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REVIEW

Review of HPV-related diseases and cancers

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SUMMARY

Human papillomavirus (HPV) is a double-stranded circular DNA virus belonging to the papillomavirus family. It is transmitted by skin-to-skin or mucosa-to-mucosa contact and enters the body via cutaneous or mucosal trauma. HPV infection is the most common sexually transmitted disease, although it is usually cured by the immune system. Worldwide, the risk of being infected at least once in a lifetime among both men and women is 50%. HPV infection causes common and anogenital warts, as well as other non-dermatological diseases. The role of HPV in cancer development has been extensively studied, primarily in cervical cancer, but also in other types of neoplasms.

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INTRODUCTION

Human papillomavirus (HPV) infection is a common and usually transient infection which has recently garnered media attention due to developments in vaccine prevention and changes in cancer-screening recommendations (Forcier *et al*., 2010). HPV is the etiological agent of common dermatologic and sexually transmitted diseases (Palefsky, 2016). HPV infection is the most common sexually transmitted disease, although it is usually cured by the immune system. Worldwide, the risk of being infected at least once in a lifetime among both men and women is 50% (Handler *et al*., 2015a). Although historically known as the cause of common and anogenital warts, there have been extensive studies since 1980 exploring the role of HPV in cervical cancer development and in other tumors (Palefsky, 2016; Reid *et al*., 1980). The most common types worldwide are HPV 16 and 18, which are the main types linked to carcinogenesis. Both HPV 16 and HPV 18 are preventable by vaccination (Palefsky, 2016).

Human papillomavirus

General features

The Papillomavirus genomes (PVs) comprise 8 kb of double-stranded, circular DNA with 8 protein-coding genes (L1 and L2 that encode capsid proteins and E1, E2, E4, E5, E6 and E7 that encode proteins involved in replication, transcription and transformation) and a noncoding, regulatory long control region (LCR) (Bernard *et al*., 2006). PVs infect keratinocytes of the skin and mucosa of different vertebrate species, including humans (De Villiers, 2013; Vinzón *et al*., 2015). Human papillomavirus (HPV) infects only humans (Palefsky, 2016). Mucosal α-genus HPV types have been extensively studied and until now they are the best characterized. Almost all of the studies on HPV are derived from analysis of the α genus and consequently most of the information reported can be only ascribed to mucosal HPVs belonging to the α genus. HPV is a virus with double-stranded circular DNA from the papillomavirus family. All HPVs have icosahedral capsids. They include genes that express nonstructural proteins needed for DNA replication, transcription, or viral assembly and release. Genes transcribed late (L-genes) include L1 and L2, which encode viral capsid proteins referred to as L1 and L2, respectively. The papillomavirus capsid is made of 2 structural proteins: the major basic protein (L1) and the minor basic protein (L2). Each capsid contains 72 pentameric capsomeres, each made of 5 L1 and L2 proteins. Viral assembly occurs in the nucleus of the cell; L1 protein self-assembles into virus-like particles, while L2 has a lesser known role, but may be involved with virion production (Handler *et al*., 2015a; Palefsky *et al*., 1995). Expression of proteins E6 and E7 is associated with integration of viral DNA into the host genome, malignant transformation, and ultimately progression to cancer (Forcier *et al*., 2010). The 3 major viral oncoproteins (E5, E6, and E7) contribute to cancer initiation and progression by altering cell cycle regulation and telomere maintenance, inducing DNA damage and genomic instability, and blocking tumor suppressor pathways and apoptosis. HPV displays tropism toward the epithelial basal layer, which houses adult epithelial stem cells responsible for replenishing the epithelium with daughter cells. The E6/E7 oncoproteins are the primary transforming viral proteins, and they play an important role in immune evasion by targeting cytokine expression to alter cell proliferation and interferon responses. E7 proteins modulate genome-wide transcription through their interactions with histone deacetylases, which activate transcription when removed from promoters. Importantly, expression of HPV viral proteins and viral integration promotes chromosomal anomalies and cellular immortalization (Moody *et al*., 2010; Pullos *et al*., 2015). More than 200 different HPV types have been identified and classified into 5 genera, α, β, γ, μ, and ν. High-risk α mucosal HPVs are the most studied and will be the focus of the following discussions. The HPV types with a proven oncogenic po-

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tential, a well-established role in cervical carcinoma and a significant percentage of other anogenital tract and oral carcinomas belong to the α genus (McLaughlin-Drubin, 2015). When integrated into the host squamous epithelial cell genome, the high-risk HPV types (16 and 18) will express gene E6, which will degrade tumor suppressor protein p53. E7, also expressed early, is an oncoprotein that binds the tumor suppressor retinoblastoma protein (pRB) and allows HPV DNA synthesis. E1 protein increases viral genome replication, E2 decreases the expression of E6 and E7. Loss of E2 repression function leads to deregulation of viral E6 and E7 oncogenes (Handler *et al*., 2015 a; Duensing *et al*., 2004; Smith *et al*., 2014) (*Figure 1*; Doorbar *et al*., 2015).

Among the low-risk types, non-oncogenic HPV are associated with anogenital warts (AGWs), (Dunne *et al*., 2013), some type of cutaneous warts (Vinzón *et al*., 2015), and recurrent respiratory papillomatosis, while high-risk oncogenic types are associated with cervical, penile, anal, vaginal, vulvar and oropharyngeal cancers (Dunne *et al*., 2013). Low-risk group HPV types 6 and 11 cause 90% of external anogenital warts (AGWs, condylomata) as well as low-grade changes in cervical cells (Forcier *et al*., 2010; Schiffman *et al*., 2009). Other low-risk HPV types include HPV 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108. High-risk HPVs, particularly HPV 16 and 18, are associated with high-grade cervical and anal dysplasia and invasive carcinoma. Other oncogenic HPV types include HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, and 82 (Schiffman *et al*., 2009; Muñoz *et al*., 2003).

Virus life cycle

Even though the general infection progression of all HPV genera will be discussed in the following chapter, the virus life cycle is derived from studies on α genus. In addition, malignant features are only ascribed to the α genus. HPV is transmitted by skin-to-skin or mucosa-to-mucosa contact and enter the body via cutaneous or mucosal trauma (Handler *et al*., 2015a). HPV infects epithelial cells via interaction with cell surface receptors such as integrin α6, which is abundant in basal cells and epithelial stem cells. In infected cells and premalignant lesions, the majority of the HPV genome remains in the episomal state (Cox *et al*., 2016). HPV infects skin and mucous membrane keratinocytes. HPV is believed to infect keratinocytes and remain dormant, suppressed by the immune system (Handler *et al*., 2015a). Transmission in either direction is typically asymptomatic (Palefsky, 2016). After the immune system resolves the infection, the virus may remain dormant within the squamous cell that will not be dysplastic; Papanicolaou (Pap) smears may be normal. The dormant virus will also be non-transmissible until a patient is immunosuppressed, at which time it may cause differentiation of the basal epithelial cells of the infected host (Handler *et al*., 2015a). The majority of HPV infections are transient and subclinical with subsequent clearance by the immune system. HPV generally avoids blood and humoral immune detection but is cleared via a cell-mediated immune response. Estimates of duration of HPV infection are 8 months. Median duration of infection for oncogenic types is estimated to be 13 months and less for nononcogenic HPV types (8 months), with time for clearance similarly affected (8 months for oncogenic and 5 months for non-oncogenic types). HPVs can be classified into mucosal and cutaneous types. Mucosal types infect the mucous membranes and can cause cervical neoplasia in adults and anogenital warts in children and adults. The most commonly found high-risk types are HPV 16, 18, 31, 33, 52, and 58, and the most commonly found low-risk types are HPV 6, 11, and 53. Cutaneous types infect the squamous epithelium of the skin and produce common warts (Verruca vulgaris), plantar warts (Verruca plantaris), filiform or digitate warts (Verruca filiformis), and flat warts (Verruca plana). The most frequent cutaneous types are HPV 1, 2, 3, 4, 27, and 57. High-risk HPV types members of the mucosal α genus family (HPV 16, 18) have been isolated in warts (Giannaki *et al*., 2013). Surprisingly, cutaneous HPV types have also been isolated from anogenital warts (Palefsky, 2016). Mixed infections with different HPV types on the same lesion are relatively common (Giannaki *et al*., 2013). Genital HPV infections caused by low-grade HPV types, or that occur in younger patients, have higher rates of viral clearance and disease regression. Approximately 90% of infections and low-grade, non-oncogenic HPV disease clears within 2 years, with only 1% progressing to invasive cancer (Forcier *et al*., 2010). Of all the HPV types, approximately 60% cause benign neoplasms (warts) on locations such as the hands and feet, and 40% infect

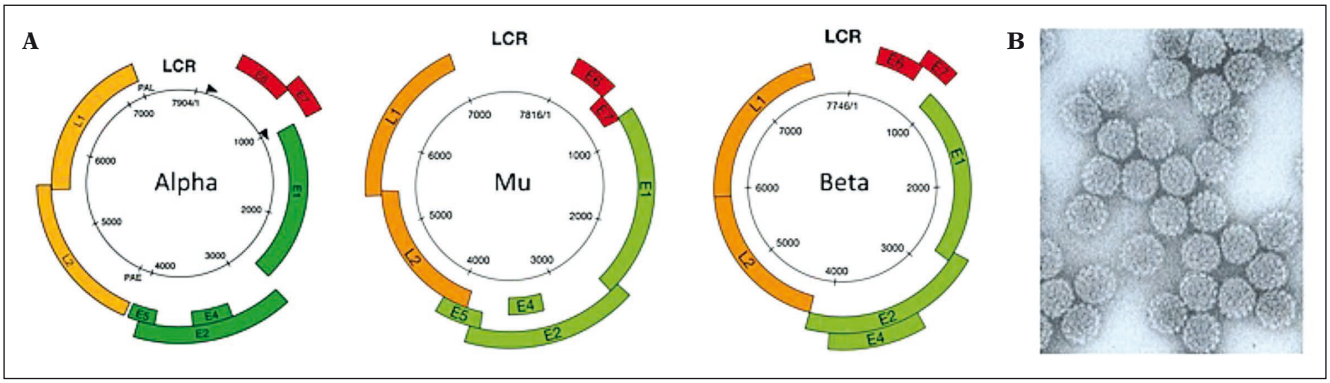

Figure 1 - *(A) Typical genome organization of the high-risk Alpha, Mu, and Beta HPV genomes. Although all share a common genetic organization, the size and position of the major Open Reading Frames (ORFs) can vary, with Beta HPV types lacking an E5 ORF. The positions of the major promoters are marked with arrows on the high-risk Alpha HPV genome map, with early and late polyadenylation sites marked as polyadenylation late and polyadenylation early. (B) Electron micrograph of negatively stained papillomavirus particles. Individual capsomeres within the capsid structure can just be visualized. Papillomavirus particles are approximately 55 nm diameter and are non-enveloped* (Doorbar et al., 2015).

mucosal surfaces, including the genitals, anus, and oropharynx, usually by sexual activity. Most HPV infections are asymptomatic, unlike other pathologies accompanied by chronic pruritus of difficult to manage (Naldi *et al*., 2010). Those infected by HPV are typically not aware that they have the virus. While most HPV infections are resolved by the body's immune system and never result in human health problems, some people develop benign genital warts, while others, affected by specific oncogenic types of HPV, develop cancer of the cervix, oropharynx, anus, vulva, vagina, and penis. As with cervical exposure, the majority of people who have anal epithelial infection with HPV will experience resolution of the infection (Handler *et al*., 2015a).

HPV-related mucosal cancers

Only infection of HPV belonging to the α genus has been clearly linked to all or nearly all squamous intraepithelial lesions and cancers of the cervix and anus. This HPV genus is also linked to a subset of penile, vulvar, and vaginal cancers. Of the 14 most common oncogenic HPV types associated with these cancers, HPV 16 is the most common and associated with the highest risk of progression to cancer (Palefsky, 2016). The same α HPV genotypes (or "types") that cause cancer of the cervix also cause most cases of anal cancer and significant proportion of oropharyngeal cancer in men and women, a significant proportion of vulvar and vaginal cancer, and significant proportion of penile cancer (Cox *et al*., 2016). A meta-analysis of anogenital cancers in North America, Europe, Asia and South America revealed that HPV 16 type was found in 75% of HPV-positive non-cervical anogenital cancers. Oncogenic HPV types have an affinity for infecting the immature squamous cells in both the anus and cervix. This area, referred to as the transformation zone, occurs where the outer cervix squamous epithelium transitions to columnar cells of the endocervix, and in the anus where the epithelium changes from the nonkeratinizing squamous epithelium of the anus to the columnar epithelium of the rectum (Handler *et al*., 2015a). The presence of a cervical transformation zone is not necessary for oncogenic HPV to infect the female genital tract. As a result, the prevalence of oncogenic HPV subtypes in the vagina is similar in women who have and have not undergone hysterectomy. Similarly, HPV may infect not only the anal canal in the anal transformation zone, but also more distal sites, including the keratinized skin of the anal verge and perianal region. An increasing body of evidence suggests a relationship between HPV infection, particularly with HPV type 16, and squamous cell carcinoma of the oral cavity, especially in people under 50-years of age (Palefsky, 2016). HPV integrates into the host genome in malignant tumors so that HPV genome integration may be the primary evidence of cancer. HPV integrants are found in multiple non-recurrent regions of amplification and in flanked regions where deletions occur. There is a strong association between HPV insertional breakpoints and genomic structural variations, including chromosomal translocations, deletions, inversions, and intrachromosomal rearrangements, ultimately resulting in genomic instability, a hallmark of HPV-positive cancers. Nevertheless, HPV alone is not sufficient to transform epithelial cells, although it plays a significant role in maintaining cancer. Genetic and epigenetic events that are secondary to HPV infection are necessary for cellular transformation and cancer development. This phenomenon may explain, in part, the latency period that occurs in cancer development (Pullos *et al*., 2015). Persistent infection with high-risk types of HPV is necessary for progression to high-grade lesions or cancer (Forcier *et al*., 2010). In stark contrast to α HPV-associated cancers, the presence of the β HPV genome does not appear to be mandatory for the maintenance of the malignant phenotype (McLaughlin-Drubin, 2015). Persistent viral infection with carcinogenic HPV types causes virtually all cancer of the cervix and most cases of anal cancer (Cox *et al*., 2016). Risk factors for progression to high-grade dysplasia and cancer include persistence of HPV infection, infection with oncogenic HPV types, age over 30-years, infection with multiple HPV types, immunosuppression, and tobacco use (Forcier *et al*., 2010). HPV-related tumors in HIV-positive patients tend to occur at a younger age and at a more advanced stage than in HIV-negative patients, consistent with HIV-related reductions in HPV clearance. Furthermore, HIV-positive patients with genital warts have greater resistance to standard treatment and HIV-positive women being treated for cervical intraepithelial neoplasia are more likely to relapse, compared to the general population (Reusser *et al*., 2015). In contrast to HPV-negative cancers, which are often associated with chronic inflammation or lichen sclerosis, HPV-associated penile and vulvar cancers occur at a younger age, exhibit basaloid instead of keratinizing pathology, do not have p53 mutations, and are associated with sexual risk factors. Women with a history of vulvar or cervical high-grade squamous intraepithelial lesions or cancer are also at increased risk of anal HPV infection and HPV-related disease. In one study of women with cervical or vulvar high-grade squamous intraepithelial lesions, 12% had an anal squamous intraepithelial lesion and 9% had an anal high-grade squamous intraepithelial lesion. In these studies anal intercourse was not a consistent risk factor for either anal HPV infection or anal squamous intraepithelial lesions (Palefsky, 2016).

Epidemiology

Diagnoses of HPV-associated cancers averaged 26,900 per year between the years 2004 and 2008 in the United States - of which approximately 4100 women die from cervical cancer (Handler *et al*., 2015 b). According to data from the National Program of Cancer Registries (NPCR) and the Surveillance, Epidemiology, and End Results (SEER) program, an average of 33,369 HPV-associated cancers are diagnosed annually, including 12,080 among males (8.1 per

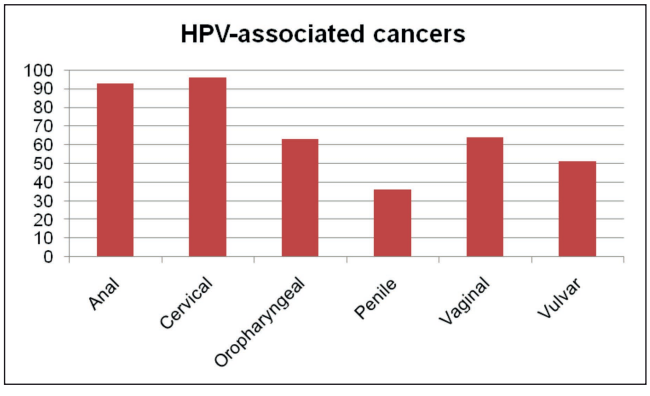

Figure 2 - *Representation of the percentage of HPV-associated cancers plotted against type of cancer.*

100,000) and 21,290 among females (13.2 per 100,000). HPV is thought to be responsible for 7-8% of all human malignancies and is associated with 96% of cervical cancers, 93% of anal cancers, 64% vaginal cancers, 51% of vulvar cancer, 36% of penile cancers and 63% of oropharyngeal carcinomas (Cobos *et al*., 2014) (*Figure 2*).
More than 600,000 cancers are attributed to HPV infection worldwide. Mortality from HPV is caused by oncogenic HPV types whose infections lead to dysplasia and cancer. The Centers for Disease Control and Prevention estimates the incidence of new HPV-associated cancers in the United States at 26,800 per year (Handler *et al*., 2015a).

HPV-related skin cancers

Although the term non-melanoma skin cancers (NMSC) includes cutaneous lymphomas, adnexal tumors, Kaposi's sarcomas, Merkel-cell carcinomas, and other rare primary cutaneous neoplasms, it is mainly used to define basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) (Abbas *et al*., 2016). BCC and SCC are the two most common subtypes of NMSC (Callens *et al*., 2016). HPV has been implicated in several NMSCs (Cobos *et al*., 2014). β PVs have been detected in NMSCs, although usually with very low viral loads. Different studies have reported HPV DNA in 30-50% of NMSCs from immunocompetent patients, whereas in lesions from immunosuppressed patients this figure goes up to 90%, as generally occurs also in other non viral infections (Vinzón *et al*., 2015; Gisondi *et al*., 2015). Borgogna *et al*. (2014) were the first to demonstrate active β-papillomavirus infection in skin lesions from kidney transplant recipients. These viruses can also be found in premalignant lesions, such as actinic keratosis, where the virus is transcriptionally active, and also in normal skin, vitiligoid areas under treatment and plucked eyebrow hairs, where several studies have found an association between presence of viral DNA and increased risk of NMSC (Vinzón *et al*., 2015; Neale *et al*., 2013; Borgogna *et al*., 2012; Dell'Oste *et al*., 2009; Cazzaniga *et al*., 2009). Remarkably, there seems to be an inverse correlation between viral load and the malignancy of the lesion, supporting a hit-and-run mechanism of carcinogenesis that is in contrast to the direct carcinogenic effect of genital HPVs (Vinzón *et al*., 2015; Quint *et al*., 2015; Howley *et al*., 2015). In other words, since some tumors either lack HPV or only one in every 10-1000 cells can be found to be virus-positive, the viral oncoproteins are not necessary to maintain a proliferative and tumorigenic phenotype. In addition to reports focused on the correlation between β PV DNA and disease, numerous seroepidemiological studies have also contributed data suggesting an association between β PV infection and NMSC or its precursors. High-risk genital HPV types are known to degrade p53, thereby blocking downstream pathways such as apoptosis (Vinzón *et al*., 2015; Moody *et al*., 2010). Although β HPV E6 protein cannot exert this direct function, it has recently been shown that the E6 proteins of some β types can inhibit HIPK2-mediated phosphorylation of p53 at serine residue in response to ultraviolet (UV) damage (Vinzón *et al*., 2015; Muschik *et al*., 2011). This prevents the stabilization of p53 in response to genome destabilizing events (Vinzón *et al*., 2015; Wallace *et al*., 2014) and blocks the transactivation of p53 target genes (i.e. MDM2, p21 and proapoptotic genes) (Vinzón *et al*., 2015; White *et al*., 2014). Additionally, β HPV E6 targets the pro-apoptotic protein Bak for degradation (Vinzón *et al*., 2015; Jackson *et al*., 2000; Underbrink *et al*., 2008). These effects, usually combined with mechanisms that delay DNA repair (like abrogation of ATR activity (Vinzón *et al*., 2015; Wallace *et al*., 2012) or impairment of the telomere/telomerase system (Vinzón *et al*., 2015; Gabet *et al*., 2008) may explain the β HPV contribution to skin carcinogenesis by favoring the accumulation of UV-damaged cells. The oncogenic potential of β HPV has also been shown in in vivo transgenic models which develop SCC in response to β HPV gene expression, either spontaneously or after UV irradiation (Vinzón *et al*., 2015; Schaper *et al*., 2005; Viarisio *et al*., 2011). Further support for E6 oncogenic potential was given by the work of Hufbauer *et al*. (2015). They demonstrated that cells expressing E6 fail to sense and mount an effective response to repair UV-induced DNA lesions and showed a physiological relevance of E6-mediated inhibition of DNA damage repair for tumor initiation. These are the first mechanistic in vivo data on the tumorigenicity of HPV 8 and demonstrate that the impairment of DNA damage repair pathways by the viral E6 protein is a critical factor in HPV-driven skin carcinogenesis (Hufbauer *et al*., 2015). Notch signaling pathway is a key determinant in keratinocyte differentiation and growth cycle arrest, and has been reported to have a tumor suppressor function in skin (Tan *et al*., 2012). Two groups showed that HPV type 8 E6 subverts NOTCH activation during keratinocyte differentiation by inhibiting RBPJ/MAML1 transcriptional activator complexes at NOTCH target DNA. NOTCH inhibition impairs epithelial differentiation potentially contributing to β-HPV replication and viral oncogenesis (Tan *et al*., 2012; Meyers *et al*., 2013). Vieira *et al*. (2014) deepened the connection between E6 protein and carcinogenesis. They studied the innate immune DNA cytosine deaminase APOBEC3B (A3B), which is a significant source of genomic uracil lesions and mutagenesis in multiple human cancers, including cervical and head and neck cancers. A3B is upregulated in these tumor types relative to normal tissues, but the mechanism is unclear. Vieira *et al*. established a mechanistic link between HPV infection and A3B upregulation. The E6 oncoprotein of high-risk, but not low-risk, HPV types triggers A3B upregulation, supporting a model in which TP53 inactivation causes a derepression of A3B gene transcription and elevated A3B enzyme levels. This virus-induced mutator phenotype provides a mechanistic explanation for A3B signature mutations observed in HPV-positive head/neck and cervical carcinomas and may also help to account for the preferential cancer predisposition caused by high-risk HPV isolates (Vieira *et al*., 2014). β HPVs (HPV 5, HPV 8, and HPV 9) are ubiquitous viruses that cause widespread, though usually asymptomatic, infections. Persistent infection with β HPVs in keratinocytes has been shown to predispose to actinic keratosis and has been detected in 40% of skin SCCs from immunocompetent individuals and 80% of SCCs from transplant recipients, as well as in a small proportion of BCCs (Reusser *et al*., 2015). In addition, β HPV 17, 20, and 38 appear to be significantly associated with SCCs (Chahoud *et al*., 2015). This phenomenon is thought to be related to the co-carcinogenicity of β HPV with UV light, as seen in both immunocompetent transgenic and immunosuppressed animals. UV irradiation of HPV-infected primary keratinocytes enhances the promoter activity of the HPV 5 and HPV 8 papillomaviruses and suppresses local cell-mediated immunity, while HPV oncoproteins disable the repair of UV-dependent DNA damage in keratinocytes (Reusser

et al., 2015). A study by Iannacone *et al*. showed that HPV may have a role in the etiology of BCC. In this study, HPV seropositivity for HPV subtypes 8 and 23 was specifically observed (Iannacone *et al*., 2013). However, a different study implicated HPV type 1 as the most common subtype in BCC patients. In another case–control study, HPV type 1 was also associated with SCC. A meta-analysis by Farzan *et al*. proved an association between SCC and β HPVs in the US population after testing for α, β and γ subtypes (Farzan *et al.,* 2013). A prospective study by Anderson *et al*. reported the presence of HPV 16 and 18 types in the sera of patients with SCC, but the absence of HPV DNA in tumor specimens questioned any causal relationship (Anderson *et al*., 2013; Cobos *et al*., 2014). A study by a Swedish group used a biobank collecting prediagnostic serum samples from 633 subjects who later developed SCC and 1,990 subjects who developed BCC. The samples from cases and matched controls were tested for IgG to pseudovirions to 16 different HPV types (3, 5, 6, 11, 15, 16, 18, 31, 32, 33, 38, 45, 52, 58, 68, and 76). Their study found that baseline seropositivity was not associated with SCC risk, and there were only weak associations with BCC risk with HPV 5 (OR 1.1; 95% confidence interval [CI], 1.0-1.3), HPV 15 (OR 1.2; 95% CI, 1.0-1.4), and HPV 38 (OR 1.2; 95% CI, 1.0-1.3). Acquisition of HPV 5 seropositivity during follow-up was associated with SCC risk (OR 3.2; 95% CI, 1.3-7.6). Persistent seropositivity for HPV 15 was weakly associated with BCC (OR 1.4; 95% CI, 1.0-1.9) and HPV 6 antibody persistence was weakly associated with SCC (OR 2.2; 95% CI, 1.0-4.8). They concluded that the weak associations found do not support any strong links between studied HPV and NMSC, with the possible exception of HPV 5 seroconversion and SCC (Faust *et al*., 2016; Perera *et al*., 2015). Epidermodysplasia verruciformis (EV) is a rare, probably autosomal recessive condition, characterized by the appearance of HPV-induced wart-like lesions early in childhood, with malignant transformation in approximately half of patients during adulthood, often in skin surfaces with sun exposure. Multiple HPV types have been isolated from these lesions, but HPV types 5 and 8 appear to have the most malignant potential in these individuals (Palefsky, 2016). EV has been linked to HPV types 5, 8, 9, 12, 14, 15, 17, 19-25, 36-38, 46, 47, 49 and 50, and a combination of HPV infection and UV radiation has been implicated in the etiology of skin cancer. In immunocompetent hosts, disruption of DNA repair activity by UV radiation, along with ubiquitously present cutaneous HPV types, increases the risk of NMSC (Cobos *et al*., 2014).

Table 1 - *Summary of the reported human papillomavirus types associated with various conditions. Mucosal cancers represent cancers affecting cervix, anus, oropharynx, vulva, vagina, and penis, while NMSCs represent SCC and BCC.*

Disease	*HPV type associated*
Cutaneous warts	1, 2, 3, 4, 27, 57
Anogenital warts	6, 11, 53
Mucosal cancers	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, 82
NMSCs	1, 5, 8, 9, 17, 20, 23, 38
Bowen disease	16, 18, 31, 32, 34
Epidermodysplasia verruciformis	5, 8, 9, 12, 14, 15, 17, 19-25, 36-38, 46, 47, 49, 50

Bowen's disease, a form of high-grade intraepithelial neoplasia, has both genital and extragenital forms. It can occur on the fingers, toes, palms, feet, and on the genital mucosa. Multiple HPV types have been isolated from these lesions; including HPV types 16, 18, 31, 32, 34, and others (Palefsky, 2016). Other types of NMSC that have shown to have an association with HPVs are: scrotal squamous cell carcinoma (Matoso *et al*., 2016), porocarcinoma (Urso *et al*., 2016), clear cell/signet-ring cell variant of cutaneous SCC (Wang *et al*., 2016), merkel cell carcinoma (Mitteldorf *et al.*, 2012), bowenoid papulosis (Hama *et al*., 2006), and erythroplasia of Queyrat (Kutlubay *et al*., 2013) (*Table 1*).

CONCLUSION

HPV infection has a critical role in common dermatologic and sexually transmitted diseases, as well as in some of the most frequent and most burdensome cancers worldwide. The role of vaccines in prevention of the consequences of this common infection is paramount. As worldwide HPV vaccination strategies are struggling against poor compliance, ignorance, and misconceptions, proper knowledge spreading among professionals and common people is the main future endeavor. Further studies showing evidence of HPV etiology with other types of cancer, other than cervical, and other diseases will also add more volume to the value, function and potential of HPV vaccination.

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Conflicts of interest
None declared.

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