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Impact of HPV infection on the development of head and neck cancer

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Abstract

Human papillomavirus (HPV)-related head and neck squamous cell carcinoma (HNSCC) is considered to be a distinct clinical entity with better prognosis than the classical tobacco- and alcohol-associated tumors. The increasing incidence of this neoplasia during the last decades highlights the need to better understand the role of HPV in the development of these cancers. Although the proportion of HNSCC attributed to HPV varies considerably according to anatomical site, overall approximately 25% of all HNSCC are HPV-DNA positive, and HPV-16 is by far the most prevalent type. In this review we discuss the existing evidence for a causal association between HPV infection and HNSCC at diverse anatomical head and neck subsites.

Key words: Human papillomavirus; Oncogenic potential; Head and neck cancer; Viral prevalence

Human papillomavirus

Biology

The Papillomaviridae family is a diverse group of small non-enveloped tumor viruses that infect, in a species-specific way, the mucosal and cutaneous epithelia of a broad variety of higher vertebrates. The human papillomavirus (HPV) virion is approximately 55 nm in diameter and encloses a single-closed circular double-stranded DNA genome of about 8000 bp bound to cellular histones. The viral genome encodes approximately eight open-reading frames that can be functionally divided into three parts: the early (E) region that encodes proteins necessary for viral replication and transcription, the late (L) region that encodes the structural proteins of the capsid (L1 and L2), and a non-coding region segment designated long control region (LCR), which contains cis-elements necessary for viral DNA replication and transcription regulation (1).

Taxonomy

HPV presents specificity for different tissues and diverse distribution among different anatomical sites. The majority of HPV genotypes belong to three different genera: α-papillomavirus, predominantly isolated from genital lesions, β-papillomavirus, referred to as HPV related to *Epidermiodisplasia verruciforme*, and γ-papillomavirus. β- and γ-papillomaviruses have been mainly isolated from cutaneous lesions (2).

In humans, over 150 different HPV genotypes have been fully sequenced and numbered in the order of their discovery (3). HPV taxonomy is based on *L1* sequence variability: viral genomes are classified as new types when they present less than 90% of identity to any other type. Differences in identity of less than 2% within the *L1* late gene define molecular variants of HPV (2). Nevertheless, nucleotide variability among variants differs across viral genes and can be as high as 5% in the LCR. Mostly, viral variants arise by nucleotide substitutions in few restricted positions within the entire genome. Nucleotide sequence analysis of HPV-16- and -18-positive cervical samples collected worldwide has categorized molecular variants into phylogenetically related lineages: European, Asian-American, Asian, and African (4). More recently, the nomenclature of variant lineages has been established for other HPV types (5,6). Distribution of HPV-16 and -18 molecular variants varies significantly among different geographical areas and correlates with the intrinsic level of admixture of each population.

Approximately 40 viral types infect the anogenital mucosa and HPVs have been further categorized as high- and low-risk types based on the risk of the virus to cause

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squamous cell carcinomas in the uterine cervix. α-papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 have been classified by the World Health Organization as carcinogenic in humans (carcinogens type I) due to their high prevalence in cervical cancer samples (7). In contrast, infections by non-oncogenic or low-risk HPV types 6, 11, 40, 42, 43, 44, and 54 are associated with the development of genital warts (8).

Oncogenic potential

The role of HPV in cervical carcinogenesis has been widely studied and documented. HPVs specifically target the undifferentiated proliferative basal cells of the epithelial mucosa exposed after tissue trauma. The virus further establishes productive infections within the stratified epithelia in such a way that the viral life cycle is closely linked to the differentiation program of the infected epithelial cell (1).

The HPV genome region sufficient for primary human keratinocyte immortalization maps to the LCR and *E6*/*E7* early genes (9). Transcription is regulated in a complex manner based on the identity of the infected epithelial cell type, the differentiation status of the stratified epithelium, and the episomal or chromosomally integrated state of the viral genome (10). HPV expression is regulated by cellular and viral transcription factors that bind to specific elements within the LCR, which varies widely among different HPV types. The E2 early regulatory protein binds to four different conserved sites in the LCR and inhibits *E6* and *E7* transcription (11). Yet, in tumor cells, viral genomes are frequently integrated into the host DNA, with interruption of the *E2* gene leading to an elevated expression of the *E6* and *E7* oncogenes.

High-risk HPV E6 and E7 proteins cooperate in the immortalization of primary human keratinocytes and in the inhibition of the differentiation of these cells induced by serum and calcium (12). These proteins bind with different affinity to host cell proteins and disturb the normal epithelial differentiation and apoptosis by stimulating cellular proliferation, DNA synthesis and inhibition of cell cycle control (1). The best-studied interactions are the association and degradation of TP53 and pRB by E6 and E7, respectively (13,14). TP53 mediates cell cycle arrest by blocking the progression at the G1/S checkpoint and E6-induced TP53 degradation abolishes this control. Additionally, high-risk HPV E6 stimulates cell proliferation by interacting with PDZ proteins including MUPP-1, hSCRIB and hDlg (15), and increases the lifespan of infected cells through the activation of telomerase (16). Functional inactivation of the pRB protein family by high-risk HPV E7 results in the release of the E2F transcription factor and further upregulation of cell cycle genes (1). In this way, high-risk HPV E7 activates DNA synthesis and cell replication mechanisms normally inactive in matured epithelial cells, initiating pathological cell growth. E6 complements E7 function by inducing cell survival and delayed apoptosis and together they mediate HPV-associated epithelial cell immortalization and cellular genomic instability that stimulates infected cells to assume a fully malignant phenotype.

Epidemiology

HPV is one of the most common sexually transmitted infections. It is the cause of a number of neoplasias, including cervical, anal, vulvar, vaginal, penile, and oropharyngeal cancers. Additionally, genital warts and the rare but very serious recurrent respiratory papillomatosis are etiologically associated with this virus (17).

HPV-induced cervical carcinogenesis is the most extensively studied malignancy associated with this virus. Infection of the uterine cervix is linked to high-risk sexual behavior including number of sex partners and age at first sexual intercourse. Other important co-factors for malignant clinical outcome include immune and nutritional status, the use of tobacco, and co-infection with other sexually transmitted agents including HIV and *Chlamydia trachomatis* (18).

Persistent infection with high-risk HPVs is responsible for the development of most, if not all, cervical cancers worldwide (19). Among these, HPV-16 is undoubtedly the most prevalent and, together with HPV-18, accounts for approximately 70% of all cervical cancer cases (20). Besides persistence of infection, the HPV type detected, the presence of multiple HPVs, whether the viral DNA is present episomally or integrated and viral load influence the development of cervical cancer.

Head and neck squamous cell carcinoma

Head and neck squamous cell carcinoma (HNSCC) comprises tumors of diverse origin, which are further categorized by the anatomical sub-site in which they emerge. Most HNSCC arise in the oral cavity, the oropharynx or the larynx. Nevertheless, in some epidemiological studies, HNSCC has been frequently treated as a single disease and not stratified according to the anatomical region affected. Grouped together, oral and pharyngeal cancers are the sixth most common neoplasias in the world (21). In Europe 67,354 new cases of oral, pharyngeal, and laryngeal cancers are estimated to occur in men every year (22), while in the United States 52,610 new cases were expected for 2012 (23). Additionally, in Brazil, 20,280 new cases of oral and laryngeal cancer were expected for 2012 (24). Worldwide, the incidence of cancer at different head and neck sites varies by geographical region. A higher prevalence of HNSCC was reported among non-Hispanic Black men aged less than 55 years (25,26). The most important risk factors associated with HNSCC development include tobacco and alcohol use, with a synergistic effect between them (27). Nevertheless, at least a fraction of oral and pharyngeal cancers cannot be attributed to these factors. In the United States it was observed that tobacco smoking

and alcohol drinking combined account for approximately 75% of all oral and pharyngeal cancers (28). The remaining 25% of affected individuals require further analysis (29). Among never smoker and never drinker (NSND) patients, the incidence of HNSCC at different anatomical subsites was shown to segregate by sex and age. It was observed that in NSND individuals, the oropharynx was the most common site of tumor occurrence. However, gender-specific differences were reported. In young to middle-aged men, tumors of the oropharynx accounted for more than half of all HNSCC. In contrast, these occurred in only 21% of NSND women under 50 years of age, in which oral tongue cancer was more commonly detected (30).

Association with HPV infection

Similarities in morphological features between genital and oral HPV-associated lesions have suggested that HPV infection could be an additional risk factor in a subset of oral cancers. For instance, the juxtaposition between the squamous cell epithelium and the lymphatic tissue in the oropharynx resembles the transformation zone of the uterine cervix, and may thus be susceptible to HPV infection. Actually, the first report suggestive of the viral etiology of oral squamous-cell carcinoma (OSCC) dates to 1983 when microscopic changes suggestive of HPV infection were detected in 40% (16/40) of the cases (31). Since then, evidence for a link between HPV infection and HNSCC development has been growing.

Strong and consistent molecular evidence demonstrating that HPV is an important etiological cause of HNSCC is based on: 1) frequent detection of HPV genomic sequences and transcription of *E6* and *E7* genes in tumor cells; 2) HPV-DNA integration in the cellular genome of tumor cells; 3) existence of a considerable viral DNA copy number in these lesions (32). In addition, serum antibodies against HPV-16 L1, E6, and E7 proteins were detected in over 60% of individuals diagnosed with oropharyngeal squamous cell carcinoma (33). Further experimental evidence involving HPV in a subset of oropharyngeal cancers was provided by the observation that *E6* and *E7* oncogene silencing induces apoptosis and restoration of TP53 and pRB tumor suppressor pathways in oropharyngeal cancer cells (34). For these reasons, during the last decade, molecular and epidemiological investigations have focused on HPV-associated HNSSC (33,35,36).

The incidence of HPV-associated HNSCC is increasing in young adults, a fact that may be explained, at least in part, by changes in sexual behavior (37). HPV infection of the oropharynx like HPV infection of the uterine cervix was shown to be associated with high-risk sexual behavior. In particular, some studies have indicated that orogenital sex is a potentially risk-related sexual practice (33). Additionally, the risk of developing HPV-associated HNSCC is increased in men and women with multiple sex partners and in men with a history of anogenital warts. It was also observed that husbands of women with cervical cancer are predisposed to develop HPV-associated HNSCC, especially tonsillar cancer (38). Furthermore, other risk factors have been consistently linked to an increased chance of prevalent oral HPV infection. Current smoking and HIV infection were both associated with significantly augmented oral HPV prevalence, suggesting that tobacco-related and HIV-related immunosuppression may possibly impact the natural history of oral HPV (39). However, patients diagnosed with HPV-positive HNSCC tend to be younger and to have a lower intake of tobacco and alcohol (40).

Detection rates of HPV-DNA in HNSCC are highly variable (Figure 1). The remarkable variation in viral prevalence among different reported studies may be due to grouping together lesions at different anatomical subsites, to small sample numbers, to the ethno-geographical origins of the subjects examined, and to differences in sampling techniques (frozen, formalin-fixed or paraffin-embedded sections, scraping or oral rinses) (41). Considering all anatomical head and neck subsites, the rate of HPV detection is usually higher in frozen biopsy samples than in formalin-fixed samples (7). In addition, the methodologies used may influence the viral prevalence measured in these samples, and for this reason rigorous criteria should be considered, such as sensitivity/limit of detection, specificity (including HPV types and variants), accuracy, and reproducibility (42). A significant

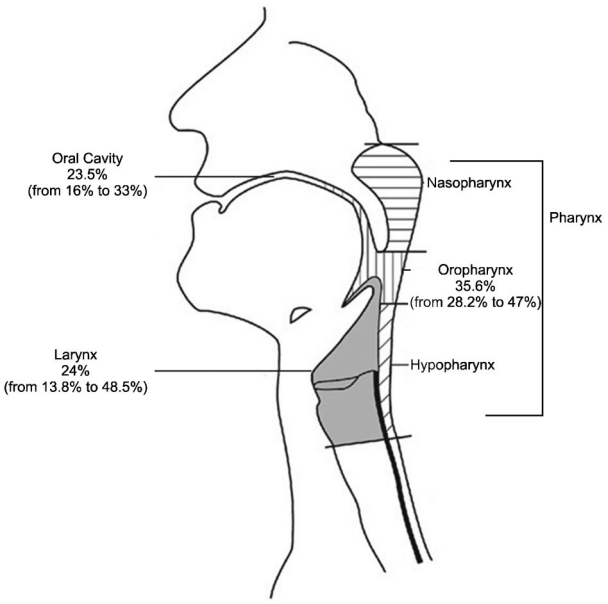

Figure 1. Overall HPV-DNA prevalence in head and neck squamous cell carcinomas at different anatomical subsites. Range values stratified by geographical location are shown in parentheses (Ref. 45).

increase in HPV detection rate was observed using an auto-nested GP5+/GP6+ protocol compared to single-PCR assays among oral mucosal samples, but not among cervical specimens (43).

While HPV is an important cause of oropharyngeal cancer, it is presently uncertain whether it may also have a role in cancer of other head and neck subsites. HPV-DNA has been detected in a subset of oral cavity (23%) and larynx (24%) tumors, although the proportion of these neoplasias that are HPV positive is markedly inferior to that observed for oropharyngeal cancer (50%) (44,45). Although HPV-16 is by far the most prevalent type detected in these tumors, a recent analysis of oral rinse samples revealed a wide spectrum of HPV types from the 3 main genera (α-, β- and γ-papillomavirus) (46). Among 317 male individuals, 168 type-specific infections were detected of which 64 and 8.3% were β- and γ-papillomavirus, respectively. Types from these genera were previously considered to be exclusively cutaneous. The finding that HPV infection is linked to the development of a subset of HNSCC has prompted new interest in a better understanding of the natural history of HPV infections in the different head and neck anatomical subsites.

Recurrent respiratory papillomatosis

Low-risk HPV-6 and -11 infections within the larynx can lead to the development of recurrent respiratory papillomatosis (RRP). This neoplasia is very uncommon and is characterized by multiple benign papillomas in the middle and lower respiratory tract (47). Despite its benign nature, RRP can involve considerably morbidity and mortality since lesions tend to grow and cause severe air obstruction. RRP exhibits a bimodal age distribution: the first peak of incidence occurs before 5 years of age and the second peak between the ages of 20 and 30 years. Boys and girls are evenly affected by juvenile onset RRP, in contrast to adult onset RRP, which preferentially affects men over women at a ratio of approximately 3:2 (48). Vertical transmission for the juvenile RRP form is the most likely route of transmission, whereas adult patients may have been exposed during sexual contact.

Although RRP is generally considered to be histologically benign, its natural history is highly variable and unpredictable and may further undergo malignant transformation. While extralaryngeal and pulmonary spread of RRP has been reported, malignant transformation of RRP is a very rare condition (49). Furthermore, HPV-11-associated RRP was observed to be more prone to malignant transformation as compared to HPV-6-associated disease (50). It is still unclear why only a fraction of HPV-exposed individuals develop RRP, and why among HPV-associated RRP cases, only a few develop cancer. The detection of serum antibodies to HPV among RRP patients refutes the hypothesis that these infections may be ignored by the immune system (51); most likely these individuals develop tolerance to HPV infection to different extents. The main determining factor proposed for RRP clinical outcome could be HPV-specific TH1-/TH2-like balance polarization. Although a considerable amount of information is available concerning the immunological aspects of HPV-induced RRP, lesion recurrence and malignization (52), more data are required and will prove important to the development of therapies that may prevent not only lesion development and recurrence, but also malignant transformation.

Oral cancer

Oral cancer includes tumors of the tongue, floor of the mouth, gum, palate, and other mouth subsites. From the mid-1970s to the latest Surveillance Epidemiology and End Results Program (SEER Program) from the U.S. National Cancer Institute Survey performed in 2004, oral cancer rates have increased by approximately 15% (53). Recent data from the SEER Program have revealed a higher incidence of this neoplasia among men (15.5 per 100,000 per year) and among Hispanic (9.2 per 100,000 per year) and Black (17.2 per 100,000 per year) individuals (54). Increased rates of oral cancer are also associated with age, starting after 50 years and peaking between 60 and 70 years. Generally, the highest rates of oral cancer are detected in Melanesia, South Central Asia, and Central and Eastern Europe, and the lowest rates in Africa, Central America and Eastern Asia (55). The most common histological type of oral cancer is OSCC (56).

In OSCC, as for the majority of HNSCC, higher tobacco and alcohol consumption constitutes the most important risk factor although 10 to 20% of the individuals diagnosed with OSCC have no history of being exposed to these agents (56). Indeed, other biological factors have been proposed to play a role in oral carcinogenesis (57,58). Based on epidemiological and clinico-pathological evidence, HPV infection has been proposed to be linked to oral cancer development (59,60). Nevertheless it is important to emphasize the weaker etiological association between HPV infection and oral cancer as compared to oropharynx cancer (44). Concerning cancer samples, the evaluation of 209 cases of oral cavity carcinomas obtained from a Hospital database in France revealed a 10.5% prevalence of HPV, with viral detection being more common among females (17.2%) than among males (8.0%) (61). On the other hand, in a multicenter study (Japan, Pakistan, and Colombia) 56% of HPV positivity was detected among 71 samples of oral cavity cancers, with HPV-16 being the most prevalent type (62). In these three countries, HPV prevalence did not vary significantly by geographical region. However, it was observed that molecular variants of HPV-16 were unevenly distributed in these samples. A meta-analysis compiling 35 studies from 24 different countries revealed an overall HPV prevalence of 23.5% among 2642 OSCC cases (45). In these tumors HPV-16 was also the most prevalent viral type (68%),

followed by HPV-18 (8%). However, among 409 OSCC cases diagnosed in North American Hospitals, only 5.9% could be attributed to HPV infection (63). The divergent records obtained in the different studies reported may be explained by differences in the socioeconomic conditions of the populations analyzed, the prevalence of other risk factors, the biological samples analyzed, and the methods used for HPV detection.

HPV has been also detected in the oral cavity of healthy individuals. Among 5579 individuals aged 14 to 69 years randomly investigated in the United States who underwent an oral rinse, the overall HPV prevalence observed was 6.9% (64). Moreover, in that cohort viral DNA was more commonly detected among men than women (10.1 versus 3.6%). In a multinational sample cohort, HPV infection was detected in 4% of 1688 healthy men aged 18 to 74 years enrolled in the United States, Mexico, and Brazil (65). Although HPV-16 was also the most frequently detected high-risk HPV type in all cohorts, HPV-55 was more common in Mexico. The significance of HPV infection in healthy oral mucosa is not fully understood although reported data indicate that the development of OSCC is associated with the practice of orogenital sex and with high-risk sexual behavior (66). In addition, tobacco smoking and increased age were found to be associated with a higher frequency of persistent oral HPV infections (33). Studies are warranted to elucidate the natural history and epidemiology of oral HPV infections.

Pharyngeal cancer

Pharyngeal tumors include cancer of the hypopharynx, nasopharynx, oropharynx, and tonsils. According to The French National Hospital Database (PMSI), 36,268 patients were hospitalized for head and neck cancer in France in 2007, and tumors were more frequently detected in the oropharynx among these individuals (n = 12,232) (67). These tumors were more frequently detected among men. Cancers of the oropharynx and tonsils are also associated with tobacco and alcohol consumption (68). However, consistent epidemiological evidence has been extensively obtained over the last decade concerning HPV-associated pharyngeal cancer. The highest incidence of HPV infection among laryngeal squamous cell carcinoma maps to the oropharynx. It was observed that HPV-related squamous cell carcinoma of the oropharynx has unique histological features (69,70); these tumors tend to present a non-keratinizing basaloid morphology and an increased expression of p16 and Ki67. In contrast, non-HPV-related tumors are keratinizing and are composed of polygonal cells with abundant mature cytoplasm.

The French National Hospital Database reports an overall HPV prevalence ranging from 33 to 72% among oropharyngeal cancers in different French public and private hospitals (61). Worldwide, HPV prevalence has been shown to vary from 14 to 57% in cancers of the oropharynx (7,45). However, a lower prevalence was reported in two large case-control studies conducted in Central Europe and Latin America in which HPV prevalence was 4.4% among oropharynx cancers and 3.8% among hypopharynx/larynx cancers (71). Among tonsillar carcinomas, HPV-DNA was detected in 52% of affected individuals (72).

In common, all studies reported that high-risk HPV-16 was undoubtedly the predominant viral type detected. Viral oropharyngeal infection has also been shown to be more common among younger subjects with high-risk sexual behavior. These individuals present higher serum HPV-16 antibody titers, use less tobacco and alcohol, and have a better survival rate compared to HPV-negative tumors (73). In addition, it was reported that detection of HPV-16 DNA in oral exfoliated cells increased the odds of oropharyngeal cancer by more than 14-fold (33).

Laryngeal cancer

Laryngeal carcinoma is the second most common malignancy of the head and neck (74). According to the global cancer statistics of 2008, the age-standardized incidence rate of this malignancy is 5.5 per 100,000 per year in men and 0.6 per 100,000 per year in women in developed areas, while in less developed areas, the incidence rate is 3.5 per 100,000 in men and 0.6 per 100,000 in women (75). In Brazil, 6110 new cases of laryngeal cancer are expected to be diagnosed in men in 2012, while no data are available for women due to the small number of females affected by this cancer in Brazil (24).

Tobacco and alcohol consumption are the primary etiologic factors for the development of laryngeal cancer. The laryngeal epithelium is known to be susceptible to HPV infection because of the well-established association of HPV-6 and -11 infections with the development of juvenile and adult onset RRP. Recently, it was suggested that HPV infection may also account for the development of a fraction of laryngeal carcinomas (76). HPV prevalence varies from 5 to 24% among larynx cancers in different public and private hospitals in France (67). In addition, a systematic analysis of 35 studies from 18 different countries involving a total of 1435 cases of larynx cancer revealed an overall HPV prevalence of 24% (45). However, as for all other HNSCC subsites, a high divergence in HPV prevalence has been reported, ranging from 16.5 to 41.5% (46,77). Nevertheless, the associations described are not as significant as documented for the tonsils and the oropharynx (78).

Future directions

HPV infection is one of the most common sexually acquired diseases. Head and neck HPV infections have not been studied to the same extent as infections of the genital tract. However, in 2007 the International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence to support the carcinogenicity of HPV

in the oral cavity, oropharynx and tonsils, and limited evidence to support the carcinogenicity of HPV in the larynx (7).

To date, limited information is available about the natural history of oral HPV infection. More longitudinal research is needed to better understand the transmission of oral HPV infections, how likely these infections are to clear and what factors are associated with persistence. This should prove important since HPV persistence is a necessary cause of cervical cancer development and may likely prove central for HPV-associated HNSCC.

Most studies conducted thus far have detected predominantly HPV-16 among cancer samples in all head and neck subsites (45,79,80). Significant differences in pathogenicity exist between molecular variants of a single type and have been elucidated most clearly for HPV-16 (4). It has been demonstrated that non-European variants of HPV-16 are more strongly associated with cancer development when compared to European variants. Furthermore, non-European variants are more prevalent in cancer samples than in normal smears. While most of the studies analyzing specific HPV variants regarding the risk for viral persistence and cancer development have been performed in cervical cancer (81,82), very few studies of this kind have been conducted in head and neck samples. In the United States, a striking similarity has been observed in the distribution of the different HPV-16 variants in HNSCC and in cervical cancers (83). In addition, the prognostic significance of HPV-16 E6 variants in HNSCC was evaluated in two recent studies (84,85). Nevertheless, HPV molecular variant analysis should be more extensively investigated in HNSCC before proving to impact lesion outcome.

Another important aspect concerns the remarkable discrepancy in documented HPV prevalence in different anatomical HNSCC subsites across studies. Thus, not only standardization of the techniques employed for HPV diagnosis and typing but also separation of samples from the diverse head and neck anatomical subsites are essential for comparing data from different geographical areas. Albeit it is not always possible to unmistakably identify the exact anatomical site of the primary tumor, anatomical site misclassification may further introduce variation in the estimate of HPV prevalence. Overall, HPV-positive HNSCCs have been shown to have a better clinical outcome than HPV-negative cases (86). A meta-analysis revealed that individuals with HPV-positive HNSCC had lower risk of dying and of recurrence especially when analysis was restricted to HPV-positive oropharyngeal cancers (87,88). It was also observed that these patients respond better to chemotherapy and radiotherapy than HPV-negative individuals (89). Additionally, the prognostic value of tumor stage was shown to be significant only among HPV-positive tonsillar cancers (90). However, not all studies show consistent results and the prognostic value of HPV remains uncertain especially among OSCC. It was observed that HPV-16-positive individuals with advanced OSCC had a poor survival rate and were at higher risk of developing distant metastases compared to HPV-16-negative cases (91).

More recently it was suggested that HPV-DNA status in HNSCC should be analyzed together with specific markers of active infection (for instance, E6/E7 mRNA transcription, cellular p16 expression) so as to better define the fraction of these tumors that can be attributable to HPV. HPV status is not always associated with p16 expression, and E6/E7 mRNA and p16 expression was detected mostly in oropharyngeal cancers (59). In fact, HPV-positive patients with oropharyngeal SSC expressing high levels of p16 were shown to have the highest rates of overall survival and disease-free survival (92). In addition, p16 expression had a major impact on the response to treatment (93), and it was suggested that individuals with HPV-DNA-positive/p16-negative oropharyngeal SCC may be treated as HPV negative for clinical purposes (94). However, more research is warranted before establishing the use of HPV status to guide treatment and to predict the outcome of HNSCC.

Prophylactic HPV vaccines are currently available. Clinical trials have demonstrated high efficacy of the vaccine for the prevention of anal, cervical, vaginal, and vulvar cancer development among individuals not previously exposed to HPV (95). Vaccination induces not only a vigorous immune response but also a B-cell immune memory response that persists for years. Direct evaluation of vaccine efficacy against head and neck HPV-16 infection and tumor development is still necessary because there are no published data on this topic. The introduction of HPV vaccination as a public health measure against anogenital HPV infection will most probably also have a favorable impact on the frequency of HPV-mediated HNSCC.

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