous fibrosis*" (OSF) was firstly presented by Joshi in 1953; however, Schwartz had described this condition in five cases originated from Kenya, a year before, as '*atropica idiopathica mucosae oris*' [65]. OSF is frequently found in South Asian and South-East Asian patients (India, Bangladesh, Sri Lanka, Pakistan, Taiwan, Southern China) aged of 20–40 years [63]. This potentially malignant disorder has been close related to chronic consumption of Betel quid and Paan [42].

Microscopically, OSF can be characterized by the submucosal deposition of connective tissue. This deposition is extremely dense and presents a reduced vascular tissue. In early-stage lesion, sub-epithelial vesicles can be observed. On the other hand, the older-stage lesion presents epithelial atrophy with hyperkeratosis. In conjunction with these epithelial changes, 10% to 15% of biopsied tissues present epithelial dysplasia [42].

Although, OSF presents a multifactorial etiology, Betel quid and Paan consumption are considered the major causative agents. In pertinent literature only four studies evaluating the HPV and OSF were found: two studies evaluating an Indian population; one study analyzing differences between HPV-infection prevalence in OCSS and pre-malignant lesion; one study comparing two different HPV detection methods). Study performed by Luo et al. [49] presented only two cases of OSF infected by HPV-virion. Although, the lesions had been positive for HPV-infection was not possible to perform other conclusions, because this study used a small number of cases. Chaudhary et al. [66], comparing two HPV-detection methods identified around of 27% (total of 208 cases) of OSF patients' positive for HPV-infection. These two reports do not allow us to establish any positive correlation between HPV-infection and malignant transformation. In addition, evaluation of a hundred thirteen cases of OSF, designed by Mehrotra et al. [67], to assess the relationship of human papilloma virus infection and OSF showed no significant correlation between these two entities. Although, the hpv-infection do not show association with OSF an Indian population study, investigating the prevalence of

HPV-16 in OSF and OSCC cases, found a 91% prevalence of HPV-DNA in OSF and speculated that epithelium lesions in OSF could be an important factor to integration of HPV in basal cells genome (Jalouli et al. [68]. In conclusion, these studies do not have strength to sustain the idea that HPV has an important role in the malignant transformation of OSF.

5.5. Smokeless tobacco keratosis and HPV

Several oral manifestations have been associated to use of *Smokeless Tobacco*. Oral manifestations occur at the site of Smokeless Tobacco placement including mucosal lesions (Smokeless Tobacco Keratosis "STK") and gingival-periodontal disorders such as gingival recession, gingival inflammation, changes in gingival blood flow and interproximal periodontal attachment loss [69]. The use of *Smokeless Tobacco* and the STK has been suggested to be involved in development of oral cancers [70].

Clinically, the site of Smokeless Tobacco placement presents a leukoplakic lesion referred as "snuff dippers" lesions [71] STK presents a non-specific histopathologic appearance [42]. Squamous epithelium is hyper keratinized [42,70] and acanthotic; in addition, the intra-cellular edema is not uncommon on superficial cells glycogen-rich. In some cases, subjacent connective tissue can present an amorphous eosinophilic material. An increased sub-epithelial vascularity and vessel engorgement also can be seen. [42]. In STK the epithelial dysplasia does not common. In a study conducted by Leopardi et al. [72] they not evidenced cases of epithelial dysplasia. However, when present, epithelial dysplasia is usually mild [42]. Studies on STK pointed to three clinical grades [73].

Studies on smokeless tobacco keratosis pointed to three clinical grades: 1) Grade I superficial lesions presenting modest wrinkling and no mucosal thickening. Grade I lesions tends to present similar color to the surrounding mucosa. 2) Grade II superficial whitish lesions with undulating areas displaying moderate wrinkling and no mucosal thickening. 3) Grade III white entities with normal mucosal color areas, STK Grade III shows mucosal thickening and wrinkling [71]. However, this lesion is reversible when the product is discontinued [42]. Related to HPV a work aimed to detect p16 (INK4a) protein expression in smokeless tobacco keratosis as reliable precancerous marker. The author detected HPV-DNA in 15 of 62 (24%) cases and an apparent relation between the three standard grades of STK lesions and HPV-infection was observed. [71]

6. Malignant oral lesions and HPV

In the oral cavity, 24 types of HPV (1, 2, 3, 4, 6, 7, 10, 11, 13, 16, 18, 30, 31, 32, 33, 35, 45, 52, 55, 57, 59, 69, 72 and 73) have been associated with benign lesions and 12 types (2, 3, 6, 11, 13, 16, 18, 31, 33, 35, 52 and 57) with malignant lesions [47-48]. Since the first report of the presence of HPV DNA in head and neck cancer, 65 high-risk types have been consistently detected at different sites; however, these types are specifically found in transcriptionally active tumor cells [74]. According to data from a review, 99% of HPV-infections in head and neck cancers are by high-risk types 16, 18, 31 and 33 [75]. Infection with HPV 33 accounts for up to 10% of

positive head and neck cancers; however, the HPV 16 type is by far the most common subtype detected in head and neck cancer ([75-77], and also, oropharyngeal cancer (OPC) is more likely to have HPV 16 than other types at head and neck sites. Just to demonstrate the high levels of HPV-16 genotype in OPC, this genotype accounts for 78% to 100% of positive cases, while HPV-18 accounts for only 1% of cases [75]. An interesting prevalence profile of the HPV types has been observed in some investigations in the countryside of Sao Paulo state in Brazil, where a higher prevalence of HPV 18 than HPV 16 was found in oral and cervical carcinomas. Furthermore, the presence of HPV 18 was found to be associated with metastasis to the lymph nodes and shorter patient survival [78-80].

Several HNSCC have been analyzed for the presence of HPV, and HPV-DNA has been found in different proportions of tumors from different head and neck sites [75,81]. Some evidence has indicated that some subtypes of HPV are specifically linked to head and neck cancer, especially those arising from specific oropharyngeal subsites (e.g., tonsil and the base of the tongue) [82]. The HPV prevalence in HNSCC ranges from 3% to 40% and could vary more according to the specific site and HPV has been found in 4-80% of oral squamous cell carcinoma. Brazilian observations in the countryside of São Paulo state have found a low prevalence of HPV in tumors of the larynx [83] and an increase in the presence of HPV-DNA in oral cavity cancers during the past two decades [79-80,84]. The wide variation in HPV prevalence can be attributed to different detection techniques, small sample numbers, differences in the lesions and sampling techniques and epidemiological characteristics of the populations studied [85]. Among the many methods to detect HPV infections, both polymerase chain reaction (PCR) and in situ hybridization assays have been well validated, although not perfect.

In terms of incidence, it is now believed that HPV-infection could be responsible for approximately 20% of oral cancers and 60-80% of OPC. Recently, in 2011, International Agency of Research of Cancer (IARC) declared that there is sufficient evidence that HPV-16 is causally associated with oral cancer cases [86]. More important, these HPV-related oral cancers are now considered to be completely different entities, differing remarkably from HPV-negative tumors in their clinical response and overall survival [76,87].

Currently, the identification of distinct epidemiological profiles in HPV-positive and HPV-negative HNSCCs is possible. The main factors studied are heavy or no tobacco/marijuana exposure, heavy or mild alcohol consumption, poor or intact dentition, low or high oral sex exposure, age > 50 years or < 45 years, lower or higher socioeconomic status and deceasing or increasing incidence [82]. The epidemiological trend suggests that HPV-positive HNSCC occurs more often in younger patients (age < 50 years), which differs from the typical characteristics of head and neck cancer (which is more frequent in men above 40 years old). Tumors that show association with the presence of HPV usually appears strawberry-like and exophytic lesions on gross inspection and occur more frequently in the tonsil and the base of tongue with a basaloid aspect, poor differentiation and cystic changes within metastatic lymph nodes [82]. In addition, gene expression profiles are known to be different in HPV- positive OPCs compared with HPV-negative cases [88].

Molecular evidences have shown that HPV-associated oral tumors differ significantly from the classic "tobacco and alcohol"-associated oral tumors. First, HPV-positive HNSCCs harbor

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wild type p53, while classical HNSCC have usually a mutated form of the protein, in accordance with the expected better development of HPV-associated lesions. Indeed, among HPV-positive tumors, the worst outcome is related to smoking, showing evidence that tobacco-derived carcinogens could potentiate the transformation effect of HPV [89-90]. But p53 status in HPV-related tumors, especially those presenting HPV-16 infection led to a confusion involving HPV detection methods and even HPV-related carcinogenesis itself. Initially, it was expected that HPV-16 positive tumors to have a predominantly mutated p53 status, given that HPV-16 E6 inactivates p53, and therefore, mutations in TP53 would be, and indeed are rarely present in cervical carcinomas. But in HNSCC, TP53 is mutated in 60-80% of all cases, and it was expected that HPV-infected tumors would be among the 20-40% of wild-type TP53, although this is not what was found in HNSCC. These findings highlighted the importance of the detection method of HPV infections. For example, the HPV DNA PCR assay is too sensitive, since it detects only a few copies of viral DNA, and may detect more than oncogenic infections, but also productive infections, laboratory artefacts and virions [91]. The following additional techniques can also provide data regarding the presence of HPV: light and electron microscopy, ELISA, gene expression by DNA microarray, Dot blot, Southern blot, hybrid capture and ligase chain reaction for probe amplification. Due to the existence of numerous options for HPV detection in HNSCC, a standardization of procedures for routine application has yet to be developed [77,85]. Among other important pathways in HPV-induced HNSCC are: (1) p53 and pRb pathways, involved in cell cycling; (2) EGFR pathway, which are an important therapeutical target in other cancers (as breast and lung cancers); (3) TGFβ pathway; (4) PI3K-PTEN-AKT pathway and (5) angiogenesis and hypoxia pathways [91].

Aimed to investigate the HPV frequency in Brazilian patients diagnosed with OSCC we performed a study to establish the HPV clinicopathological profile and its possible influence on prognosis of disease [84]. HPV expression in primary tumors (PTs), and their matched samples (MSs) of recidives, lymph nodal metastasis (LNM) or necropsies were correlated with survival of patients. Through polymerase chain reaction using one general and two type-specific HPV primers, 87 PTs and their corresponding MSs were tested. As first step, HPV-DNA detection was performed, using a GP5+/GP6+ primer (Bioneer Inc.) to amplify a 150-bp fragment from L1 gene of general HPV types (GP5+, 5'-TTTGTT ACTGTGGT AGA T ACT AC-3'; GP6+, 5'- GAAAAATAAACTGTAAATCATATTC-3'). At second step, PCR reaction was performed on HPV-positive DNA samples to determine if contained the genotypes -16 and -18, using specific primers targeting ~100 bp in the E7 ORF: HPV-16E7.667 (5'- GAT-GAAATAGATGGTCCAGC-3'), HPV-16E7.774 (5'-GCTTTGTACGCACAACCGAAGC- 3'), HPV-18E7.696 (5'-AAGAAAACGATGAAATAGATGGA-3') and HPV-18E7.799 (5'-GGCTTCACACTTACAACACA-3') (Bioneer Inc.). All of 87 OSCC patients analyzed, 17 (19.5%) presented tumors HPV-DNA positive. Analyses of all paraffin-embedded samples (87 primary tumors plus 87 matched samples) revealed the presence of HPV-DNA in 18 of 174 samples (10.4%), 10 samples (11.5%) from PTs, and 8 samples (9.2%) from MSs. In addition, no virus infection was detected in 7 (8.1%) MSs samples, and only one patient has demonstrated HPV-DNA positivity in both samples. HPV genotypes -16 and -18 were detected in 4 (22.2%) and 3 (16.7%) of the positive samples, respectively. Infection with both genotypes was found in 6 (33.3%) investigated samples, and HPV genotype was not identified in 5 (27.8%)

samples. The most prevalent infected anatomical site was the tongue. The main result of the present study was the significant number of positive HPV samples among non-smoking patients and although, a possible influence of HPV infection on carcinogenesis cannot be ruled out, the low frequency of HPV-positive OSCC cases found in our analysis leads us to suggest that this virus has not the same etiological influence on patients, as tobacco consumption does. Although we cannot to exclude a possible transient role for HPV in the OSCC induction, we believe that occasional detection of HPV-infection in OSCC resulting from the incidental colonization of tumoral lesions might reflect the true correlation of HPV in most analysis. [84].

7. HPV — Prognosis and treatment

In last decades no significant improvement of overall survival has been observed in patients with HNSCCs. It is believed that loco-regional recurrences, distant metastases and a second primary tumor are factors for this phenomenon [91]. Several studies have now established that head and neck HPV-positive tumors have better prognoses [76,88] and treatment-response rates when compared with HPV-negative tumors [88]. In a study comparing tumors in the same stage Leemans et al., [91] observed favorable prognoses after treatment of HPV-infected HNSCCs as compared to HPV-negative tumors. Univariate analyses for 5-year survival rate have pointed that HPV-positive patients surviving longer than HPV-negative patients ($p < 0.05$); the 5-year survival rate was 54% for HPV-positive versus 33% for HPV-negative tumors [92]. In addition, a study performed by Fakhry et al. [76] evaluating the correlation between HPV infection and survival rate suggested that HPV-positive HNSCC have a significantly better survival (5-year survival of approximately 70%) when compared with HPV-negative patients (5-year survival of approximately 35%). Dayyani et al. [87] published a Meta-analysis, analyzing the impact of human papillomavirus (HPV) on head and neck squamous cell carcinomas, described that patients HPV-positive presented increased risk for HNSCC (adjusted OR = 1.83; 95% CI = 1.04-2.62; $p < 0.0001$). However, survival rate was improved in HPV-positive patients when compared to HPV-negative patients (HR = 0.42; 95% CI = 0.27-0.56, $p < 0.0001$). In other example, evaluation of prognosis and response rates to chemotherapy of oropharyngeal or laryngeal carcinomas showed that HPV-positive tumors present a significantly better overall 2-year survival rate than HPV-negative patients (2-year survival rate of HPV-positive tumors 95% (95% CI = 87%-100%), and 2-year survival rate of HPV-negative tumors 62% (95% CI = 49%- 74%)). The same study found that HPV-positive oropharyngeal carcinomas present higher response rates to chemotherapy compared with HPV-negative (82% vs 55%, difference = 27%, 95% CI = 9.3% to 44.7%, P =.01). Additionally, Dayyani et al. [87] described that HPV-positive head and neck squamous cell carcinomas presented an improved response to radiotherapy (non-adjusted OR = 4.07; 95% CI = 1.48-11.18, p = 0.006) and had a better response to chemo-radiation (non- adjusted OR = 2.87; 95% CI = 1.29-6.41, p = 0.01) as compared to HPV-negative head and neck squamous cell carcinomas.

A meta-analysis performed by Ragin & Taioli [93] aimed to analyze the impact of tumor HPV status on survival outcomes showed that patients diagnosed with head and neck squamous cells carcinoma HPV-positive had a lower risk of dying in comparison with HPV-negative

tumors (combined HR: 0.85, 95% CI: 0.7–1.0). At the same study, HPV-positive patients had lower risk of disease-failure (recurrence of tumor) as compared to HPV-negative patients (meta HR, 0.62; 95%CI, 0.5–0.8). The evidence for association of OSCC with HPV-infection and its possible role as an oncogenic agent remains controversial. Schwartz et al. (2001) evaluating the HPV-16 influence on survival rate in OSCC demonstrated that patient's HPV-16 positive presented significantly reduced disease-specific mortality in OSCC (HR = 0.17, 95% CI = 0.04, 0.76) when compared with HPV-16 negative patients. This result suggests the HPV-16 infection could be associated with a favorable prognosis in OSCC. However, the mechanism responsible for this improved prognosis conferred by HPV is still unclear [94].

Several hypotheses have been proposed to explain the improved prognosis in tumors HPV-positive. The benefit on survival rate has been attributed to an enhanced radiosensitivity of tumors HPV-positive [95-96], and an improvement of apoptotic secondary response to the presence of unmutated p53 in HPV-associated tumors [95,97]. The improvement of disease-specific survival rate could be associated with a reduction risk of second primary tumor, since these HPV-positive patients tend to have no prior history of tobacco and/or high alcohol consumption [95]. This finding reduces the field cancerization process (upper respiratory epithelium repeatedly exposed to carcinogens) [98].

8. HPV vaccines (Therapeutic and prophylactic)

Several epithelial lesions are originated by infection with human papillomaviruses (HPVs), mainly benign hyperplasia with low malignant potential like warts or papillomas. However, there is a subgroup of HPVs that are associated with precancerous lesions, which could become a cancer in a small fraction of people [99]. As example of those high-risk HPV subtypes, HPV 16 and 18 [100] are responsible for approximately 70% of cervical cancer cases and are present in more than 60% of HPV-infected penile cancer and HPV-16 is the genotype most frequently detected in head and neck carcinomas, found in up to 90% of HPV-positive cases [99]. Other high-risk HPV types account for virtually all of the remaining cases of cervical cancer, although in other primary sites they do not appear to have a similarly important role [101]. Therefore, cancer of the uterine cervix is most widely accepted malignancy as being associated with HPV infection. HPV high-risk subtypes are also associated with some others anogenital carcinomas, including penile, anal and vulvar cancers [102-103] and a subset of head-and-neck squamous cell carcinomas [104].

Taken together, these findings supports in several countries, vaccination against some HPV types on girls and young women with the goal of protecting them against HPV-induced cervical cancer [105-106]. Trials with vaccines against cervical cancer shown that cross-protection is possible, because this vaccines also have the potential to prevent other cancers that are caused by the same types of HPV, including some of head and neck cancers [107], and the most of anogenital cancers outside the cervix, including cancer of the vulva, vagina, penis, and anus [108-109]. In theory, these vaccines should target the same viruses at other anatomical sites, as head and neck. This approach could provide important information about the final proof of HPV etiology in these tumors [110].

Prophylactic vaccines work primarily by inactivating HPV before the virus infects the host cells, stimulating humoral immunity [111]. Nowadays, there are two types of prophylactic HPV vaccine available in United States: the quadrivalent vaccine (Gardasil®) and bivalent vaccine (Cervarix®). The quadrivalent vaccine was first licensed for use in females to prevent cervical, vaginal and vulvar cancers and are effective against infection with HPV types 6, 11, 16 and 18 [112]. In 2009 the licensure was expanded to include males demonstrating effectiveness to prevent genital warts in both genders [113]. Bivalent vaccine was licensed for use in the U.S. in 2009 providing cervical cancers protection against HPV types 16 and 18 [114]. The impact of HPV prophylactic vaccination will address not only the incidence of cervical and anogenital cancers in women and men but also the incidence of some head and neck tumors. Growing number of head and neck cancers HPV-positive highlights the importance of routine prophylactic vaccination against HPV and, associated with alcohol and tobacco control, may be crucial in head and neck cancer prevention [115].

Also, therapeutic vaccines against HPV have to request cell mediated immunity and can also help prevent the progression of low-grade disease and lead existing lesions to regress, avoiding the recurrence of cancer lesions after treatment [116,117]. However, recent studies demonstrated the reduced effectiveness of therapeutic HPV-vaccine in established tumors. This could be explained by the fact that they have especially been tested in patients with compromised immune systems due advanced stage cancer [118]. A vaccine that possesses both prophylactic and therapeutic properties could be most effective HPV-vaccine strategy, preventing new and clear established HPV-infections. Additionally, the vaccine could be administered in, sexually inexperienced young individuals or older individuals HPV-infected, beneficiating them [119].

9. Final considerations

In recent decades, controversial results were not being able to provide the real role of HPV infection in OSCC genesis. An interesting fact that supports the controversial role of HPV-infection in OSCC is the highly fluctuating HPV-prevalence in comparison with cervical cancer. It may be due to HPV-detection influenced by: a reduced number of viral-copies, a viral-infection in a particular cell population, biopsy samples and detection methods (numerous methods and protocols for detection). Several details elucidating the relationship between pre-cancerous lesions, OSCC with HPV-infection must to be understood. The genomic detection of HPV-DNA, primarily in Pre-Cancerous lesions, provides stronger support for a viral etiology of HNSCC and OSCC. However the correlation between malignant transformation of Pre-Cancerous lesions and HPV-infection were not completely elucidated. Recently, numerous studies have suggested that HPV-infection could play an important role in oral carcinogenesis through the Oral leukoplakia malignant transformation. Although some synergies between HPV oncogenes and other carcinogens have been hypothesized, some researchers have showed, specifically in oral mucosa, that positive HPV-infection in OSCC might not result from viral infection but rather from an incidental HPV colonization. In addition, targeted therapy for HNSCCs and OSCC currently request an increased number of predictive biomarkers, such as the HPV-infection status and mutation-status of crucial genes,

to personalize the treatment for individual patients. However, for a better understanding about real therapeutic implications of HPV-status of tumors on OSCC clinical outcome, the next generation of clinical trials could be significantly improved and standardized in their design. According to exposed in the present issue, and defended by our research group and other authors [36-37], we believe that diagnosis strategy based in early detection in oral Pre-Cancerous lesions and OSCC reduces the treatment at the advanced stage, thereby increasing the cancer cure chances. Our group also believes that the increasing effects of HPV vaccination in several cancers could help to reduce the number of new HNSCC and OSCC cases. Although knowledge of the accurate effects of HPV vaccination on cancer incidence will probably continue for several years, monitoring the current effects of HPV vaccination is crucial, not only in cervical cancer, but also in HNSCC and OSCC.

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