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The Role of Human Papillomavirus in Head and Neck Cancers

Lucinei Roberto Oliveira[1], Andrielle Castilho-Fernandes[2],
Alícia Greyce Turatti Pessolato[2], Régia Caroline Peixoto Lira[2],
João Paulo Oliveira-Costa[2], Luciana Souza Chavasco[1],
Fabiana Alves Miranda[2], Ivan de Oliveira Pereira[1],
Edson Garcia Soares[2] and Alfredo Ribeiro-Silva[2]

1. Introduction

Tobacco and alcohol are well-established risk factors for head and neck squamous cell carcinomas (HNSCC), but it can also develop in individuals not exposed to them. However, only a small proportion of tobacco exposed individuals have developed HNSCC, and there is an emerging tumoral population who lack exposure to these mentioned risk factors, suggesting that others factors can play a role in head and neck carcinogenesis. Over the past two decades, the role of high-risk human papilloma virus (HPV) has been studied through several studies worldwide, and data supporting its role as a causative agent in the development and progression of a subset of HNSCC has been controversial, with considerable variability in frequency depending on the population studied, tumor localization, quality of samples and technical resources utilized for HPV detection. As is the case in cervical and anogenital carcinomas, the most frequently detected high-risk HPVs in HNSCC are the 16 and 18 genotypes. The tonsils and oropharynx are the specific sites associated with higher risk of HPV oncogenic transformation, and investigations suggest that HPV infection in these anatomic sites is an independent risk factor for carcinogenesis. The establishment and maintenance of HPV genomes in the squamous epithelium and HPV-related HNSCC cancer is believed to be originated by oncogenic potential of HPV integration into host DNA genome and their ability to manipulate cell cycle regulators, resulting in deregulated expression of oncoproteins such as E6, which promotes degradation of the tumor suppressor protein p53, allowing cells to evade cell cycle checkpoints, and also E7, which binds to retinoblastoma protein (pRb) and could promote the entrance in S1 phase of cell cycle, leading to disruption of normal cell cycle controls. Following cell division, infected cells leave the basal layer, migrate towards the suprabasal regions and begin to differentiate. Increased understanding of cervical pathogenesis has led to confirmation of HPV as an etiological agent for cancers and consequently to the development of preventive vaccines targeting HPV antigens for the control of cervical cancer. The HPV vaccine was developed as a result of the achievement of core technologies able to produce virus-like

[1]Vale do Rio Verde University, Brazil
[2]Ribeirao Preto Medical School, University of Sao Paulo, Brazil

particles (VLPs). The recombinant DNA was used to generate VLPs able to mimicking the natural virus and eliciting high-titers of virus neutralizing antibodies. With the progress through advanced stages of clinical trials and further exploration of combinatorial strategies, there is a great promise for significant advances also in the field of therapeutic HPV vaccine development. We recently conducted a study with the purpose of investigate the presence of HPV in a Brazilian population sample of HNSCC patients. In cases with positive specimens, the analysis was extended to clinicopathological profile characterization and to the correlation between patient survival and HPV DNA presence in primary HNSCC tumors as well as in their corresponding matched samples of recurrences, lymph nodal metastasis and necropsies. This research was conducted on the medical files of patients with head and neck tumors, the histopathological diagnosis of HNSCC was confirmed and paraffin-embedded specimens were selected for investigation. Moreover, in this chapter we discuss the current status of HPV vaccines as well as the main associated factors that interfere on establishment of strategies that better could act to control the infections and development of malignant neoplasias.

2. Historical aspects

One of the earliest manifestations of HPV infection was observed during an autopsy performed in 1974 on the embalmed body of an ancient Egyptian worker from 12th century BC who had a wart on the sole of his foot (Onon, 2010, as cited in McCaffery, 1974). The Ancient Greeks and Romans had already recognized that genital warts could be sexually transmitted (Onon, 2010, as cited in Claude Moore Health Sciences Library, 2011); however, the viral origin of warts was only confirmed in the 19th century (Onon, 2010, as cited in Ciuffo, 1907). By the early 1970s, the herpes simplex virus type 2 was thought to be the sexually transmitted etiologic factor that was responsible for cervical cancer (Onon, 2010, as cited in Klein, 1973). However, Harald Zur Hausen, a young German professor of virology, was not convinced of this hypothesis, and in 1976, he postulated that papilloma viruses play a role in cancer of the cervix. Papilloma viruses have now been well established as the cause of almost 100% of cervical carcinomas (Kumaraswamy & Vidhya, 2011).

The link between HPV and HNSCC was first studied by Syrjänen et al. (1983) in a light microcopy examination of 40 biopsy specimens from oral squamous cell carcinomas (OSCC), when the authors observed changes that are characteristic of HPV infection in 16 of the lesions. Recently, several studies have addressed the presence and prevalence of HPV in these types of tumors (Kumaraswamy & Vidhya, 2011). However, although the discovery of HPV has suggested that the virus may be a possible etiologic factor of oral pre-cancer and cancer, this association has not been as consistent as in cervical cancers.

3. Head and neck cancer

Head and neck malignancies compose a heterogeneous group and are believed to originate from sequential mutations that can occur as a consequence of progressive genetic instability and/or environmental factors, such as tobacco and alcohol consumption. These pathologies include a number of different types of cancer that arise from a variety of sites in the upper aerodigestive tract. Analysis of these tumors has revealed a heterogeneous neoplastic process that involves numerous sites with unique sets of epidemiologic, histopathologic,

and treatment considerations. Approximately 40% of head and neck cancers occur in the oral cavity, 15% occur in the pharynx, 25% occur in the larynx and the remaining tumors occur in other sites (Dobrossy, 2005). The most frequent histological type is the squamous cell carcinoma, which occurs in over 95% of cases. Squamous cell carcinomas originate from the epithelial surface of the oral cavity, oropharynx, hypopharynx, and larynx and affect approximately 500.000 patients worldwide each year (Popović et al., 2010). Low survival rates have been presented across several studies worldwide and reflect the need for more careful attention to HNSCCs. Because the mortality rates have essentially remained unchanged over the last several decades, considerable interest lies in discovering prognostic markers to guide therapeutic planning.

4. HPV

Papillomaviruses are a family of pathogens that infect exclusively the epithelial tissues of amphibians, reptiles, birds and mammals (Franceschi, 2007). The viruses are grouped according to the anatomic site of infection and their preference for either cutaneous or mucosal squamous epithelium. The cutaneous types, or beta papillomaviruses, are usually found in the general population and cause common warts. In contrast, the alpha, or mucosotropic, papillomaviruses have been implicated in mucosal infections (Snow & Laudadio, 2010; Vidal & Gillison, 2008). The mucosotropic group of human papillomavirus comprises 15 species and infects the anogenital tract, upper aerodigestive tract and other head and neck mucosa. Because they are sexually transmitted and play important roles in diseases, these viruses have received much attention and research and clinical investment (Chow et al., 2010).

The HPV genome is a small (55 nm), double-stranded DNA molecule of approximately 8.000 base pairs, and it contains three identified regions: a late region (L) containing two genes, L1 and L2, which encode the viral capsid proteins; an early region (E) encoding proteins involved in viral DNA replication and the control of viral transcription, such as E1 and E2, and the main transforming genes E6, E7 and E5; and a long control region (LCR), found between the L and E regions, which contains several binding sites for nuclear and viral transcriptional factors, promoter sequences and an open reading frame (ORF) region (Fernandes et al., 2009). The early and late gene regions are both protein-encoding, but the LCR is non-encoding. The LCR possesses numerous binding sites for many repressors and activators of transcription, suggesting that this region may play a role in determining the range of hosts for specific HPV types (Tanzi et al., 2009).

Traditionally, the papillomaviruses have been classified by type and by the ORF L1 region because this region is greatly conserved along the viral genome and has been used to detect new types of papillomavirus for more than 15 years. However, other genomic regions can also be used (i.e., E6 and E7). Each genotype is characterized as being more than 10% different from all other genotypes in their specific regions of DNA sequences. Differences of 2% to 10% define a subtype and less than 2% define a viral variant. Closely related types (approximately 80–90% identical) are classified as members of the same species, and they tend to share important biological properties, such as tissue tropism, disease manifestation, and pathogenicity (Chow et al., 2010; De Villiers et al., 2004). Currently, well over 120 different genotypes of HPVs have been isolated, sequenced and phylogenetically characterized. Thirty-three percent of these 120 genotypes are known to infect the human

genital tract (De Villiers et al., 2004; Hennessey et al., 2009, as cited in Longworth & Laimins, 2004; Martinez et al., 2007). Mucosotropic HPVs can be further classified into non-oncogenic, or low-risk, types or as potentially oncogenic, or high-risk, types. Mucosal and genital HPVs can be divided into low-risk (HPVs 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81) and high-risk (HPVs 16, 18, 31, 33, 35, 51, 52) types according to their presence in malignant lesions (Bosch et al., 2002; Muñoz et al., 2003). HPVs 31, 33, 35, 51 and 52 are sometimes regarded as "intermediate risk" viruses because they are more common in mild or severe dysplastic lesions than in carcinomas (Fernandes et al., 2009).

The late region units L1 and L2 encode for viral capsid proteins during the late stages of virion assembly (Park et al., 1995). The protein encoded by L1 is highly conserved among different papilloma virus species; accordingly, antibodies against the bovine papilloma virus have been used to identify HPV capsid proteins in human tissues. The minor capsid protein encoded by L2 has more sequence variations than that of the L1 protein; hence, the L2 protein has been a source of antigen for specific types of HPV antibodies. The E1 and E2 region units encode proteins that are vital for extrachromosomal DNA replication and completion of the viral life cycle. The E2 protein is modular and contains an N-terminal activation domain that is important for viral transcription and replication and for interaction with host chromosomes during mitosis. The E2 region also encodes two proteins, one of which inhibits transcription of the early region, while the other increases the transcription of the early region (Ward et al., 1989). The HPV E5 proteins are small, extremely hydrophobic, and located mainly at the endosomal membranes, Golgi apparatus and, to a lesser extent, the plasma membranes. Moreover, E5 proteins are traditionally known to interact with the transmembrane domain of the EGF receptor and to modulate its concentration and phosphorylation (Villa et al., 2002). When present, E5 interacts with various transmembrane proteins, such as the EGF receptors, platelet-derived growth factor β, and colony stimulating factor-1 (Talbert-Slagle & DiMaio, 2009).

The multiplicity of functions of the three small papillomavirus oncoproteins, E5, E6 and E7, continues to be amazing. Specifically, more than a dozen protein-protein interactions between E6 and cellular proteins have been published (Villa et al., 2002). In the protein-encoding regions, the E6 and E7 ORF are considered to play the most important roles. These units encode for oncoproteins that allow viral replication and the immortalization and transformation of the cell that host the HPV DNA (Doorbar et al., 1991).

Mucosal high-risk E6 proteins are best known for their ability to associate with the cellular tumor suppressor p53. The association of E6 with p53 leads to degradation of p53 via recruitment of an ubiquitin ligase, E6-AP, and results in the inhibition of the transcriptional regulatory activities of the p53 protein in tissue culture cells (Gonzalez et al., 2001; Jones & Münger, 1997). Similarly, the high-risk HPV E7 proteins are best known for their ability to associate with the cellular tumor suppressor pRb, and this association can promote pRb degradation (Jones & Münger, 1997) through a proteasome-mediated pathway that disrupts the capacity of pRb to bind and inactivate functionally cellular E2F transcription factors (Gonzalez et al., 2001). In addition to binding pRb, high-risk E7 proteins can bind to other pocket proteins (p107 and p130) that are related to pRb and interact with different members of the E2F family of transcription factors (Dyson et al., 1992). The inactivation of pocket proteins by E7 is necessary but not sufficient to elicit the transforming potential of E7 (Phelps et al., 1992). High-risk E7 is also purported to complex with cyclins (Dyson et al.,

1992) and to inactivate the cyclin associated kinase inhibitors p21 and p27 (Jones & Münger, 1997). Thus, E7 can associate with and/or alter the activities of multiple cellular factors that normally contribute to the regulation of the cell cycle. The oncogenic properties of E6 and E7 and their effects on p53 and pRb have provided the general basis for further investigations of the role of HPV in carcinogenesis. The research examining the actions of these two oncoproteins has shown how they can subvert key cell cycle and regulatory processes, such as cyclins, cyclin-dependent kinases (CDKs) and cyclin-dependent kinase inhibitors (CDIs), to transform and immortalize the host cells (Southern & Herrington, 2000).

Proving the importance of p53 and pRb in cell cycle progression, the repression of HPV 16 E6 and E7 expression by dual shRNA transfection has been shown to be capable of restoring the p53 and pRb tumor suppressor pathways and activating apoptosis (Psyrri et al., 2009, Rampias et al., 2009). Thus, the demonstration of this tumor suppressor inactivation by the E6 and E7 HPV oncoproteins has provided a basic explanation for how the high-risk HPV types exert their oncogenic effects on cervical cells.

5. The route of cellular conquest by HPV

Unlike other viruses, HPV does not infect or replicate in antigen-presenting cells of the epithelium nor induce cell lysis, so there is no chance for antigen-presenting cells to present antigens derived from the virion to the immune system. Despite the observation that more than 50% of infections present seroconversion in the patients, the production of antibodies usually occurs only months after the initial infection (Vidal & Gillison, 2008, as cited in Tindle, 2002). The life cycle of papillomaviruses is closely tied to the epithelial differentiation process. Infection occurs exclusively in squamous epithelial cells (keratinocytes) with preference for the keratinocyte stem cell as the initial target of HPV infection (Vidal & Gillison, 2008). The route of entry for HPV infection is microtraumas or small wounds in the skin or mucosal surface. These breaks in the epithelial surface allow the virus to access and persist in the nuclei of infected basal layer cells of the epithelium. Until now, no single receptor has been definitively identified and established as being responsible for HPV entry. Some reports have suggested that a6 integrin may be a candidate receptor because it is expressed primarily during wound healing. The glycosaminoglycan heparin, a polysaccharide expressed on the cell surface, may also play a role in the attachment necessary for the initiation of HPV infection (Vidal & Gillison, 2008).

HPV uses the host cell DNA machinery to maintain the production of viral progeny. This mechanism of viral-induced cell growth is very well known and is analogous to other viruses that disrupt the control of cell growth (Hebner & Laimins, 2006). Following cell division, as the basal cells divide into squamous epithelial cells, HPV establishes its DNA genome in the host cell nuclei, replicates and reaches a high copy number. Infected cells then leave the basal layer, migrate toward the suprabasal regions and begin to differentiate. In the basal layer phase, the HPV genome is maintained at a low copy number, providing a type of stock of viral DNA for further use in cell divisions. At the same time, 'early' viral genes (E5, E6 and E7) are expressed, resulting in enhanced proliferation of the infected cells and their lateral expansion. While the basal cells and viral DNA divide, some daughter cells may be maintained in the basal layers, whereas other daughter cells move toward the upper layers of the epithelium and begin to differentiate. During the process in which the infected cells enter into the suprabasal layers, the viral genome replicates to a higher copy number;

'late' viral gene (L1 and L2) expression is initiated; and structural proteins, as such capsid proteins, are formed. Subsequently, virions are assembled and released as the upper layer of epithelium is shed, as shown in Figure 1 (Fehrmann & Laimins, 2003; Scheurer et al., 2005; Vidal & Gillison, 2008).
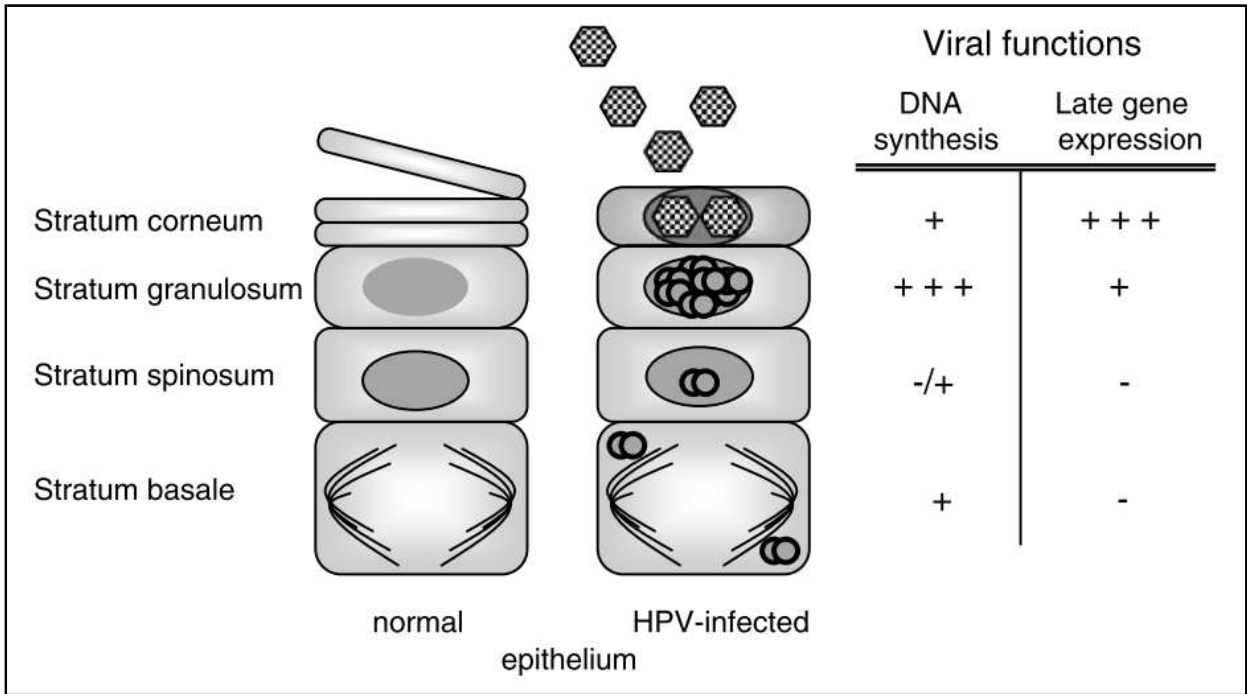

Fig. 1. Representation of normal and HPV-infected epithelium according to the cellular differentiation and the differentiation-dependent viral functions (Adapted from Fehrmann & Laimins, 2003).

HPV replication occurs through two mechanisms. The first mechanism occurs in the basal layer cells where the viral genome is distributed to daughter cells. In this mechanism, viral genome integration ensures a persistent infection in the proliferative cells from the basal layer and is associated with a higher risk of malignant cellular transformation. In the second mechanism, which is known as episomal or vegetative, HPV replication occurs in the more differentiated layers of the epithelium and the integration of viral DNA into the host cell genome is not necessary. Despite the fact that the replication processes and gene expression are controlled by the cell differentiation process, much about this mechanism is still unknown, and cervical cancer serves as a model for understanding HPV pathogenesis in other sites, such as in head and neck cancers (Zur Hausen, 2002). During cervical infection, the viral genome frequently integrates into the host cell genome. This integration occurs preferentially at fragile sites. The integration of viral DNA most likely disrupts the E2 coding region, causing the loss of the role of E2 in transcriptional control; therefore, the expression of the E6 and E7 oncoproteins becomes deregulated (Vidal & Gillison, 2008).

In tonsillar carcinomas, the absence of integrated HPV DNA does not suppress the expression of viral oncogenes, indicating that viral DNA integration is not an essential step for carcinogenesis and that the virus continues to be present in an episomal form (Hebner & Laimins, 2006; Vidal & Gillison, 2008). The mechanism used by HPV to remain in cancer tissue as an episomal form and produce high copy numbers is still unclear. However, some

observations have shown that the oncoprotein E2 may serve as an 'anchor' that links episomal HPV to the cellular mitotic spindles (Psyrri et al., 2009).

6. How does HPV reach the head and neck sites?

Generational changes have occurred in sexual practices around the world, where the young people are having their first sexual experience at an earlier age, with greater numbers of sexual partners and with a higher probability of engaging in oral sex compared to individuals from earlier decades (Heck et al., 2010). These differences in sexual behavior can also be seen between patients with HPV-positive HNSCCs, especially among those with the high-risk type HPV-16 (Gillison et al., 2008).

In oropharyngeal cancers (OPCs) that are positive for HPV, a frequent association with sexual behavior has been found (D'Souza et al., 2007). An investigation of more than 5000 cases of head and neck cancer and more than 6000 control cases from 12 different countries has indicated that a history of six or more lifetime sexual partners and four or more oral sex partners increases the odds of developing OPC. In cancer at the base of tongue, this association was found among individuals who have two sexual partners compared to those with only one, while little evidence has indicated any association between sexual practice and cancers of the oral cavity or of the larynx. Additionally, an increased risk of tonsillar cancer is associated with a history of four or more oral sex partners (3-fold increased risk), age at sexual debut < 18 years among men (2-fold increased risk) and in husbands of women who presented cervical dysplasia or cancer (Lajer & Von Buchwald, 2010). In addition to oral sexual activity, open-mouthed kissing has been found to be associated with oral HPV infections. Because this practice is common among young people in many countries, it may contribute to HPV circulation and increase the risk of HPV infection among individuals who might not otherwise be exposed. The prevalence of HPV in control patients from the studies of oral cancer varies from 5% to 9%; however, the same sexual behaviors associated with HNSCC can increase the odds of HPV infection in this population. Interestingly, in patients with HNSCCs, heavier smoking and alcohol use is associated with risky sexual behaviors, but this association is not observed in control individuals without cancer (D'Souza et al., 2009).

No difference was noticed between men and women according the outcomes of oral sex or number of oral sex partners and lifetime sexual partners, and the prevalence of oral HPV was found to be similar between heterosexual and bisexual women. In contrast, the presence of oral HPV infection is unlikely in virgins and women who have sex with women, which suggests that oral HPV is more likely to be associated with sexual exposure to male partners than to female partners (Ragin et al., 2011).

7. HPV and oral lesions

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 (Bouda et al., 2000; Kojima et al., 2002). The low-risk HPV types cause benign oral hyperplasias that are usually painless and non-ulcerated (Cleveland, 2011). Verruca vulgaris (caused by HPV 2, HPV 4 and other HPV

types) usually occurs on the lips, hard palate and gingiva. Condyloma acuminata or genital warts (caused by HPV 6 and HPV 11) may also affect the oral mucosa and are found more commonly on keratinized mucosa (Cleveland et al., 2011; D'Souza et al., 2007; Dayyani et al., 2010). Notwithstanding, 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 (Vidal & Gillison, 2008). 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 (Kreimer et al., 2005). Additionally, several others HPV types (6, 11, 35, 45, 51, 52, 56, 58, 59 and 68) have rarely been detected in head and neck cancer. 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 type detected in head and neck cancer (Fakhry et al., 2008; Kreimer et al., 2005; Snow & Laudadio, 2010), and oropharyngeal tumors are more likely to have HPV 16 than other types at head and neck sites. The genotype 16 accounts for 78% to 100% of positive oropharyngeal cases, while HPV-18 accounts for only 1% of cases (Kreimer et al., 2005). Seropositivity for HPV 16 has a greater association with an increased risk of OPC (OR = 14.4) than with the development of oral cavity cancer (OR = 3.6). This association is particularly strong in individuals without a history of smoking or drinking (OR = 33.6) (Hennessey et al., 2009). 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 (Guimarães et al., 2010; Lira et al., 2010; Mazon et al., 2011).

The results from recent studies have suggested that some of these cancers, primarily those that originate in the oropharynx (and, more specifically, at the base of the tongue and the tonsils), are associated with high-risk HPV infection (Lopes et al., 2011). This association is strengthened by the fact that the same oncogenic HPV types detected in cervical carcinomas have been identified in head and neck cancers. In recent oral cancer guidelines published by the American Dental Association (ADA), HPV was recognized as a risk factor for OPCs, but whether HPV is also responsible for some oral cavity cancers was questioned (Rethman, 2010).

Several head and neck tumors 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 (Kreimer et al., 2005; Syrjanen, 2005). Some evidence has indicated that some subtypes of HPV are linked to head and neck cancer, especially those arising from some oropharyngeal subsites (e.g., tonsil and the base of the tongue) (Gillespie et al., 2009). The overall HPV prevalence in HNSCC ranges from 3% to 40% and could vary more according to the specific site. HPV has been found in 4-80% of oral cancers, 15-85% of tonsillar cancers, approximately 24% of non-tumor site-specific HNSCC and 14-57% of OPCs (IARC, 2007; Kreimer et al., 2005; Machado et al., 2010; Syrjanen, 2005; Termine et al., 2008). Brazilian observations in the countryside of Sao Paulo state have found a low prevalence of HPV in tumors of the larynx (Miranda et al., 2009) and an increase in the presence of HPV DNA in oral cavity cancers during the past two decades (Lira et al., 2010; Mazon et al., 2011; Oliveira et al., 2008). 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 (Feller et al., 2010). Among the many methods to detect HPV infections, both polymerase chain reaction (PCR) and in situ hybridization assays have been well validated.

Because of the high sensitivity of the PCR assay, it may detect not only oncogenic infections but also productive infections, virions or laboratory artifacts, which are common problems in HPV screening for cervical cancer (Leemans et al., 2011). 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. Despite the existence of innumerable options for HPV detection in HNSCC, a standardization of procedures for routine application has yet to be developed (Feller et al., 2010; Kumaraswamy & Vidhya, 2011; Snow & Laudadio, 2010).

A global consensus exists regarding the increasing risk of OPCs with HPV, mainly in the tonsils and at the base of the tongue (Attner et al., 2010; Heck et al., 2010). A survey of the Surveillance, Epidemiology and End Results (SEER) database revealed that the incidence rates for HPV at the base of the tongue and in the tonsils increased by 2% and 4%, respectively, between 1973 and 2001 in younger US populations (ages 20-44 years). At the same time, the incidence in all other oral and pharyngeal sites remained constant or decreased (Gillespie et al., 2009). Other countries, such as Sweden, have seen a similar increase in the incidence of tonsil cancer from 1997-2002; HPV could be isolated in 23% of specimens in the 1970s, 28% in the 1980s, 57% in the 1990s and 68% in specimens since 2000 (Hammarstedt et al., 2006). A review of 60 studies of HPV prevalence, which was published in 2005, observed an overall prevalence of 26% of HPV in HNSCCs, with a greater percent at the oropharynx (36%) (Kreimer et al., 2005). Similar numbers were obtained from the results of a recent meta-analysis that included more than 5000 patients. Among all HNSCCs, 22% of cases presented HPV infection, and the subgroup of OPCs presented a prevalence of 41% (Dayyani et al., 2010). In the USA, approximately 40-80% of OPC cases are associated with HPV, whereas in Europe, the proportion ranges from 90% in Sweden to 20% in populations that contain a great number of heavy smokers (Marur et al., 2010).

Confirming the importance of HPV infection in HNSCC, the 2007 International Agency for Research on Cancer (IARC) monograph on HPV found sufficient evidence for HPV carcinogenicity in the oral cavity and oropharynx and limited evidence for HPV carcinogenicity in the larynx (IARC, 2007). Currently, the identification of distinct epidemiological profiles in HPV-positive and HPV-negative HNSCCs is possible. Although studies have shown no concordance regarding some of these epidemiological aspects, we may have to look at HPV-positive and HPV-negative HNSCCs in a separate manner in the future, including scientific, diagnostic, epidemiological and clinical aspects and the management of treatment. 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 (Gillespie et al., 2009). 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). The tumors associated with the presence of HPV usually appear strawberry-like and exophytic 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

(Gillespie et al., 2009). In addition, gene expression profiles are known to be different in HPV-positive OPCs compared with HPV-negative cases (Lajer & Von Buchwald, 2010).

8. HPV in oropharyngeal cancer

The OPCs comprises tumors arising in posterior regions of oral cavity, and its incidence has been increasing, especially between individuals aged 40 to 55 years. It is accepted that a great part of OPCs, especially in lingual and palatine tonsils, are originated by HPV infection. Compared to non-contaminated individuals, the relative risk is 15- to 200- fold in HPV infected patients, and may not show a history of known risk factors for OPC, such tobacco and alcohol consumption, highlighting a different pattern for non-HPV-related OPC (Marur et al., 2008). Moreover, the presence of HPV is also associated to positive cervical lymph nodes of patients in different sites of HNSCCs, but mainly in oropharynx (Goldenberg et al., 2008; Lira et al., 2010; Machado et al., 2010).

Although oral and oropharyngeal HPV infections are primarily sexually acquired, other methods of contamination such as mouth to mouth contact between partners and between family members, besides autoinoculation, are also potential routes where HPV infection of oropharyngeal sites can be established. As oral and oropharyngeal subclinical HPV infection is not uncommon, it is possible that the epithelium may serve as a reservoir of virus (Feller et al., 2010).

The most common morphological presentation of HPV-related OPC is different of non-HPV tumors. The HPV OPCs usually are not associated with dysplasia of surface epithelium, show lobular growth, are usually infiltrated by lymphocytes and have prominent basaloid morphology. Two microscopic features of HPV-related OPCs are likely to cause diagnostic ambiguity. First, HPV-related HNSCC is customarily misperceived as a poorly differentiated carcinoma based on the immature appearance of the tumor cells. In point of fact, the appearance of the tumor cells closely emulates the appearance of the reticulated epithelium—the specialized epithelium lining the tonsillar crypts from which HPV-related cancers arise. Thus, HPV-related OPCs are in fact highly differentiated. Clinically, HPV-related tumors present mostly at an early T stage, but show an advanced nodal stage, generally presenting as stage III or IV tumors, although HPV-related OPCs usually have a better prognosis when compared to non-HPV tumors. Despite the HPV-associated OPC patients have a relatively better disease-free survival rate, some individuals develop recurrence of their cancers after treatment and dies from recurrent disease. Based in this condition, screening tests could be beneficial for the detection of disease persistence or of early disease, using unique markers associated with HPV infection (Feller et al., 2010).

9. HPV in laryngeal cancer

The relative frequency of HPV genotypes in carcinoma of the larynx is still unknown; several studies have demonstrated variable frequencies ranging from 8 to 58.8% (Hobbs et al., 2006; Psyrri et al., 2008). The larynx forms of contamination and transmission of the virus are sometimes speculative. Infections of the larynx, pharynx and esophagus can occur, especially at birth when the newborn passes through the birth canal and comes in contact with the fluid-contaminated site. Together with oral-genital transmission, puerperal infection is one explanation for the presence of HPV in the oral cavity, larynx and esophagus (Zur Hausen, 1996).

The potential oncogenic importance of low-risk types of HPV in the development of laryngeal papillomas is well established, and the predominant types are HPV 6 and 11 (Herrero et al. 2003; Madkan et al., 2007), which are pathogens of laryngeal papillomatosis. According to the clinical characteristics and natural history of disease, four different forms of laryngeal papillomas exist, namely isolated juvenile papillomatosis, juvenile multiple, adult and adult isolated multiple (Madkan et al. 2007; Torrente & Ojeda, 2007). More recently, this nomenclature has been replaced by recurrent respiratory papillomatosis (RRP), which more accurately describes the extent of the disease and its tendency to recur (Muenscher et al., 2008). Juvenile-onset laryngeal papillomas are associated with HPV transmitted by vertical transmission from a mother with active or latent anogenital infection. More than 30% of mothers with genital warts gave birth to children who developed juvenile-onset laryngeal papillomatosis. This disease occurs most commonly in first-born children and those who were delivered vaginally to young mothers with genital warts. Cases of children with laryngeal papillomatosis who were born by cesarean section are rare. The progression of papillomas is slow, causing the progressive symptoms of shortness of breath, persistent cough and dysphonia. Juvenile laryngeal papillomatosis affects both sexes equally. The most worrisome aspect of the disease is the spread of the virus thorough the tracheobronchial tree, progressing to pulmonary papillomatosis and often resulting in an uncontrollable and fatal infection. Another important event is the malignant transformation of laryngeal papillomas, which despite being a rare event, occurs in approximately 3-7% of cases.

The laryngeal papillomas of adult onset generally affect individuals with a higher number of sexual partners and greater frequency of orogenital contacts. The oral-genital transmission hypothesis is based on the fact that laryngeal papillomatosis and genital warts have the same associated HPV infections (HPV 6 and 11). The area of transition from cuboidal and cylindrical epithelium in the larynx and uterine cervix may favor the occurrence of HPV in this location (Torrente & Ojeda, 2007).

The premalignant lesions of the larynx are defined as morphologically altered tissue in which the occurrence of cancer is more likely than in apparently normal tissues. The detection of HPV DNA in premalignant lesions shows that HPV infection can be involved in the development of some lesions. Premalignant oral lesions usually develop as a result of several factors, such as tobacco and alcohol, and the synergistic interaction of HPV infection with these factors may play a role in the progression to cancer (Torrente & Ojeda, 2007). However, although HPV has been found in a large proportion of laryngeal cancers, more epidemiological and experimental studies are needed to clarify the role of HPV in laryngeal carcinomas.

10. Interaction between traditional risk factors and HPV infection in HNSCCs

Smoking and alcohol consumption are characteristics of patients with oral, oropharyngeal, hypopharyngeal, and laryngeal cancer. However, in the last 30 years, the presence of HPV associated with the increase in the incidence of HNSCCs at specific sites has suggested that the HPV infection can be a potential risk factor, independent of tobacco abuse and ethanol consumption (Blomberg et al., 2011; Chaturvedi et al., 2008; D'Souza et al., 2007; Hammarstedt et al., 2006; Klozar et al., 2010).

Several clarifying findings have recently been made in the scene of HPV in the head and neck. The traditional prototype of an OSCC patient used to be an older man who had

smoked and consumed alcohol for many years. However, this profile no longer represents patients who are now diagnosed with oral cancer. The patients now are usually younger (< 60 years) Caucasians with no history of smoking or alcohol drinking (D'Souza et al., 2007; Gillison et al., 2008). The main risk factors, tobacco and alcohol, have been supplanted by other risk factors associated with HPV and sexual behavior, which include the number of sexual partners, a history of oral-genital and oral-anal sex. As a biomarker, the detection of HPV infection is emerging as a powerful method for identifying oral cancer. The presence and progress of the disease affects the selection of patients for specific treatments and tumor surveillance (Westra, 2009, as cited in Begum et al., 2003).

Whether the use of tobacco or alcohol and HPV are synergistic in the etiopathogenesis of oral and oropharyngeal cancers is not yet clear (Feller et al., 2010). Notably, many studies of HPV infection and exposure to tobacco have concluded that patients with tumors containing HPV DNA are characterized by moderate or no consumption of tobacco and alcohol, unlike individuals in the typical head and neck cancer patient population (D'Souza et al., 2007; Hafkamp et al., 2008; Klussmann et al., 2003). In research performed by Koch et al. (1999) a 2-fold higher rate of HPV-associated tumors was observed in noncurrent smokers compared to current smokers, although the group classified as noncurrent smokers included both never and former smokers (Sinha et al., 2011). However, small sized groups, weak statistical evidence, and inconsistent definitions of smoking status could limit some of these studies. No consensus exists regarding the definition of current, never or former smokers or the criteria of light vs. heavy smoking (Sinha et al., 2011).

In contrast, most of the studies that have noted a positive association between tobacco and HPV infection have had large sample sizes and adequate controls, which support consistent conclusions. A study that evaluated 201 cases of HNSCC using an ELISA assay to assess anti-HPV virus-like particles observed no interaction with alcohol in the oral cavity or oropharynx cancer, but a significant interaction between HPV and tobacco among oropharyngeal cases was obtained (Herrero et al., 2003; Smith et al., 2010). Other information provided by these studies is the influence of smoking intensity on disease survival. Heavy smoking of more than 20 pack-years has been associated with an increased hazard ratio of death (hazard ratio, 1.79) in patients with HPV-positive OPC compared to patients who smoke less than 20 pack-years (Gillison et al., 2009).

Although much of our understanding of HPV in HNSCCs is based on the model of cervical cancer, the degree of interaction between smoking and HPV in this type of cancer is still not well known. Biologically, smoking can suppress the mediators of immune function, facilitating the persistence of HPV infection and the development of cancer (Sinha et al., 2011). The DNA damage caused by smoking may impede the cell's ability to recuperate from mutagenic insults; together with an increase in p53 mutations, this impairment can produce fragile sites or "hot spots" of DNA breakage, which facilitates the integration of the virus into the host DNA (Sinha et al., 2011). Thus, genetic or epigenetic alterations caused by tobacco have also been postulated to accelerate disease progression in HPV-infected individuals (Maxwell et al., 2010; Sinha et al., 2011).

11. What can HPV tell us about prognosis and treatment?

Due to locoregional recurrences, distant metastases and second primary tumors, no substantial improvement in survival has been observed in patients with HNSCCs in recent

decades (Leemans et al., 2011). Because multivariate analyses have pointed to HPV status as significant prognostic information in addition to the traditional established factors, the data suggest that HPV is the most important independent prognostic factor in HNSCC (Hannisdal et al., 2010; Lajer & Von Buchwald, 2010). HPV-infected HNSCCs have favorable prognoses upon treatment compared with HPV-negative tumors at a similar clinical stage (Leemans et al., 2011). Most investigations that have evaluated HPV infection and survival agree that HPV-positive patients have a significantly better survival (5-year survival of approximately 70%) than HPV-negative patients (5-year survival of approximately 35%) (Fakhry et al., 2008; Klozar et al., 2008; Vidal & Gillison, 2008). A prospective multicentric study has shown that individuals presenting HPV-positive OPCs had better response rates to chemotherapy than individuals with no HPV infection (Fakhry et al., 2008). Numerically, in the same study, the overall 2-year survival rate for those presenting HPV-positive tumors was 95% (95% CI = 87%-100%), compared with a 2-year survival rate of 62% (95% CI = 49%-74%) for those without HPV infection (Henessey et al., 2009). In other multicenter prospective trials evaluating treatment responses in oropharyngeal or laryngeal carcinomas, the HPV-positive OPCs were found to have higher response rates to chemotherapy (82% versus 55%) than HPV-negative cases (Fakhry et al., 2008). Other similar findings have been obtained in treatment response to radiotherapy associated with the presence and titer of the high-risk HPV 16 (Dayyani et al., 2010; Vidal & Gillison, 2008). This improved survival is more pronounced in OPCs (Dayyani et al., 2010; Hannisdal et al., 2010), and even in investigations with no significant associations, there is a tendency toward HPV positivity in patients with longer survival.

Although the improved prognosis conferred by HPV seems to be independent of the treatment strategy, the mechanism responsible for this survival difference is still unclear. Several hypotheses have been proposed, which include the fact that patients presenting HPV-related HNSCCs are usually non-smokers and non-drinkers and do not show comorbid disorders. Moreover, despite the lack of conclusion regarding the correlation of HPV positivity in some HNSCC sites with p53 status, an enhanced radiosensitivity of HPV-positive tumors due to an improved apoptotic response secondary to the absence of mutations in TP53 of HPV-positive tumors has been proposed, as has immune surveillance to viral-specific tumor antigens (Vidal & Gillison, 2008) and lack of field cancerization characteristics of individuals with tobacco- and alcohol-related HNSCCs (Hennessey et al., 2009).

12. Our results regarding HPV infection in Brazilian oral squamous cell carcinoma patients

The true prevalence of HPV DNA in OSCC and its role as a possible oncogenic agent are still controversial. We performed a study that aimed to investigate the HPV frequency in Brazilian patients with OSCC in order to establish a clinicopathological profile and its possible influence on prognosis (Oliveira et al., 2008). We examined the correlation between patient survival and HPV expression in primary tumors (PTs), and their matched samples (MSs) of recidives, lymph nodal metastasis (LNM) or necropsies. Eighty-seven PTs and their corresponding 87 MSs were tested for HPV infection through PCR using general and type-specific HPV primers. For HPV DNA detection, we utilized the GP5+/GP6+ (Bioneer Inc.) consensus general primer pair to amplify a 150-bp fragment from the L1 gene of

general HPV types (GP5+, 5'-TTTGTTACTGTGGTAGATACTAC-3'; GP6+, 5'-GAAAAATAAACTGTAAATCATATTC-3'). After, PCR was then performed on the HPV-positive DNA samples to determine if they contained genotypes 16 and 18, using specific primers targeting ~100 bp in the E7 ORF: HPV-16E7.667 (5'-GATGAAATAGATGGTCCAGC-3'), HPV-16E7.774 (5'-GCTTTGTACGCACAACCGAAGC-3'), HPV-18E7.696 (5'-AAGAAAACGATGAAATAGATGGA-3') and HPV-18E7.799 (5'-GGCTTCACACTTACAACACA-3') (Bioneer Inc.). Of the 87 patients investigated, 17 (19.5%) were found to have HPV DNA in their tumors. An investigation of all the paraffin-embedded specimens revealed the presence of HPV DNA in 18 of the 174 samples (10.4%), 10 (11.5%) from PTs and 8 (9.2%) from MSs. Notwithstanding, no virus infection was detected in the corresponding PT of 7 (8.1%) MSs, and only a patient demonstrated HPV DNA positivity in both samples. The 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 the HPV genotype was unidentified in 5 (27.8%) samples. The tongue was the most prevalent infected anatomical site. Our main result was a significant number of positive HPV samples among non-smoking patients, and albeit a possible influence of HPV on tumoral induction cannot be ruled out, the low frequency of HPV positive OSCC cases found in our investigation does not suggest that this virus has the same etiological influence on patients as tobacco consumption does, and although we cannot rule out a possible transient role for HPV in the induction of OSCC, we think that the occasional detection of HPV in OSCC resulting from the incidental colonization of tumoral lesions might reflect the true involvement of HPV in most investigations.

13. HPV vaccine

In many countries, vaccines against some HPV types are administered to girls and young women with the goal of protecting them against HPV-induced cervical cancer (Villa et al., 2005; Muñoz et al., 2010). The introduction of HPV vaccines has also drawn more attention to the fact that HPV is associated not only with cervical cancer and genital warts but also with other tumors, such as head and neck and anogenital cancers (Zur Hausen, 2006).

Although the majority of HPV vaccine research has focused on cervical cancer, some vaccine developers have targeted other diseases related to different strains of HPV, including two types of HPV (6 and 11) that can cause genital warts and recurrent respiratory papillomatosis in the larynx. Vaccines against these other strains have attracted the interest of vaccine developers because these vaccines may qualify for orphan drug status and fast-track licensing in the United States (Nventa Biopharmaceuticals Corporation, 2005; Path, 2006).

Emerging results from vaccine trials have suggested that some cross-protection is possible. Vaccines against cervical cancer also have the potential to prevent other cancers that are caused by the same types of HPV, including a subset of head and neck cancers (notably the OPC) (Herrero et al., 2003, Kreimer et al., 2005), and half or more of anogenital cancers outside the cervix, including cancer of the vulva, vagina, penis, and anus (Daling et al., 2005, Gross & Pfister 2004). Theoretically, these vaccines should also work against the same viruses at other anatomical sites. If proven to do so, this approach would represent a major conceptual breakthrough, not only in prevention of these diseases, but equally importantly,

by providing the 'missing link' in the chain of evidence for the final proof of HPV etiology of these tumors (Syrjänen, 2010).

13.1 Types of HPV vaccines

The development of prophylactic and therapeutic vaccines targeting HPV antigens for the control of tumors caused by HPV is increasing worldwide. These upcoming vaccines are part of a new generation of vaccines that employ genetic engineering, using the ability to manipulate and transfer genes from one organism to another (Path, 2006).

Prophylactic vaccines work primarily by stimulating humoral immunity and inactivating HPV before the virus infects the host cells (Zinkernagel, 2003). This strategy requires high levels of antibodies at mucosal surfaces over long periods of time (Path, 2006). Maintaining these high levels is difficult, so it is recommended that prophylactic vaccines should also stimulate a cellular immune response that is capable of eliminating early stages of infection in host cells (Duggan-Keen et al., 1998; Galloway, 1998).

In contrast, therapeutic vaccines aim to generate cell-mediated immune responses using killer T cells that actively destroy HPV-infected cells and may exert immediate effects on lowering HPV-related disease incidence. To be effective, therapeutic HPV vaccines must prompt cell-mediated immunity because antibodies cannot reach and eliminate the virus once it has been incorporated into host cells (Ling et al., 2000; Chu, 2003; Maclean et al., 2005). This type of vaccine could help people who are already infected with HPV. Used alone or in combination with standard therapies, a therapeutic vaccine could help prevent the progression of low-grade disease and cause existing lesions to regress, avoiding the recurrence of cancer lesions after treatment (Chu, 2003; Stanley, 2003).

In a broad revision, Path (2001) described the existence of five types of HPV vaccines: recombinant live vector vaccines; protein and peptide vaccines; virus-like particles (VLPs); "naked" DNA vaccines; and edible vaccines (in which plants are genetically engineered to express HPV antigens in fruits and vegetables, leading to immunization through ingestion of the modified foods).

The following three categories of HPV proteins represent potential targets for vaccines, each of which is expressed during different stages of infection and disease:

1. The capsid proteins L1 and L2 compose the outside coat of HPV particles. These proteins interact with the surface molecules of epithelial cells during early stages of infection to gain entry for the viral DNA. Because L1 and L2 are present during the initial infection, they are ideal targets for a prophylactic vaccine (Lowy & Schiller, 1998). However, once HPV has integrated into the tumor cells, the capsid proteins are not always present and they are not reliable targets for a therapeutic vaccine.
2. The oncoproteins E6 and E7 continue to be expressed during later stages of disease and are the primary targets of therapeutic vaccines. These proteins bind the human tumor suppressor genes p53 and pRB (Duggan-Keen et al., 1998) and are involved in the malignant transformation of HPV-infected cells (Van Driel et al., 1999).
3. The proteins E1 and E2 are necessary for HPV replication within cells before the virus integrates into the host DNA (Duggan-Keen et al., 1998; Van Driel et al., 1999). Because E1 and E2 are expressed at higher levels than E6 and E7 at the early stages of HPV infection,

they may represent the best targets for a therapeutic vaccine designed to treat the early stages of disease, such as low-grade dysplasias (Tindle, 1996; Lowy & Schiller, 1998).

13.2 The HPV prophylactic vaccines

The current HPV prophylactic vaccines are based on VLPs (Van Monsjou et al., 2010). At present, two prophylactic HPV vaccines are commercially available: the bivalent (HPV 16/18) vaccine Cervarix® (GlaxoSmithKline, Middlesex, UK) and the quadrivalent (HPV 6/11/16/18) Gardasil® (Merck, NJ, USA). Licensed globally, these two vaccines have produced great expectations that they will prevent infections and tumors induced by different HPV types (Syrjänen, 2010).

The US Food and Drug Administration (FDA) approved Gardasil for females ages 9–26 in 2006. In October 2009, the FDA approved Cervarix for use in females ages 10–25 and approved Gardasil for use in males ages 9–26 to prevent genital warts and to prevent the spread of cervical cancer. Moreover, the FDA (2010 and 2010a) has proclaimed that the dosing and administration schedule should be 0.5 mL administered intramuscularly (preferably in a deltoid muscle) on a 3-dose schedule. The second dose should be administered 1 to 2 months later, and the third dose should be administered 6 months after the first dose.

These vaccines target the HPV major capsid protein L1 and can assemble to form VLP morphologically resembling native virions to generate robust antibody responses and prevent HPV infection. However, Gardasil and Cervarix differ in their adjuvants, which are substances added to a vaccine to enhance its impact by stimulating immune responses. In Gardasil, each type of VLP is purified and adsorbed on an aluminum-containing adjuvant (amorphous aluminum hydroxyphosphate sulfate), which is widely used. In contrast, Cervarix is formulated with a novel adjuvant, AS04, developed by the Corixa Corporation to strengthen and prolong the immune response to vaccines. Like aluminum hydroxide, AS04 includes MPL® (3-deacylated monophosphoryl lipid A), which is a derivative of the lipid A molecule found in gram-negative bacteria and a potent immune system stimulant because it primes innate immunity and may stimulate adaptive immunity and enhance antibody titers (Ma; Roden; Wu, 2010).

Although clinical trials of Gardasil and Cervarix have been extremely promising, these first generation VLP vaccines may not be the ideal vaccine candidates, especially in low-resource settings. Researchers are now actively working to develop other prophylactic HPV vaccines that may be effective against a broader range of HPV types and have a longer shelf life.

13.3 The HPV therapeutic vaccines and its perspectives

Immunotherapy offers an attractive alternative treatment strategy because it can address both the underlying HPV infection and the visible lesions. Moreover, immunotherapy can target all HPV-associated lesions, regardless of location, and induce long-lasting immunity, thus preventing recurrence (Chu, 2003; Stanley, 2003).

A judgment of whether therapeutic HPV vaccine candidates have a real effect on disease has been difficult because most trials have not been placebo-controlled. The vaccines have also shown, at best, limited efficacy in eradicating established tumors, although the fact that they

have mostly been tested in advanced stage cancer patients with compromised immune systems may have limited their impact (Brinkman et al., 2005).

Perhaps the most effective HPV vaccine strategy calls for a vaccine that possesses both prophylactic and therapeutic properties. A chimeric vaccine of this type could both prevent new HPV infections and clear existing infections. Moreover, such a vaccine would benefit and could be administered to both sexually inexperienced young individuals and older individuals who already harbor HPV (Franceschi, 2005). Opportunities for primary and secondary prevention should be assessed, including the use of HPV vaccines to prevent infection and therapeutic vaccines in the adjuvant setting for locoregional recurrence and distant disease (Marur et al. 2010). Combined with the fact that no therapeutic vaccines currently exist for other diseases, this goal makes therapeutic HPV vaccine development a challenging task.

The eventual routine of HPV prophylactic vaccination will most likely have an impact not only on the incidence of cervical and anogenital cancers in women and men but also on the incidence of some groups of head and neck tumors, as in OPC. The increasing proportion of HPV-positive head and neck cancers underlines the increasing importance of routine prophylactic vaccination against HPV, and together with tobacco and alcohol control, this vaccination could have a decisive position in the prevention of head and neck cancer (Klozar et al., 2010). Vaccines directed against HPV 16, which accounts for 80–90% of all HPV-positive HNSCC, currently exist in Europe and USA (Dahlstrand & Dalianis, 2005; Sturgis & Cinciripini, 2007; Hammarstedt et al., 2006; Lindquist et al., 2007; Mellin et al., 2002; Gillison et al., 2008; Ang et al., 2010; Marur et al., 2010; Näsman et al., 2009; Attner et al., 2010).

14. Final considerations

Several aspects still remain to be discovered in the field of head and neck cancers and HPV infection, but the epidemiological analysis of the last decade demonstrates a rapid increase in the incidence of HPV-associated HNSCCs, and sufficient evidence now exists for a causal role of HPV in HNSCC. The genomic detection of HPV DNA, primarily in OPCs, provides stronger support for a viral etiology in HNSCC. Although some synergies between HPV oncogenes and other carcinogens have been hypothesized, non-smoking and non-drinking patients and those who sexually debut at a younger age have an increased risk of HPV-positive HNSCCs but show a favorable prognosis. Specifically in oral mucosa, some authors have suggested that the occasional finding of HPV DNA in OSCC specimens might not result from viral infection but rather from an incidental HPV colonization. However, a relative HPV contribution to oral carcinogenesis may occur in a subgroup of patients, mainly in areas where tobacco use is less common.

Targeted therapy for HNSCCs now demands more predictive biomarkers, such as the HPV infection status and mutation status of crucial genes, which could contribute to personalized treatment for individual patients and decrease the inherent morbidities. However, for a better understanding of whether the HPV status of tumors has real therapeutic implications in affecting the clinical outcome, upcoming clinical trials should be significantly standardized in their design and performed on HNSCCs that have been adequately selected and classified with respect to the different head and neck anatomical sites. Moreover, we

suggest that other methodologies should be utilized to improve HPV detection and that additional population studies should be performed to confirm these findings.

We believe that the increasing proportion of HPV-positive HNSCCs highlights the importance of vaccination against HPV. Although detection of the true effects of HPV vaccination on cancer incidence will probably continue for several decades, monitoring the current effects of HPV vaccination is crucial, not only in cervical cancer, but also in head and neck cancer.

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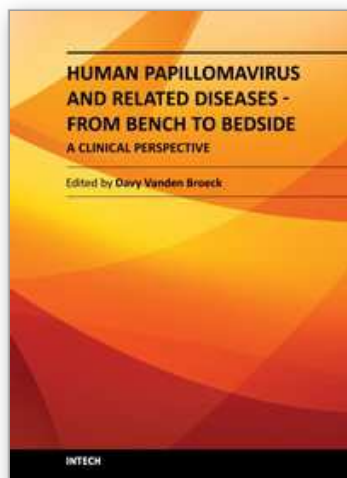
Human Papillomavirus and Related Diseases - From Bench to Bedside - A Clinical Perspective

Edited by Dr. Davy Vanden Broeck

Cervical cancer is the second most prevalent cancer among women worldwide, and infection with Human Papilloma Virus (HPV) has been identified as the causal agent for this condition. The natural history of cervical cancer is characterized by slow disease progression, rendering the condition, in essence, preventable and even treatable when diagnosed in early stages. Pap smear and the recently introduced prophylactic vaccines are the most prominent prevention options, but despite the availability of these primary and secondary screening tools, the global burden of disease is unfortunately still very high. This book will focus on the clinical aspects of HPV and related disease, highlighting the latest developments in this field.

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