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Review

The role of human papillomaviruses in cancer progression

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ABSTRACT

The importance of human papillomavirus (HPV) infection and its role in the progress of cancer have been widely evaluated. The understanding of HPV association with certain cancers, such as cervical cancer, is very well established. A big step forward in the prevention of HPV associated cancers with the use of early detection by screening strategies has also been taken. In the last decade, development of HPV vaccination has reduced the number of cases in HPV infections and infection induced cancers. In this report, we review the HPV pathogenesis and highlight the mechanism of HPV involvement in cancer development.

Key words: Human papillomavirus; cancer; immune response; human papillomavirus vaccine

INTRODUCTION

Human papillomavirus (HPV) is considered to be one of the viral infections associated with cancers and other diseases worldwide. HPVs are non-enveloped viruses with double stranded circular DNA.[1,2] The genome of papillomavirus constitutes three segments; early, late and genomic regions. The early region with E1, E2, E4-E8 forms half of the HPV genome. The early fragments function at different stages, in such both E1 and E2 is involved in the regulation of DNA replication, E2 in transcription (E2), E5, E6 and E7 in cell transformation [Table 1]. The late region (L) with L1 and L2 forms 40% of the genome and the genomic regulatory region forms the rest of the genome.[3] The late region of the genome involves the structural proteins of the virion [Table 1].[4]

HPVs are characterised according to their tissue tropism and they are subdivided into five main genera (Alpha-, beta-, gamma-, nu- and mu-papillomaviruses) depending on the DNA sequences, HPV life cycle characteristics and disease associations.[5-8] Alpha-HPVs infect mucosal tissues, whereas beta-, gamma-, nu- and mu-papillomaviruses infects cutaneous sites causing cutaneous lesions in humans.[9,10] However, as in recent years the number of HPV genotypes identified in healthy skin is increased, it is difficult to assign the cutaneous HPV types with a given cutaneous pathology. The HPVs can be further subdivided according to the epidemiological classification as ones with low, intermediate and high risk oncogenic potentials depending on the viruses' ability to promote the proliferation of infected cells and lead to malignant transformations.[1,11] The low risk HPVs including HPV6, 11, 42, 43 and 44 may cause condylomas and benign cervical lesions that do not form malignancies.[1,4,12,13] The intermediate oncogenic risk HPVs involves HPV31, 33, 35, 51 and 52 and there is still an ongoing debate whether the intermediate oncogenic risk HPVs cause malignant transformation as much as the high risk HPV types.[2,14] High oncogenic potential HPVs include HPV16, 18, 45 and 56 and these HPVs mostly cause neoplastic transformations.[2,4,14] Unlike alpha-HPVs, most of the beta- and gamma-HPVs results in asymptomatic infections in immune-competent individuals and these viruses adapt to their host and complete the life-cycle without causing any apparent diseases.[8,15-17]

Although the molecular defects caused by HPV infection leads to malignant transformation, it is not well established how they predispose to disease and whether keratinocyte[18,19] or the immune system is being compromised.[20,21] Therefore, although mainly the high risk HPV types cause malignant transformation and the low risks do no, it is possible that the low-risk viruses

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Table 1: List of HPV proteins and their function

HPV proteins	Function
E1	Viral DNA replication Repressive agent in transcription Inhibition of DNA replication[24,199]
E2	DNA replication Functions with E1, especially in HPV6, 11 and 16[24] Responsible for coding proteins regulating viral DNA transcription[199] cell transformation, initiating and inhibiting apoptosis, transcriptional regulation, and in the modulation of the immortalizing and transformation poten-tial of HPV[24]
E4	When inactive, it promotes E6 and E7 expression and influence tumor lesion development When active, it inhibits E6 and E7 transciption leading to increased p53 expression and apoptosis of infected cells[199] Affects the formation of the HPV-1 triggered nodules[24] may be involved in the cell cycle regulation[199]
E5	Transformation of viral DNA Viral DNA replication[24,199]
E6	Maintains the viral replication Synthesis of the genes via epithelium differentiation[200] Involved in HPV dependent malignant transformation via destructing the control of cell cycle regulation and cell maturation[199]
E7	Maintains the viral replication Contributes to the genetic instability of HPV-infected cells by interfering with the normal replication of centrosomes Synthesis of the genes via epithelium differentiation[200] Involved in HPV dependent malignant transformation via destructing the control of cell cycle regulation and cell maturation[199]

HPV: human papillomavirus

may also be associated with human cancers. The current understanding indicated that HPVs infect cells found in germ layers of the skin and mucous membranes, keranocyte or cells with differentiation potential of keranocyte. The mechanism of HPV infection is suspected to be similar among different tissues; in such the HPV infects the basal layer of the cervix causing exposure of the basement membrane, and HPV enters the basal layer of the tonsillar epithelium infecting and exposing the crypt cells.[22,23]

TRANSMISSION OF HPV

The most common sexually transmitted infection is presumed to be the HPV infection. HPV infection can be transmitted via both sexual and nonsexual contacts. HPVs penetrate the body through the skin and epidermis injuries, mucous membranes and skin abrasions.[24] Genital types of HPVs are mostly transmitted sexually. Generally in women, epidemiological studies have shown that the HPV infection is associated with the number of sexual partners, initial age of sexual intercourse and the likelihood of one of the sexual partners with an HPV infection.[25,26] Therefore for HPV associated cancers, such as cervical, penile or urethra, the sexual partner plays a key role as much as the individual's own sexual behaviour.[25,27]

More rarely, HPVs can be transmitted via perinatal transmission during birth from the mother to child that is also observed in the transmission of other microbial and viral infections.[28,29] Horizontal transmission of HPV is also possible and it was first reported with a 5 year old boy of HPV2 infection presented as warts on the hands and anus of the child via genital-finger transmission.[30]

IMMUNE RESPONSES TO HPV AND VACCINE-INDUCED PROTECTION

HPVs that cause persistent visible papillomas, especially at oral and genital sites, are the main concern for the individuals. It is known that under some circumstances the virus is cleared and although the underlying mechanism of the virus clearance is not well understood, the immune response, particularly T cells, seems to play the main role.[31-33] Lesion persistency and progression are increased in both animals and humans with genetic, iatrogenic or acquired cell mediated immune deficiencies, such as in patients with severe combined immunodeficiency,[34] in immunosupressed organ recipient patients,[35] in patients with epidermodysplasia verruciformis[35] and sun-exposed sites of patients with non-melanoma skin cancer.[35-37] Moreover, HPVs can escape the immune system and down regulate the innate immune signalling pathways.[38]

The clearance of high risk HPV types are believed to be harder since these types weaken the immune defences causing infection to continue and progress to neoplasias. However, it should be noted that progression from infections to cancer is a rare event and the first defence against HPV is the natural immunity. High risk HPV types are believed to destabilize the immune responses via obstructing the interferon pathway, down regulating major histocompatibility complex class I genes and changing the antigen production.[39] High risk HPV types continue to express the E6 and E7 oncoproteins that leads to genomic

aberrations and malignancies. Furthermore, differences in cell tropism and disease progression patterns are believed to be one of the reasons of higher cancer association with certain HPV types, such as higher association of HPV18 with adenocarcinoma and in cervical intraepithelial neoplasias grade 2 (CIN2). The high risk HPV types causing adenocarcinomas may infect cells that already have a potential glandular differentiation.[40] Therefore abortive or semipermissive infection of these cells may play an important role in the adenocarcinoma development. Recently, in silico models and epidemiological studies showed that the immune response may only contribute less than 20% of HPV clearance in individuals with normal immunity.[41] Ryser and colleagues (2015) further proposed that the virus is mainly cleared by stem cell divisions in immunocompromised individuals.[41]

Overall balance between the positive and negative immune factors may vary and these may lead to clearance of lesions. Therefore, therapeutic vaccines against HPV infections may play a strong role in prevention HPV associated lesions and cancers.[42] In 2006, the Food and Drug Administration approved the use of recombinant quadrivalent HPV vaccine gardasil for protection against HPV6, HPV11, HPV16 and HPV18 L1 proteins in females in the age between 9 and 26 years old.[43] It is proposed that in three doses of this vaccination at 0, 1 to 2 and 6 months, the HPV associated genital warts and the cervical cancer can be prevented.[44] This vaccination is also proposed to protect against the vulvar and vaginal cancers as well as intraepithelial neoplasias.[45] In 2009, the bivalent vaccine against HPV16 and HPV18 was licensed[46] and this vaccine is intended to protect against anogenital warts, precancerous lesions and cervical cancer.[45] Both the bivalent and quadrivalent HPV vaccines have been actively used in more than 80 countries.[47] Both of the vaccines are shown to be safe, having enduring protection against primary infection and stable protection.[48] These vaccines have a moderate cross-protection against high risk HPV types, HPV31, 33, 45, 52 and 58.[49,50] However, only 70% of cervical cancer cases can be avoided by using these vaccines.[51] Quadrivalent vaccines also protects against low risk HPV types, HPV6 and HPV11 that causes 90% of genital warts.[43] The development of these vaccinations has brought a new era in the prevention of HPV and these vaccinations are great promise; however there is still room for much more development. In general, therapeutic vaccines have been proposed but only few of them reached clinical trials. The current vaccinations do not protect against all the HPV types and the cost of these vaccinations make them impossible to be used in some parts of the world, especially in newly developing countries. Therefore, although vaccinations enabled a tremendous step towards prevention of HPV associated diseases, more feasible and affordable vaccinations with protection against all the HPV types are required.

GLOBAL BURDEN OF HPV IN CANCERS AND DISEASES: PREVALENCE AND ROLE OF HPV

The highest HPV prevalence is observed to be 24% in Saharan Africa, 21% in Eastern Europe and 16% in Latin America.[52] In majority of the populations, the highest prevalence of HPV is observed in women younger than 25 years. The prevalence reduces in older women with some having an increased rate in pri- or early-menopause. Although these prevalences are observed for many populations, in some others like China, the HPV prevalence is age-independent. On the other hand, HPV prevalence remains to be at a constant rate across all age groups in countries like Asia and Africa.[53] The reason of different prevalences observed in different populations worldwide are not very well understood, but it is possible that it varies due to the age of initial sexual activity, the number of partners and the habits of the sexual activities.

Different HPV genera cause both non-cancerous and cancerous diseases. Formation of warts on the skin and uretra, mucous membranes of the oral cavity, respiratory tract, throat and genitals have been associated with HPV infections. Current data indicates that the prevalences of the genital HPV infections are considerably higher compared to the oral HPV. Globally HPV infections are associated with approximately 50% of HPV caused cancers in women and 5% in men.[54] Different carcinogenesis is detected at different anatomical sites and at different level that is most likely because of the differences in the expression of the viral genome, in such HPV associated genital tract infections are observed at higher incidence compared to the head and neck cancer incidence. Genital HPV infections are connected with more than 99% of cervical cancers,[55] 97% of anal cancer,[56] 70% of vaginal cancers,[57] 47% of penile cancers,[58] 40% of vulval cancers,[57] 47% of oropharynx cancers and 11% of oral cavity cancer cases.[59]

ROLE OF HPV IN CANCER DEVELOPMENT

The mechanism of cancer progression in patients with HPV infection is not well established. However, there are a number of hypothesis on the possible routes of HPV in cancer progression. One of the hypotheses suggests that the cancer progression is associated with the increased accessibility and proliferation of the basal layers at the metaplastic epithelial site and therefore this increases the risk of metastasis. This becomes even more apparent at the puberty time and the onset of sexual activity.[60]

The initial infection of the cell and the relation of this to the disease outcome are not well understood. Generally HPV infection causes cell destruction as well as cell transformation and tumour development. HPVs interfere with cell cycle regulation and prevent apoptosis in cells

with unscheduled DNA replication. It is possible that HPV infection mainly affects the cells located near the squamo-columnar junctions that form the stratified epithelial layers of the transformation zone as the cervix matures, such as the epithelial reserve cells.[61,62] It is believed that the formation of the lesion starts with the infection of the basal stem cell and the formation of a persistent lesion depends on the longevity of the stem cell.[6,63,64] This hypothesis is especially convincing for the low-risk HPV types since they do not usually lead to neoplasia and do not particularly stimulate the basal cell proliferation. The viral replication proteins E1 and E2 may play a role in the amplification of the viral genome.[63,65,66] One of the hypotheses suggests that E2 may be possibly involved in genome partitioning where the viral transcription is regulated by E2.[67] A viral DNA helicase, such as E1, may separate the viral DNA replication from cellular DNA replication during establishment and amplification of the genome.[6,68] Of all the HPV proteins, E6 and E7 are the key ones associated in cancers via eliminating the tumour suppressors p53 and Rb leading to anti-apoptosis, genetic instability and formation of skin or mucosa lesions.[22,23,69] In low-risk HPV types, the wound healing process may hold an important role in the initial proliferation of the infected cells.[70] For the high-risk HPV types, viral proteins E6 and E7 function in the cell proliferation in the basal and parabasal cell layers. This function is particularly important at cervical sites where neoplasias may occur.[6] The functions of viral proteins E6 and E7 vary between the high and low-risk HPV types and these are associated with different pathologies.[71] The low risk HPV E6 and E7 proteins cause weak transformation or no transformation at all. RB1 is targeted and degraded by the high risk HPV E7 proteins, whereas E6 proteins target TP53 and stimulate telomerase (TERT). Telomerase activation is a fundamental stage for the high risk HPV type mediated cell immortalization *in vitro*.[72] However, more studies involving animal models are required to understand the HPV integration *in vivo*. On the contrary, even though the low risk HPV E7 proteins bind to RB1, it is not involved in the degradation. Low risk E6 does not bind to TP53 and it does not stimulate TERT.[73] The mechanism of oncogenesis associated with HPV is proposed to be through p16-INK4a expression. High risk HPV E7 triggers p16-INK4a through KDM6B histone demethylase causing p16-INK4a mediated CDK4/6 inhibition and RB1 mediated cell cycle arrest and senescence.[74-76] More aberrations including abnormal number of centromeres, multipolar mitotic spindles, chromosome lagging and anaphase bridges are also observed in cells expressing HPV16 E6 and E7 genes.[77] These aberrations may occur in cells with HPV infection at the early stages, but they can be easily detected in invasive cancers. Therefore, these abnormalities that originates during mitosis increases the risk of mutation accumulation that may cause malignant transformation *in vitro*. One of these aberrations is the allelic loss, such as losses in 3p and 10p that are associated with telomerase activation.

LOWER GENITAL TRACT NEOPLASIAS: CERVICAL, VAGINAL AND VULVAR CANCER

Neoplasias of the genital tract includes cervical (CIN), vaginal and vulvar intraepithelial neoplasias and a fraction of these neoplasias progresses to invasive cancers. HPV infection is detected in almost all cervical, half of the vulvar and approximately 70% of vaginal tumors.[78]

The organisation of the life cycle of HPVs in the development of lower genital tract neoplasias is well established.[79-82] Retrospective studies have reported that almost all the women with cervical cancers are infected with HPV and in the more severe cases, that are squamous cell carcinomas, HPV16 is the most prevalent type observed in 90% of the cases[40,52,83,84] Ten percent of the cervical cancers are adenocarcinomas that are mostly caused by HPV infections.[40] Women with HPV16 (61%) and HPV18 (10%) were shown to have 200 fold higher risks for the development of cervical cancers.[1,85] The prevalence of other HPV types are less observed in cervical cancer cases, in such HPV45 was observed in 6%, HPV31 in 4%, HPV52 in 3%, HPV35 in 2% and HPV58 in 2% of cervical cancer cases.[86]

The risk factors for cervical cancers follow the similar parameters for the general HPV infection risks, such as high parity (more than 4 vaginal deliveries), full term pregnancy at earlier age (18 years old or earlier) and use of hormonal oral contraceptives.[83,87] Progression of the cervical cancer can be affected by several factors including coinfection with other sexually transmitted infection, such as Chlamydia trachomatis, herpes simplex virus, HIV or tobacco smoking and immune suppression.[55,83] Therefore, counselling adolescents at earlier age for avoiding tobacco use, initiation of sexual intercourse and limiting the number of partners may help to reduce the cervical cancer.

The HPV proteins E6 and E7 are proposed to play a role in the pathogenesis of HPV associated cervical cancers.[88] The phenotype of the cervical neoplasia was suggested to vary depending on the expression levels of E6 and E7 were suggested to increase from cervical intraepithelial neoplasia grade 1 to 3 (CIN1 to CIN3). These interactions of HPV proteins with cellular pathways of the host cell will give a chance for potential targets for HPV based cancer treatment strategies. Additionally, E2 gene is also believed to take a part in cervical cancer since in about 35% of HPV induced cervical cancers full length viral genomes are expressed.[89,90] The regulation of gene expression is changed when the viral DNA integrates with the cell chromosomes. This integration leads to a continuous expression of E6 and E7 proteins causing accumulation of mutations of the cellular DNA and promoting malignancies.[77,91] These accumulations of mutations, mostly monosomies, trisomies, structural changes, chromatid gaps and breaks and double minutes,

are often detected in cervical cancers as well as other epithelial tumors.

The underlying mechanism of the progression from CIN1 through CIN2, CIN3 and eventually cancer is not well established, it may be due to the early integration events in CIN1 or due to deregulation of viral gene expression. It is also possible that the initial deregulation leads to instability of chromosomes and causes integration. It is believed that the integration arises in high grade lesions, such as CIN2 and CIN3 and the deregulation of E6 and E7 expression may increase or remain at a constitute level.[92,93] In this scheme, flat warts can be resembled in CIN1 lesions, however the proliferation level of the cell is lower in the basal and parabasal layers.[13] Increased expression levels of E6 and E7 in high-risk HPV type infections causes CIN2+ phenotypes. This phenotype leads genetic changes that contribute to cancer progression. These suggest that low expression levels of E6 and E7 does not affect the function of the cellular targets in CIN1 and therefore does not contribute to cancer progression. In CIN2/ CIN3+, the viral deregulation assists the viral episome into the host cell chromosome. This may further cause deregulation of E6 and E7 expression. In clinical vaccine trials it was shown that young women can have CIN2+ soon after infection[94-97] for these cases, it is possible that deregulation of the gene expression is due to cell signaling changes[98] or epigenetic modifications, such as viral DNA methylation.[99]

An important step has been taken towards prevention of HPV induced cervical cancers with the use of vaccines against HPV. However, due to various reasons, including the unavailability of the vaccines in certain regions of the world or the high costs of the vaccines, the wide application of the vaccines is not available. Therefore, in case of cervical cancer development, early detection strategies and treatment play a vital role to prevent any deaths. The treatment for the early cervical cancers is usually performed by conisation or radical hysterectomy. For the more advanced tumors, cisplatin based chemo-radiotherapy is preferred that results in 65-80% survival rates. Surgical excisions are usually the standard for the HPV associated anogenital lesions.[100] The treatment strategy for CIN is to eliminate the abnormal HPV infected precancerous cells and maintain the cervical integrity. One of the most commonly used treatments for CIN involves loop electrosurgical excision procedure, electrofulgaration and cryotherapy.[101]

The other lower genital cancers include vulvar and vaginal cancers. Majority of the vulvar and vaginal cancers are squamous cell carcinomas.[57] In majority of the cancers of the vagina HPV DNA is detected; approximately half of the vaginal cancers are caused by HPV16 (54%) followed by HPV18 (8%).[57] Similarly, HPV DNA is detected in most of the vulvar intraepithelial neoplasia, however only half of these neoplasias causes cancer. HPV16 is associated with 32% and HPV18 with 4% of the cases.[57,102-104] Therefore, although HPV may play a role in vulvar cancer, this association is not clear.

BREAST CANCER

Several epidemiological studies reported HPV detection in breast cancer samples.[105-109] Nevertheless the role of HPV in breast carcinogenesis is by far not certain and further randomized control trials are required to establish the definite role of HPV in breast cancer development.

HEAD AND NECK CARCINOMAS

Head and neck carcinomas involve a wide range of tumors and is one of the most common cancers worldwide.[110] The prevalence of HPV DNA in head and neck cancers depends on the cancer site, geography and ethnicity.[104] The most consistent prevalence of HPV infection is the oropharyngeal cancers with an association of 35-50% in developed cancers, whereas the HPV is detected in approximately 5-15% within the rest of the oral cavity.[52,84] The overall risk factors for head and neck carcinomas include tobacco smoking and alcohol consumption.

The first cases of HPV relationships with oral cell squamous cell carcinomas were reported in 2008 for lingual cancer, tonsil cancer and oropharyngeal cancers.[111,112] Overall the prevalence of these cancers are higher in men compared to women.[113] Oropharyngeal carcinomas (OPCs) are the most studied and the most characterised type of head and neck carcinomas. In the last decade the incidence of HPV related OPCs have doubled in number of patients and therefore more attention has drawn to these cancer types.[114] HPV positive oropharyngeal cancers are mainly associated with oral sex and rare p53 mutation.[115] Interestingly HPV infection was shown to improve the prognosis of OPC with better survival is reported in HPV positive OPCs[116] and therefore these patients may have a chance to benefit from a less intense treatment strategy.[117] Chemotherapy using paclitaxel, cisplatin on centuximab; followed by concurrent radiation has been used in treatment of OPC patiens.[118] With the increasing number of HPV associated OPC patients, the use of antiviral and immunotherapeutic strategies show an improved outcome.[42] Although HPV related OPC have increased through the years, the HPV negative OPCs still account for the majority of the OPC patients.

The HPVs, mostly HPV16 and HPV33, were detected in quarter of the patients with invasive laryngeal cancers and are predominantly detected in women compared to men.[119-121] HPV is also associated with potential malignant disorders, such as erythroplakia, oral leukoplakia and oral lichen planus.[122] Erythroplakia has the highest risk of malignant transformation. Half of the cases with erythroplakias alone is associated with HPV infection[123] and the frequency of the HPV detection influences the severity of the lesions. In one study the HPV prevalence was 32.8% in oral lichen planus, 40.9% in oral leukoplakia

and 47.7% in oral squamous cell carcinomas.[124] Oral leukoplakia is associated with HPV6, HPV11 and HPV16 and these may lead to malignant oral diseases.[125-127] Similarly, HPV is detected more often with increased prevalence in oral lichen planus.[128]

The overall prognosis of head and neck squamous cell carcinomas seems to be better with HPV infected patients. Young individuals appear to have increased risk of having HPV positive tonsillar and oropharyngeal carcinomas[129,130] with better prognosis and lower relapse risks compared to HPV negative head and neck squamous cell carcinoma (HNSCC) patients.[131] Approximately 6% prevalence was reported for HPV positive OSCCs.[132] However, more than half of the patients with HNSCC (57%) were shown to have metastases to the brain where all are HPV positive.[133]

LUNG CANCER

Lung cancer is one the foremost causes of cancer associated deaths worldwide. Although cigarette smoking plays a crucial role in lung cancer development, less than 20% of the smokers have lung cancer.[134] Therefore, other factors including inactivation of tumour suppressor genes, such as p53, Rb and p16, and HPV infection have been proposed to be involved in the development of lung carcinogenesis.[134,135] The possible role of HPV in lung cancer was initially proposed due to the similarities of the morphological epithelial changes detected in bronchial carcinomas with genital HPV lesions.[136,137] HPV detection in lung cancer was confirmed in 1988[138] and the association of HPV with lung cancer was then verified by detection of HPV DNA in lung cancer samples.[139,140] However, the issue is debated and controversial studies have been reported.[141,142] Some groups reported that E7 proteins of high risk HPV16 and HPV18 are detected,[143,144] some reported that none of the HPV types are present in non-small lung cancer.[145] An international pooled analysis of HPV association with lung cancers revealed that HPV DNA is present but in a very small number of lung tumors.[146] Therefore, the direct relevance of lung cancer with HPV requires further analysis. A recent meta-analysis data showed that HPV infection has a strong relationship with lung cancer with significantly increased risk of lung squamous cell carcinoma upon HPV16 and HPV18 infection and in this meta-analysis, it is proposed that the HPV vaccination may lower the lung cancer risk.[147]

Respiratory papillomatosis (RRP) is a serious condition that may spread to lungs and can progress to cancer.[148,149] Patients with RRP have an increased risk of developing laryngeal neoplasias and carcinomas.[150] RRP is mainly caused by the alpha-HPVs, HPV6 and/or HPV11.[151] The transmission of upper respiratory tract infections may be passed on by sexual contact and from mother to child during child birth canal.[4,152] Although many therapies have applied for RRP patients, such as surgical, treatment with antivirals and chemotherapeutic drugs; there is limited success with mostly side effects.[153] Therefore like all the other cancers, early detection and vaccines can play a crucial role in RRP. Although the present HPV vaccines protect against HPV 11, there is the need for development of vaccines for other HPV types, especially HPV6 for the prevention of RRP.

BLADDER CANCER

The first association of HPV and bladder tumors was reported in 1988.[154] The prevalence of HPV infection in bladder carcinomas ranges from 0% to 81%.[155-159] Overall, the involvement of bladder cancer with HPV is controversial. Although some studies reported a positive correlation between HPV infection through contribution of E6 and E7 oncogenic proteins,[160-163] some reported no association between HPV infected bladder carcinoma.[164,165] Furthermore, p16-INK4a was reported to be involved in the development of bladder cancer through suppressing the inactivation of Rb protein association with HPV infected bladder carcinoma.[163,166,167] The controversy continues with the inverted papiloma of the urinary tract and urothelial carcinomas. In some reports HPV is associated with inverted papilloma of the urinary bladder[168] and urothelial carcinomas,[167,169] but in the others no association was reported.[170,171]

HPVs, especially HPV16 and HPV18, were detected mostly in low grade (grade 1) tumours and never have they been reported for grade 3 carcinomas.[163,167,172-175] Therefore potentially HPV is only associated with low grade carcinomas.

PENILE CARCINOMA AND ANAL CARCINOMA

Penile carcinomas mainly originate in the squamous mucosa of the glans, coronal sulcus or inner surface of the foreskin of the penile. Penile cancers are rare and they usually occur in uncircumcised men.[176] About half (40-50%) of the penile squamous cell carcinomas are related to the high risk HPV infection[52,177-180] and mostly the basaloid and warty types of penile cancers are consistently related to HPV infection, whereas HPV DNA was only detected in some of the keratinizing and verrucous penile carcinomas.[179] Mainly HPV16 (69%) and HPV18 (13%) play a role in the development of penile squamous cell carcinomas.[57] High risk HPV types, generally HPV16 and HPV18, are detected in Bowenoid papulosis, which resemble genital warts but with high grade squamous cell carcinoma *in situ*, can be found on the external genitalia, perineum or perinally.[181] HPV16 and HPV18 are also associated with Eryhtroplasia Queyrat, which is *in situ* carcinoma of the penile mucosa. This carcinoma can also be present on the urethra, vulva, tongue and oral mucosa. Buschke-Löwenstein tumors, which cause destruction of the underlying tissues leading to transformation into squamous cell carcinoma and are

located on the penile glans, prepuce, vulva, vagina and perianal sites, are also associated with low risk HPVs, HPV6 and HPV 11.[182,183] Additionally, in both males and females, approximately 85-95% of the anal cancers are HPV DNA positive.[52,104] Of these, HPV16 (75%) and HPV18 (3%) are the causes for almost all the cases of anal cancers.[56,184]

SKIN CANCER

Similar to the head and neck, bladder and breast cancers, the involvement of HPV in cutaneous squamous cell carcinoma has not been surely established. A range of nonmelanoma skin cancer forms contain DNA from beta HPV types.[185] HPV induced skin cancers include cutaneous squamous cell carcinoma and superficial squamous cell carcinoma, such as Bowen's disease.[186] Approximately 30% individuals with infection develop invasive squamous cell carcinomas with 90% of these tumors correlated with HPV5 and HPV8.[36,187] Genetic susceptibility to HPV is demonstrated with epidermodysplasia verruciformis; however, HPV infection alone is not enough to develop cancerogenesis in epidermodysplasia verruciformis.[42] Mainly, these tumors are induced by sun explosion and ultraviolet radiation. Cells with HPV5 and HPV8 E6 proteins disturb DNA double strand break repair[188] and reduces the efficiency of base excision repair pathway[189] causing higher sensitivity to UV-B exposure. It may be possible that because of impaired DNA repair activity, patients with acquired immunodeficiency syndrome or patients with epidermodysplasia verruciformis are more subjected for the infections and at a higher risk of developing HPV associated cutaneous malignancies.[185,190,191] In order to reduce the prevalence of HPV induced skin cancers, diagnosis of skin manifestations caused by HPV should be routinely checked.[186]

ROLE OF HPV IN NON-CANCEROUS DISEASES

One of the most common non-oncogenic HPV diseases involves genital warts and the clinical manifestations extend from flat and common warts and cauliflower like or filiform warts.[186] The genital warts are mostly common in younger people with the age of less than 25 years old and the transmission is more than 60% with an incubation time between 2 to 8 months.[192] Various clinical presentations are observed when keratinocytes respond to the HPV infection depending on the HPV type and the anatomical site. Genital warts are mainly associated with HPV6 and HPV11. Although mainly low risk HPV types, HPV6 (89%) and HPV11 (11%),[193] both high and low risk HPV types may cause genital warts.[194] Bowenoid papulosis is described by several flat patches in genital area. Similarly, condylomata plana are flat warts that have been associated with HPV infection.[195] Recurrence of genital warts with progression of lesions even after 3 months are reported in one-third of individuals with presence of genital warts.[196]

Genital warts can be found on penile shaft, base of the penis, scrotum, pubic region, glans and rectal area. In women, they are mostly present in the labia minora and vaginal opening.[197] In the decision of the therapy strategy, many factors, such as morphology of the lesion, HPV classification and immune competent status, are taken into account. Unfortunately, none of the treatment strategies, including targeted lesion destruction or immunologic modification, are shown to clear the HPV infection or avoid the recurrence. With the use of HPV vaccines, the incidence of the warts has been decreased.[198] If these warts remain untreated, they can either regresses spontaneously or they can grow larger and become more numerous resulting in complicated cases.[192] Therefore, prevention HPV infection and therefore formation of these warts will be the optimum goal.

CONCLUSION

In the recent years, the biology of HPV infection and its role in the progress of cancer have been widely evaluated. All the data discussed in this review point out the significance of HPV infection in several benign and malignant diseases. Although the understanding of association of HPVs with cervical cancer is very well established further studies are required to analyse the relationships between HPV and certain cancers including breast, lung, bladder, some types of head and neck cancers and penile cancers.

To improve the mortality and morbidity of HPV associated cancers and diseases, there is an enormous need for early detection and prevention strategies. Although screening programs for early detection strategies have been developed for some cancers, such as cervical, there is still a big gap to be filled for other precancerous lesions, such as for some of the head and neck carcinomas. One of the examples of these screening strategies may involve oral examination, cytology and salivary HPV DNA tests which may provide a better early diagnosis for oral and oro-pharyngeal cancers. Moreover development and spread of more cost-effective vaccines is mandatory. Availability of low cost screening may prevent the future generations to develop HPVs induced cancers. In light of this knowledge, HPV vaccines are useful in the protection against cervical, oral and oro-pharyngeal cancers. However, it should be kept in mind that the current HPV vaccines do not protect against all HPV types, particularly beta-HPV types and their associated diseases. Therefore, despite all these advances, other strategies for early detection and prevention for different HPV types are required.

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REFERENCES

1. Munoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, Snijders PJ, Meijer CJ; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003;348:518-27.
2. Schiffman M, Clifford G, Buonaguro FM.Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline. *Infect Agent Cancer* 2009;4:8.
3. Hafkamp HC, Manni JJ, Speel EJ. Role of human papillomavirus in the development of head and neck squamous cell carcinomas. *Acta Otolaryngol* 2004;124:520-6.
4. Devaraj K, Gillison ML, Wu TC. Development of HPV vaccines for HPV-associated head and neck squamous cell carcinoma. *Crit Rev Oral Biol Med* 2003;14:345-62.
5. Bernard HU, Burk RD, Chen Z, van Doorslaer K, zur Hausen H, de Villiers EM.Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology* 2010;401:70-9.
6. Doorbar J. Molecular biology of human papillomavirus infection and cervical cancer. *Clin Sci (Lond)* 2006;110:525-41.
7. Bosch FX, Burchell AN, Schiffman M, Giuliano AR, de Sanjose S, Bruni L, Tortolero-Luna G, Kjaer SK, Muñoz N. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. *Vaccine* 2008;26 Suppl 10:K1-16.
8. Ekström J, Bzhalava D, Svenback D, Forslund O, Dillner J. High throughput sequencing reveals diversity of Human Papillomaviruses in cutaneous lesions. *Int J Cancer* 2011;129:2643-50.
9. de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. *Virology* 2004;324:17-27.
10. Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, Stanley MA. The biology and life-cycle of human papillomaviruses. *Vaccine* 2012;30 Suppl 5:F55-70.
11. zur Hausen H. Human papillomaviruses in the pathogenesis of anogenital cancer. *Virology* 1991;184:9-13.
12. Biedermann K, Dandachi N, Trattner M, Vogl G, Doppelmayr H, Moré E, Staudach A, Dietze O, Hauser-Kronberger C. Comparison of real-time PCR signal-amplified *in situ* hybridization and conventional PCR for detection and quantification of human papillomavirus in archival cervical cancer tissue. *J Clin Microbiol* 2004;42:3758-65.
13. Middleton K, Peh W, Southern S, Griffin H, Sotlar K, Nakahara T, El-Sherif A, Morris L, Seth R, Hibma M, Jenkins D, Lambert P, Coleman N, Doorbar J. Organization of human papillomavirus productive cycle during neoplastic progression provides a basis for selection of diagnostic markers. *J Virol* 2003;77:10186-201.
14. Cogliano V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F; WHO International Agency for Research on Cancer. Carcinogenicity of human papillomaviruses. *Lancet Oncol* 2005;6:204.
15. Nindl I, Gottschling M, Stockfleth E. Human papillomaviruses and non-melanoma skin cancer: basic virology and clinical manifestations. *Dis Markers* 2007;23:247-59.
16. Gottschling M, Göker M, Köhler A, Lehmann MD, Stockfleth E, Nindl I. Cutaneotropic human beta-/gamma-papillomaviruses are rarely shared between family members. *J Invest Dermatol* 2009;129:2427-34.
17. Bottalico D, Chen Z, Dunne A, Ostoloza J, McKinney S, Sun C, Schlecht NF, Fatahzadeh M, Herrero R, Schiffman M, Burk RD. The oral cavity contains abundant known and novel human papillomaviruses from the Betapapillomavirus and Gammapapillomavirus genera. *J Infect Dis* 2011;204:787-92.
18. Chow KY1, Brotin É, Ben Khalifa Y, Carthagena L, Teissier S, Danckaert A, Galzi JL, Arenzana-Seisdedos F, Thierry F, Bachelerie F. A pivotal role for CXCL12 signaling in HPV-mediated transformation of keratinocytes: clues to understanding HPV-pathogenesis in WHIM syndrome. *Cell Host Microbe* 2010;8:523-33.
19. Lazarczyk M, Cassonnet P, Pons C, Jacob Y, Favre M. The EVER proteins as a natural barrier against papillomaviruses: a new insight into the pathogenesis of human papillomavirus infections. *Microbiol Mol Biol Rev* 2009;73:348-70.
20. Gulino AV. WHIM syndrome: a genetic disorder of leukocyte trafficking. *Curr Opin Allergy Clin Immunol* 2003;3:443-50.
21. Ortak T, Uysal AC, Alagoz MS, Orbay H, Sensoz O. Epidermodysplasia verruciformis: an unusual presentation. *Dermatol Surg* 2006; 32:302-6.
22. Woodman CB, Collins SI, Young LS. The natural history of cervical HPV infection: unresolved issues. *Nat Rev Cancer* 2007;7:11-22.
23. Howard JD, Chung CH. Biology of human papillomavirus-related oropharyngeal cancer. *Semin Radiat Oncol* 2012;22:187-93.
24. Beutner KR, Tyring S. Human papillomaviruses and human disease. *Am J Med* 1997;5: 9-15.
25. Kjaer SK, Chackerian B, van den Brule AJ, Svare EI, Paull G, Walbomers JM, Schiller JT, Bock JE, Sherman ME, Lowy DR, Meijer CL. High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse). *Cancer Epidemiol Biomarkers Prev* 2001;10:101-6.
26. Castellsagué X, Ghaffari A, Daniel RW, Bosch FX, Muñoz N, Shah KV. Prevalence of penile human papillomavirus DNA in husbands of women with and without cervical neoplasia: a study in Spain and Colombia. *J Infect Dis* 1997;176:353-61.
27. Bosch FX, Castellsagué X, Muñoz N, de Sanjosé S, Ghaffari AM, González LC, Gili M, Izarzugaza I, Viladiu P, Navarro C, Vergara A, Ascunce N, Guerrero E, Shah KV. Male sexual behavior and human papillomavirus DNA: key risk factors for cervical cancer in Spain. *J Natl Cancer Inst* 1996;88:1060-7.
28. Cason J. Perinatal acquisition of cervical cancer-associated papillomaviruses. *Br J Obstet Gynaecol* 1996;103:853-8.
29. Favre M, Majewski S, De Jesus N, Malejczyk M, Orth G, Jablonska S. A possible vertical transmission of human papillomavirus genotypes associated with epidermodysplasia verruciformis. *J Invest Dermatol* 1998;111:333-6.
30. Bosch FX, YL Qiao, X Castellsagué. The epidemiology of human papillomavirus infection and its association with cervical cancer. *Int J Gynecol Obstet* 2006;94:S8-21.
31. Stern PL, MH Einstein. From HPV infection to oncogenesis: a brief review of the complex immunobiological events. *Curr Cancer Ther Rev* 2010: 110-6.
32. van der Burg SH, Melief CJ. Melief, Therapeutic vaccination against human papilloma virus induced malignancies. *Curr Opin Immunol* 2011;23:252-7.
33. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646-74.
34. Laffort C, Le Deist F, Favre M, Caillat-Zucman S, Radford-Weiss I, Debré M, Fraitag S, Blanche S, Cavazzana-Calvo M, de Saint Basile G, de Villartay JP, Giliani S, Orth G, Casanova JL, Bodemer C, Fischer A. Severe cutaneous papillomavirus disease after haemopoietic stem-cell transplantation in patients with severe combined immune deficiency caused by common gammac cytokine receptor subunit or JAK-3 deficiency. *Lancet* 2004;363:2051-4.
35. Gewirtzman A, Bartlett B, Tyring S. Epidermodysplasia verruciformis and human papilloma virus. *Curr Opin Infect Dis* 2008;21:141-6.
36. Dubina M, Goldenberg G. Viral-associated nonmelanoma skin cancers: a review. *Am J Dermatopathol* 2009;31:561-73.
37. Weissenborn S, Neale RE, Waterboer T, Abeni D, Bavinck JN, Green AC, Harwood CA, Euvrard S, Feltkamp MC, de Koning MN, Naldi L, Quint WG, Tessari G, Proby CM, Wieland U, Pfister H; EPI-HPV-UV-CA group. Beta-papillomavirus DNA loads in hair follicles of immunocompetent people and organ transplant recipients. *Med Microbiol Immunol* 2012;201:117-25.
38. Kanodia S, Fahey LM, Kast WM. Mechanisms used by human

papillomaviruses to escape the host immune response. *Curr Cancer Drug Targets* 2007;7:79-89.
39. O'Brien PM, Saveria Campo M. Evasion of host immunity direct by papillomavirus-encoded proteins. *Virus Res* 2002;88:103-17.
40. de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, Tous S, Felix A, Bravo LE, Shin HR, Vallejos CS, de Ruiz PA, Lima MA, Guimera N, Clavero O, Alejo M, Llombart-Bosch A, Cheng-Yang C, Tatti SA, Kasamatsu E, Iljazovic E, Odida M, Prado R, Seoud M, Grce M, Usubutun A, Jain A, Suarez GA, Lombardi LE, Banjo A, Menéndez C, Domingo EJ, Velasco J, Nessa A, Chichareon SC, Qiao YL, Lerma E, Garland SM, Sasagawa T, Ferrera A, Hammouda D, Mariani L, Pelayo A, Steiner I, Oliva E, Meijer CJ, Al-Jassar WF, Cruz E, Wright TC, Puras A, Llave CL, Tzardi M, Agorastos T, Garcia-Barriola V, Clavel C, Ordi J, Andújar M, Castellsagué X, Sánchez GI, Nowakowski AM, Bornstein J, Muñoz N, Bosch FX; Retrospective International Survey and HPV Time Trends Study Group. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol* 2010;11:1048-56.
41. Ryser MD, Myers ER, Durrett R. HPV Clearance and the Neglected Role of Stochasticity. *PLoS Comput Biol* 2015;11:e1004113.
42. Stern PL, van der Burg SH, Hampson IN, Broker TR, Fiander A, Lacey CJ, Kitchener HC, Einstein MH. Therapy of human papillomavirus-related disease. *Vaccine* 2012;30 Suppl 5:F71-82.
43. Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007;356:1915-27.
44. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, Tang GW, Ferris DG, Steben M, Bryan J, Taddeo FJ, Railkar R, Esser MT, Sings HL, Nelson M, Boslego J, Sattler C, Barr E, Koutsky LA; Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007; 356:1928-43.
45. Choi YH, Chapman R, Gay N, Jit M. Potential overestimation of HPV vaccine impact due to unmasking of non-vaccine types: quantification using a multi-type mathematical model. *Vaccine* 2012;30:3383-8.
46. Wheeler CM, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Perez G, Brown DR, Koutsky LA, Tay EH, García P, Ault KA, Garland SM, Leodolter S, Olsson SE, Tang GW, Ferris DG, Paavonen J, Steben M, Bosch FX, Dillner J, Joura EA, Kurman RJ, Majewski S, Muñoz N, Myers ER, Villa LL, Taddeo FJ, Roberts C, Tadesse A, Bryan J, Lupinacci LC, Giacoletti KE, James M, Vuocolo S, Hesley TM, Barr E. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16-26 years. *J Infect Dis* 2009;199:936-44.
47. Aggarwal P. Cervical cancer: Can it be prevented? *World J Clin Oncol* 2014;5:775-80.
48. Schiller JT, Castellsagué X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. *Vaccine* 2012;30 Suppl 5:F123-38.
49. Donovan B, Franklin N, Guy R, Grulich AE, Regan DG, Ali H, Wand H, Fairley CK. Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data. *Lancet Infect Dis* 2011;11:39-44.
50. Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007;356:1915-27.
51. Kjær SK, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. *J Natl Cancer Inst* 2010;102:1478-88.
52. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, Vignat J, Ferlay J, Bray F, Plummer M, Franceschi S. Global burden of human papillomavirus and related diseases. *Vaccine* 2012;30 Suppl 5:F12-23.
53. de Sanjosé S. Human Papillomavirus and cancer. Epidemiology and prevention. 4th monograph of the Spanish Society of Epidemiology. Barcelona, Spain: Spanish Society of Epidemiology; 2006. p. 143-7.
54. zur Hausen H. Papillomaviruses in the causation of human cancers - a brief historical account. *Virology* 2009;384:260-5.
55. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Muñoz N. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12-9.
56. Abramowitz L, Jacquard AC, Jaroud F, Haesebaert J, Siproudhis L, Pradat P, Aynaud O, Leocmach Y, Soubeyrand B, Dachez R, Riethmuller D, Mougin C, Pretet JL, Denis F. Human papillomavirus genotype distribution in anal cancer in France: the EDiTH V study. *Int J Cancer* 2011;129: 433-9.
57. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. *Int J Cancer* 2009;124:1626-36.
58. Miralles-Guri C, Bruni L, Cubilla AL, Castellsagué X, Bosch FX, de Sanjosé S. Human papillomavirus prevalence and type distribution in penile carcinoma. *J Clin Pathol* 2009;62:870-8.
59. St Guily JL, Jacquard AC, Prétet JL, Haesebaert J, Beby-Defaux A, Clavel C, Agius G, Birembaut P, Okaïs C, Léocmach Y, Soubeyrand B, Pradat P, Riethmuller D, Mougin C, Denis F. Human papillomavirus genotype distribution in oropharynx and oral cavity cancer in France--The EDiTH VI study. *J Clin Virol* 2011;51:100-4.
60. Grayson W, Rhemtula HA, Taylor LF, Allard U, Tiltman AJ. Detection of human papillomavirus in large cell neuroendocrine carcinoma of the uterine cervix: a study of 12 cases. *J Clin Pathol* 2002;55:108-14.
61. Gravitt PE, Lacey JV Jr, Brinton LA, Barnes WA, Kornegay JR, Greenberg MD, Greene SM, Hadjimichael OC, McGowan L, Mortel R, Schwartz PE, Zaino R, Hildesheim A. Evaluation of self-collected cervicovaginal cell samples for human papillomavirus testing by polymerase chain reaction. *Cancer Epidemiol Biomarkers Prev* 2001;10:95-100.
62. Bouvard V, Baan RA, Grosse Y, Lauby-Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Straif K; WHO International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of malaria and of some polyomaviruses. *Lancet Oncol* 2012;13:339-40.
63. Egawa K. Do human papillomaviruses target epidermal stem cells? *Dermatology* 2003;207: 251-4.
64. Schmitt A, Rochat A, Zeltner R, Borenstein L, Barrandon Y, Wettstein FO, Iftner T. The primary target cells of the high-risk cottontail rabbit papillomavirus colocalize with hair follicle stem cells. *J Virol* 1996;70:1912-22.
65. Kim K, Lambert PF. E1 protein of bovine papillomavirus 1 is not required for the maintenance of viral plasmid DNA replication. *Virology* 2002;293:10-4.
66. Angeletti PC, Kim K, Fernandes FJ, Lambert PF. Stable replication of papillomavirus genomes in Saccharomyces cerevisiae. *J Virol* 2002;76:3350-8.
67. McBride AA. Replication and partitioning of papillomavirus genomes. *Adv Virus Res* 2008;72:155-205.
68. Blakaj DM, Fernandez-Fuentes N, Chen Z, Hegde R, Fiser A, Burk RD, Brenowitz M. Evolutionary and biophysical relationships among the papillomavirus E2 proteins. *Front Biosci (Landmark Ed)* 2009;14:900-17.
69. Chung CH, Gillison ML. Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. *Clin Cancer Res* 2009;15:6758-62.
70. Valencia C, Bonilla-Delgado J, Oktaba K, Ocádiz-Delgado R, Gariglio P, Covarrubias L. Human papillomavirus E6/E7

oncogenes promote mouse ear regeneration by increasing the rate of wound re-epithelization and epidermal growth. *J Invest Dermatol* 2008;128:2894-903.
71. Klingelhutz AJ, Roman A. Cellular transformation by human papillomaviruses: lessons learned by comparing high- and low-risk viruses. *Virology* 2012;424:77-98.
72. von Knebel Doeberitz M. New markers for cervical dysplasia to visualise the genomic chaos created by aberrant oncogenic papillomavirus infections. *Eur J Cancer* 2002;38:2229-42.
73. Moody CA, Laimins LA. Human papillomavirus oncoproteins: pathways to transformation. *Nat Rev Cancer* 2010;10:550-60.
74. Agger K, Cloos PA, Rudkjaer L, Williams K, Andersen G, Christensen J, Helin K. The H3K27me3 demethylase JMJD3 contributes to the activation of the INK4A-ARF locus in response to oncogene- and stress-induced senescence. *Genes Dev* 2009;23:1171-6.
75. Barradas M, Anderton E, Acosta JC, Li S, Banito A, Rodriguez-Niedenführ M, Maertens G, Banck M, Zhou MM, Walsh MJ, Peters G, Gil J. Histone demethylase JMJD3 contributes to epigenetic control of INK4a/ARF by oncogenic RAS. *Genes Dev* 2009;23:1177-82.
76. Gonzalez SL, Stremlau M, He X, Basile JR, Münger K. Degradation of the retinoblastoma tumor suppressor by the human papillomavirus type 16 E7 oncoprotein is important for functional inactivation and is separable from proteasomal degradation of E7. *J Virol* 2001;75:7583-91.
77. Duensing S, Münger K. Mechanisms of genomic instability in human cancer: insights from studies with human papillomavirus oncoproteins. *Int J Cancer* 2004;109:157-62.
78. Lowy DR, Schiller JT. Reducing HPV-associated cancer globally. *Cancer Prev Res (Phila)* 2012;5:18-23.
79. Wikström A, Hedblad MA, Syrjänen S. Penile intraepithelial neoplasia: histopathological evaluation, HPV typing, clinical presentation and treatment. *J Eur Acad Dermatol Venereol* 2012;26:325-30.
80. Silva RJ, Casseb J, Andreoli MA, Villa LL. Persistence and clearance of HPV from the penis of men infected and non-infected with HIV. *J Med Virol* 2011;83:127-31.
81. Szentirmay Z, Pólus K, Tamás L, Szentkuti G, Kurcsics J, Csernák E, Tóth E, Kásler M. Human papillomavirus in head and neck cancer: molecular biology and clinicopathological correlations. *Cancer Metastasis Rev* 2005;24:19-34.
82. Syrjänen K, Syrjänen S, Lamberg M, Pyrhönen S, Nuutinen J. Morphological and immunohistochemical evidence suggesting human papillomavirus (HPV) involvement in oral squamous cell carcinogenesis. *Int J Oral Surg* 1983;12:418-24.
83. Harper DM, Demars LR. Primary strategies for HPV infection and cervical cancer prevention. *Clin Obstet Gynecol* 2014;57:256-78.
84. Bosch FX, Broker TR, Forman D, Moscicki AB, Gillison ML, Doorbar J, Stern PL, Stanley M, Arbyn M, Poljak M, Cuzick J, Castle PE, Schiller JT, Markowitz LE, Fisher WA, Canfell K, Denny LA, Franco EL, Steben M, Kane MA, Schiffman M, Meijer CJ, Sankaranarayanan R, Castellsagué X, Kim JJ, Brotons M,Alemany L, Albero G, Diaz M, de Sanjosé S. Comprehensive control of human papillomavirus infections and related diseases. *Vaccine* 2013;31 Suppl 8:I1-31.
85. Bosch FX, Lorincz A, Muñoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002;55:244-65.
86. Schiffman M, Kjaer SK. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. *J Natl Cancer Inst Monogr* 2003:14-9.
87. Wen LM, Estcourt CS, Simpson JM, Mindel A. Risk factors for the acquisition of genital warts: are condoms protective? *Sex Transm Infect* 1999;75:312-6.
88. Münger K, Howley PM. Human papillomavirus immortalization and transformation functions. *Virus Res* 2002;89:213-28.
89. Klaes R, Woerner SM, Ridder R, Wentzensen N, Duerst M, Schneider A, Lotz B, Melsheimer P, von Knebel Doeberitz M. Detection of high-risk cervical intraepithelial neoplasia and cervical cancer by amplification of transcripts derived from integrated papillomavirus oncogenes. *Cancer Res* 1999;59:6132-6.
90. Li K, Jin X, Fang Y, Wang C, Gong M, Chen P, Liu J, Deng D, Ai J. Correlation between physical status of human papilloma virus and cervical carcinogenesis. *J Huazhong Univ Sci Technol Med Sci* 2012;32:97-102.
91. Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. *J Clin Virol* 2005;32 Suppl 1:S16-24.
92. Melsheimer P, Vinokurova S, Wentzensen N, Bastert G, von Knebel Doeberitz M. DNA aneuploidy and integration of human papillomavirus type 16 e6/e7 oncogenes in intraepithelial neoplasia and invasive squamous cell carcinoma of the cervix uteri. *Clin Cancer Res* 2004;10:3059-63.
93. Häfner N, Driesch C, Gajda M, Jansen L, Kirchmayr R, Runnebaum IB, Dürst M. Integration of the HPV16 genome does not invariably result in high levels of viral oncogene transcripts. *Oncogene* 2008;27:1610-7.
94. Paavonen J, Jenkins D, Bosch FX, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter DL, Kitchener HC, Castellsague X, de Carvalho NS, Skinner SR, Harper DM, Hedrick JA, Jaisamrarn U, Limson GA, Dionne M, Quint W, Spiessens B, Peeters P, Struyf F, Wieting SL, Lehtinen MO, Dubin G; HPV PATRICIA study group. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet* 2007;369:301-14.
95. Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter D, Kitchener H, Castellsague X, Teixeira JC, Skinner SR, Hedrick J, Jaisamrarn U, Limson G, Garland S, Szarewski A, Romanowski B, Aoki FY, Schwarz TF, Poppe WA, Bosch FX, Jenkins D, Hardt K, Zahaf T, Descamps D, Struyf F, Lehtinen M, Dubin G; HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009;374:301-14.
96. Szarewski A, Poppe WA, Skinner SR, Wheeler CM, Paavonen J, Naud P, Salmeron J, Chow SN, Apter D, Kitchener H, Castellsagué X, Teixeira JC, Hedrick J, Jaisamrarn U, Limson G, Garland S, Romanowski B, Aoki FY, Schwarz TF, Bosch FX, Harper DM, Hardt K, Zahaf T, Descamps D, Struyf F, Lehtinen M, Dubin G; HPV PATRICIA Study Group. Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in women aged 15-25 years with and without serological evidence of previous exposure to HPV-16/18. *Int J Cancer* 2012;131:106-16.
97. Quint W, Jenkins D, Molijn A, Struijk L, van de Sandt M, Doorbar J, Mols J, Van Hoof C, Hardt K, Struyf F, Colau B. One virus one lesion - Individual components of CIN lesions contain a specific HPV type. *J Pathol* 2012;227:449-65.
98. Gariglio P, Gutiérrez J, Cortés E, Vázquez J. The role of retinoid deficiency and estrogens as cofactors in cervical cancer. *Arch Med Res* 2009;40:449-65.
99. Ding DC, Chiang MH, Lai HC, Hsiung CA, Hsieh CY, Chu TY. Methylation of the long control region of HPV16 is related to the severity of cervical neoplasia. *Eur J Obstet Gynecol Reprod Biol* 2009;147:215-29.
100. van de Nieuwenhof HP, Massuger LF, van der Avoort IA, Bekkers RL, Casparie M, Abma W, van Kempen LC, de Hullu JA. Vulvar squamous cell carcinoma development after diagnosis of VIN increases with age. *Eur J Cancer* 2009;45:851-6.
101. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D; 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. 2006 consensus

guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol* 2007;197:346-55.
102. Ambrosio MR, Onorati M, Rocca BJ, Santopietro R. Vulvar cancer and HPV infection: analysis of 22 cases. *Pathologica* 2008;100:405-7.
103. Gormley RH, Kovarik CL. Human papillomavirus-related genital disease in the immunocompromised host: Part I. *J Am Acad Dermatol* 2012;66:867.e1-14; quiz 881-2.
104. Bosch FX, Broker TR, Forman D, Moscicki AB, Gillison ML, Doorbar J, Stern PL, Stanley M, Arbyn M, Poljak M, Cuzick J, Castle PE, Schiller JT, Markowitz LE, Fisher WA, Canfell K, Denny LA, Franco EL, Steben M, Kane MA, Schiffman M, Meijer CJ, Sankaranarayanan R, Castellsagué X, Kim JJ, Brotons M, Alemany L, Albero G, Diaz M, de Sanjosé S; authors of ICO Monograph Comprehensive Control of HPV Infections and Related Diseases Vaccine Volume 30, Supplement 5, 2012. Comprehensive control of human papillomavirus infections and related diseases. *Vaccine* 2013;31 Suppl 7:H1-31.
105. Antonsson A, Spurr TP, Chen AC, Francis GD, McMillan NA, Saunders NA, Law M, Bennett IC. High prevalence of human papillomaviruses in fresh frozen breast cancer samples. *J Med Virol* 2011;83:2157-63.
106. Khan NA, Castillo A, Koriyama C, Kijima Y, Umekita Y, Ohi Y, Higashi M, Sagara Y, Yoshinaka H, Tsuji T, Natsugoe S, Douchi T, Eizuru Y, Akiba S. Human papillomavirus detected in female breast carcinomas in Japan. *Br J Cancer* 2008;99:408-14.
107. Kroupis C, Markou A, Vourlidis N, Dionyssiou-Asteriou A, Lianidou ES. Presence of high-risk human papillomavirus sequences in breast cancer tissues and association with histopathological characteristics. *Clin Biochem* 2006;39:727-31.
108. Lawson JS, WH Gunzburg, NJ Whitaker. Viruses and human breast cancer. *Future Microbiol* 2006;1:33-51.
109. Frega A, Lorenzon L, Bononi M, De Cesare A, Ciardi A, Lombardi D, Assorgi C, Gentile M, Moscarini M, Torrisi MR, French D. Evaluation of E6 and E7 mRNA expression in HPV DNA positive breast cancer. *Eur J Gynaecol Oncol* 2012;33:164-7.
110. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61:69-90.
111. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, Liu L, Lynch CF, Wentzensen N, Jordan RC, Altekruse S, Anderson WF, Rosenberg PS, Gillison ML. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol* 2011;29:4294-301.
112. Arbyn M, de Sanjosé S, Saraiya M, Sideri M, Palefsky J, Lacey C, Gillison M, Bruni L, Ronco G, Wentzensen N, Brotherton J, Qiao YL, Denny L, Bornstein J, Abramowitz L, Giuliano A, Tommasino M, Monsonego J. EUROGIN 2011 roadmap on prevention and treatment of HPV-related disease. *Int J Cancer* 2012;131:1969-82.
113. Leemans CR, BJ Braakhuis, RH Brakenhoff. The molecular biology of head and neck cancer. *Nat Rev Cancer* 2010;11:9-22.
114. Psychogios G, Alexiou C, Agaimy A, Brunner K, Koch M, Mantsopoulos K, Tomppert A, Iro H. Epidemiology and survival of HPV-related tonsillar carcinoma. *Cancer Med* 2014;3:652-9.
115. van Seters M, van Beurden M, ten Kate FJ, Beckmann I, Ewing PC, Eijkemans MJ, Kagie MJ, Meijer CJ, Aaronson NK, Kleinjan A, Heijmans-Antonissen C, Zijlstra FJ, Burger MP, Helmerhorst TJ. Treatment of vulvar intraepithelial neoplasia with topical imiquimod. *N Engl J Med* 2008;358:1465-73.
116. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, Forastiere A, Gillison ML. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst* 2008;100:261-9.
117. Schache AG, Liloglou T, Risk JM, Filia A, Jones TM, Sheard J, Woolgar JA, Helliwell TR, Triantafyllou A, Robinson M, Sloan P, Harvey-Woodworth C, Sisson D, Shaw RJ. Evaluation of human papilloma virus diagnostic testing in oropharyngeal squamous cell carcinoma: sensitivity, specificity, and prognostic discrimination. *Clin Cancer Res* 2011;17:6262-71.
118. Brown LM, Check DP, Devesa SS. Oropharyngeal cancer incidence trends: diminishing racial disparities. *Cancer Causes Control* 2011;22:753-63.
119. Morshed K. Association between human papillomavirus infection and laryngeal squamous cell carcinoma. *J Med Virol* 2010;82:1017-23.
120. Rodrigo JP, Hermsen MA, Fresno MF, Brakenhoff RH, García-Velasco F, Snijders PJ, Heideman DA, García-Pedrero JM. Prevalence of human papillomavirus in laryngeal and hypopharyngeal squamous cell carcinomas in northern Spain. *Cancer Epidemiol* 2015;39:37-41.
121. Hernandez BY, Goodman MT, Lynch CF, Cozen W, Unger ER, Steinau M, Thompson T, Saber MS, Altekruse SF, Lyu C, Saraiya M; HPV Typing of Cancer Workgroup. Human papillomavirus prevalence in invasive laryngeal cancer in the United States. *PLoS One* 2014;9:e115931.
122. Syrjänen S, Lodi G, von Bültzingslöwen I, Aliko A, Arduino P, Campisi G, Challacombe S, Ficarra G, Flaitz C, Zhou HM, Maeda H, Miller C, Jontell M. Human papillomaviruses in oral carcinoma and oral potentially malignant disorders: a systematic review. *Oral Dis* 2011;17 Suppl 1:58-72.
123. H Nielsen, B Norrild, P Vedtofte, F Prætorius, J Reibel, P Holmstrup. Human papillomavirus in oral premalignant lesions. *Eur J Cancer B Oral Oncol* 1996;32B:264-70.
124. Szarka K, Tar I, Fehér E, Gáll T, Kis A, Tóth ED, Boda R, Márton I, Gergely L. Progressive increase of human papillomavirus carriage rates in potentially malignant and malignant oral disorders with increasing malignant potential. *Oral Microbiol Immunol* 2009;24:314-8.
125. Welters MJ, Kenter GG, Piersma SJ, Vloon AP, Löwik MJ, Berends-van der Meer DM, Drijfhout JW, Valentijn AR, Wafelman AR, Oostendorp J, Fleuren GJ, Offringa R, Melief CJ, van der Burg SH. Induction of tumor-specific CD4+ and CD8+ T-cell immunity in cervical cancer patients by a human papillomavirus type 16 E6 and E7 long peptides vaccine. *Clin Cancer Res* 2008;14:178-87.
126. Tseng CW, Hung CF, Alvarez RD, Trimble C, Huh WK, Kim D, Chuang CM, Lin CT, Tsai YC, He L, Monie A, Wu TC. Pretreatment with cisplatin enhances E7-specific CD8+ T-Cell-mediated antitumor immunity induced by DNA vaccination. *Clin Cancer Res* 2008;14:3185-92.
127. Tseng CW, Trimble C, Zeng Q, Monie A, Alvarez RD, Huh WK, Hoory T, Wang MC, Hung CF, Wu TC. Low-dose radiation enhances therapeutic HPV DNA vaccination in tumor-bearing hosts. *Cancer Immunol Immunother* 2009;58:737-48.
128. Haas AR, Sun J, Vachani A, Wallace AF, Silverberg M, Kapoor V, Albelda SM. Cycloxygenase-2 inhibition augments the efficacy of a cancer vaccine. *Clin Cancer Res* 2006;12:214-22.
129. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol* 2008;26:612-9.
130. Hammarstedt L, Lindquist D, Dahlstrand H, Romanitan M, Dahlgren LO, Joneberg J, Creson N, Lindholm J, Ye W, Dalianis T, Munck-Wikland E. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. *Int J Cancer* 2006;119:2620-3.
131. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol* 2010;11:781-9.
132. Krüger M, Pabst AM, Walter C, Sagheb K, Günther C, Blatt S, Weise K, Al-Nawas B, Ziebart T. The prevalence of human papilloma virus (HPV) infections in oral squamous cell carcinomas: a retrospective analysis of 88 patients and literature overview. *J Craniomaxillofac Surg* 2014;42:1506-14.
133. Ruzevick J, Olivi A, Westra WH. Metastatic squamous cell carcinoma to the brain: an unrecognized pattern of distant spread in patients with

HPV-related head and neck cancer. *J Neurooncol* 2013;112:449-54.
134. Wood ME, Kelly K, Mullineaux LG, Bunn PA Jr. The inherited nature of lung cancer: a pilot study. *Lung Cancer* 2000;30:135-44.
135. Matakidou A, Eisen T, Houlston RS. TP53 polymorphisms and lung cancer risk: a systematic review and meta-analysis. *Mutagenesis* 2003;18:377-85.
136. Syrjänen K. Papillomavirus infections and cancer Papillomaviruses and Human Disease, ed. K Syrjänen, L Gissmann, LG Koss. 1987, Heidelberg: Springer-Verlag.
137. Syrjänen KJ. Epithelial lesions suggestive of a condylomatous origin found closely associated with invasive bronchial squamous cell carcinomas. *Respiration* 1980;40:150-60.
138. Trillo A, Guha A. Solitary condylomatous papillomas of the bronchus. *Arch Pathol Lab Med* 1988;112:731-3.
139. Stremlau A, Gissmann L, Ikenberg H, Stark M, Bannasch P, zur Hausen H. Human papillomavirus type 16 related DNA in an anaplastic carcinoma of the lung. *Cancer* 1985;55:1737-40.
140. Byrne JC, Tsao MS, Fraser RS, Howley PM. Human papillomavirus-11 DNA in a patient with chronic laryngotracheobronchial papillomatosis and metastatic squamous-cell carcinoma of the lung. *N Engl J Med* 1987;317:873-8.
141. Syrjanen KJ. HPV infections and lung cancer. *J Clin Pathol* 2002;55:885-91.
142. Gorgoulis VG, Zacharatos P, Kotsinas A, Kyroudi A, Rassidakis AN, Ikonomopoulos JA, Barbatis C, Herrington CS, Kittas C. Human papillomavirus (HPV) is possibly involved in laryngeal but not in lung carcinogenesis. *Human Pathol* 1999;30:274-83.
143. Rezazadeh A, Laber DA, Ghim SJ, Jenson AB, Kloecker G. The role of human papilloma virus in lung cancer: a review of the evidence. *Am J Med Sci* 2009;338:64-7.
144. Storey R, Joh J, Kwon A, Jenson AB, Ghim SJ, Kloecker GH. Detection of Immunoglobulin G against E7 of Human Papillomavirus in Non-Small-Cell Lung Cancer. *J Oncol* 2013;2013:240164.
145. Isa SI, Kurahara Y, Yamamoto S, Tamiya A, Omachi N, Asami K, Okishio K, Utsumi T, Ito N, Yoon HE, Matsumura A, Atagi S, Kawaguchi T. Molecular analysis of human papillomavirus in never-smokers with non-small cell lung cancer. *Oncol Lett* 2015;9:927-9.
146. Ragin C, Obikoya-Malomo M, Kim S, Chen Z, Flores-Obando R, Gibbs D, Koriyama C, Aguayo F, Koshiol J, Caporaso NE, Carpagnano GE, Ciotti M, Dosaka-Akita H, Fukayama M, Goto A, Spandidos DA, Gorgoulis V, Heideman DA, van Boerdonk RA, Hiroshima K, Iwakawa R, Kastrinakis NG, Kinoshita I, Akiba S, Landi MT, Eugene Liu H, Wang JL, Mehra R, Khuri FR, Lim WT, Owonikoko TK, Ramalingam S, Sarchianaki E, Syrjanen K, Tsao MS, Sykes J, Hee SW, Yokota J, Zaravinos A, Taioli E. HPV-associated lung cancers: an international pooled analysis. *Carcinogenesis* 2014;35:1267-75.
147. Zhai K, Ding J, Shi HZ. HPV and lung cancer risk: a meta-analysis. *J Clin Virol* 2015;63C:84-90.
148. Hsueh PR. Human papillomavirus, genital warts, and vaccines. *J Microbiol Immunol Infect* 2009;42:101-6.
149. Derkay CS. Task force on recurrent respiratory papillomas. A preliminary report. *Arch Otolaryngol Head Neck Surg* 1995;121:1386-91.
150. Omland T, Lie KA, Akre H, Sandlie LE, Jebsen P, Sandvik L, Nymoen DA, Bzhalava D, Dillner J, Brøndbo K. Recurrent respiratory papillomatosis: HPV genotypes and risk of high-grade laryngeal neoplasia. *PLoS One* 2014;9:e99114.
151. Major T, Szarka K, Sziklai I, Gergely L, Czeglédy J. The characteristics of human papillomavirus DNA in head and neck cancers and papillomas. *J Clin Pathol* 2005;58:51-5.
152. Bharti AH, Chotaliya K, Marfatia YS. An update on oral human papillomavirus infection. *Indian J Sex Transm Dis* 2013;34:77-82.
153. Gallagher TQ, Derkay CS. Pharmacotherapy of recurrent respiratory papillomatosis: an expert opinion. *Expert Opin Pharmacother* 2009;10:645-55.
154. Kitamura T, Yogo Y, Ueki T, Murakami S, Aso Y. Presence of human papillomavirus type 16 genome in bladder carcinoma *in situ* of a patient with mild immunodeficiency. *Cancer Res* 1988;48:7207-11.
155. Gutiérrez J, Jiménez A, de Dios Luna J, Soto MJ, Sorlózano A. Meta-analysis of studies analyzing the relationship between bladder cancer and infection by human papillomavirus. *J Urol* 2006;176:2474-81.
156. Griffiths TR, Mellon JK. Human papillomavirus and urological tumours: II. Role in bladder, prostate, renal and testicular cancer. *BJU Int* 2000;85:211-7.
157. Youshya S, Purdie K, Breuer J, Proby C, Sheaf MT, Oliver RT, Baithun S. Does human papillomavirus play a role in the development of bladder transitional cell carcinoma? A comparison of PCR and immunohistochemical analysis. *J Clin Pathol* 2005;58:207-10.
158. Lopez-Beltran A, Escudero AL, Vicioso L, Muñoz E, Carrasco JC. Human papillomavirus DNA as a factor determining the survival of bladder cancer patients. *Br J Cancer* 1996;73:124-7.
159. Sano T, Sakurai S, Fukuda T, Nakajima T. Unsuccessful effort to detect human papillomavirus DNA in urinary bladder cancers by the polymerase chain reaction and *in situ* hybridization. *Pathol Int* 1995;45:506-12.
160. Li N, Yang L, Zhang Y, Zhao P, Zheng T, Dai M. Human papillomavirus infection and bladder cancer risk: a meta-analysis. *J Infect Dis* 2011;204:217-23.
161. Jimenez-Pacheco A, Exposito-Ruiz M, Arrabal-Polo MA, Lopez-Luque AJ. Meta-analysis of studies analyzing the role of human papillomavirus in the development of bladder carcinoma. *Korean J Urol* 2012;53:240-7.
162. Tenti P, Zappatore R, Romagnoli S, Civardi E, Giunta P, Scelsi R, Stella G, Carnevali L. p53 overexpression and human papillomavirus infection in transitional cell carcinoma of the urinary bladder: correlation with histological parameters. *J Pathol* 1996;178:65-70.
163. Shigehara K, Sasagawa T, Kawaguchi S, Nakashima T, Shimamura M, Maeda Y, Konaka H, Mizokami A, Koh E, Namiki M. Etiologic role of human papillomavirus infection in bladder carcinoma. *Cancer* 2011;117:2067-76.
164. Moonen PM, Bakkers JM, Kiemeney LA, Schalken JA, Melchers WJ, Witjes JA. Human papilloma virus DNA and p53 mutation analysis on bladder washes in relation to clinical outcome of bladder cancer. *Eur Urol* 2007;52:464-8.
165. Kamel D, Pääkkö P, Pöllänen R, Vähäkangas K, Lehto VP, Soini Y. Human papillomavirus DNA and abnormal p53 expression in carcinoma of the urinary bladder. *APMIS* 1995;103:331-8.
166. Steinestel J, Cronauer MV, Müller J, Al Ghazal A, Skowronek P, Arndt A, Kraft K, Schrader M, Schrader AJ, Steinestel K. Overexpression of p16(INK4a) in urothelial carcinoma *in situ* is a marker for MAPK-mediated epithelial-mesenchymal transition but is not related to human papillomavirus infection. *PLoS One* 2013;8:e65189.
167. Kim SH, Joung JY, Chung J, Park WS, Lee KH, Seo HK. Detection of human papillomavirus infection and p16 immunohistochemistry expression in bladder cancer with squamous differentiation. *PLoS One* 2014;9:e93525.
168. Shigehara K, Sasagawa T, Doorbar J, Kawaguchi S, Kobori Y, Nakashima T, Shimamura M, Maeda Y, Miyagi T, Kitagawa Y, Kadono Y, Konaka H, Mizokami A, Koh E, Namiki M. Etiological role of human papillomavirus infection for inverted papilloma of the bladder. *J Med Virol* 2011;83:277-85.
169. Shaker OG, Hammam OA, Wishahi MM. Is there a correlation between HPV and urinary bladder carcinoma? *Biomed Pharmacother* 2013;67:183-91.
170. Alexander RE, Davidson DD, Lopez-Beltran A, Montironi R, MacLennan GT, Compérat E, Idrees MT, Emerson RE, Cheng L. Human papillomavirus is not an etiologic agent of urothelial inverted papillomas. *Am J Surg Pathol* 2013;37:1223-8.
171. Alexander RE, Davidson DD, Lopez-Beltran A, Montironi R, MacLennan GT, Compérat E, Idrees MT, Emerson RE, Cheng L. The

expression patterns of p53 and p16 and an analysis of a possible role of HPV in primary adenocarcinoma of the urinary bladder. *PLoS One* 2014;9:e95724.
172. Badawi H, Ahmed H, Ismail A, Diab M, Moubarak M, Badawy A, Saber M. Role of human papillomavirus types 16, 18, and 52 in recurrent cystitis and urinary bladder cancer among Egyptian patients. *Medscape J Med* 2008;10:232.
173. Nakashima K, Shigehara K, Kawaguchi S, Wakatsuki A, Kobori Y, Nakashima K, Ishii Y, Shimamura M, Sasagawa T, Kitagawa Y, Mizokami A, Namiki M. Prevalence of human papillomavirus infection in the oropharynx and urine among sexually active men: a comparative study of infection by papillomavirus and other organisms, including Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma spp., and Ureaplasma spp. *BMC Infect Dis* 2014;14:43.
174. Barghi MR, Rahjoo T, Borghei M, Hosseini-Moghaddam SM, Amani D, Farrokhi B. Association between the evidence of human papilloma virus infection in bladder transitional cell carcinoma in men and cervical dysplasia in their spouses. *Arch Iran Med* 2012;15:572-4.
175. Berrada N, Al-Bouzidi A, Ameur A, Abbar M, El-Mzibri M, Ameziane-El-Hassani R, Benbacer L, Khyatti M, Qmichou Z, Amzazi S, Attaleb M. Human papillomavirus detection in Moroccan patients with bladder cancer. *J Infect Dev Ctries* 2013;7:586-92.
176. Castellsagué X, Bosch FX, Muñoz N, Meijer CJ, Shah KV, de Sanjose S, Eluf-Neto J, Ngelangel CA, Chichareon S, Smith JS, Herrero R, Moreno V, Franceschi S; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *N Engl J Med* 2002;346:1105-12.
177. Bezerra SM, Chaux A, Ball MW, Faraj SF, Munari E, Gonzalez-Roibon N, Sharma R, Bivalacqua TJ, Burnett AL, Netto GJ. Human papillomavirus infection and immunohistochemical p16 expression as predictors of outcome in penile squamous cell carcinomas. *Hum Pathol* 2015;46:532-40.
178. Lohneis P, Boral S, Kaufmann AM, Lehmann A, Schewe C, Dietel M, Anagnostopoulos I, Jöhrens K. Human papilloma virus status of penile squamous cell carcinoma is associated with differences in tumour-infiltrating T lymphocytes. *Virchows Arch* 2015;466:323-31.
179. Rubin MA, Kleter B, Zhou M, Ayala G, Cubilla AL, Quint WG, Pirog EC. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. *Am J Pathol* 2001;159:1211-8.
180. Giuliano AR, Nielson CM, Flores R, Dunne EF, Abrahamsen M, Papenfuss MR, Markowitz LE, Smith D, Harris RB. The optimal anatomic sites for sampling heterosexual men for human papillomavirus (HPV) detection: the HPV detection in men study. *J Infect Dis* 2007;196:1146-52.
181. Schwartz RA, Janniger CK. Bowenoid papulosis. *J Am Acad Dermatol* 1991;24:261-4.
182. Chao MW, Gibbs P. Squamous cell carcinoma arising in a giant condyloma acuminatum (Buschke-Lowenstein tumour). *Asian J Surg* 2005;28:238-40.
183. Handisurya A, Rieger A, Bago-Horvath Z, Schellenbacher C, Bankier A, Salat A, Stingl G, Kirnbauer R. Rapid progression of an anal Buschke-Lowenstein tumour into a metastasising squamous cell carcinoma in an HIV-infected patient. *Sex Transm Infect* 2009;85:261-3.
184. Daling JR, Sherman KJ. Relationship between human papillomavirus infection and tumours of anogenital sites other than the cervix. *IARC Sci Publ* 1992;(119):223-41.
185. Forslund O, Iftner T, Andersson K, Lindelof B, Hradil E, Nordin P, Stenquist B, Kirnbauer R, Dillner J, de Villiers EM; Viraskin Study Group. Cutaneous human papillomaviruses found in sun-exposed skin: Beta-papillomavirus species 2 predominates in squamous cell carcinoma. *J Infect Dis* 2007;196:876-83.
186. Tschandl P, Rosendahl C, Kittler H. Cutaneous human papillomavirus infection: manifestations and diagnosis. *Curr Probl Dermatol* 2014;45:92-7.
187. Cobb MW. Human papillomavirus infection. *J Am Acad Dermatol* 1990;22:547-66.
188. Wallace NA, Robinson K, Howie HL, Galloway DA. HPV 5 and 8 E6 abrogate ATR activity resulting in increased persistence of UVB induced DNA damage. *PLoS Pathog* 2012;8:e1002807.
189. Iftner T, Elbel M, Schopp B, Hiller T, Loizou JI, Caldecott KW, Stubenrauch F. Interference of papillomavirus E6 protein with single-strand break repair by interaction with XRCC1. *EMBO J* 2002;21:4741-8.
190. Iftner A, Klug SJ, Garbe C, Blum A, Stancu A, Wilczynski SP, Iftner T. The prevalence of human papillomavirus genotypes in nonmelanoma skin cancers of nonimmunosuppressed individuals identifies high-risk genital types as possible risk factors. *Cancer Res* 2003;63:7515-9.
191. Andersson K, Waterboer T, Kirnbauer R, Slupetzky K, Iftner T, de Villiers EM, Forslund O, Pawlita M, Dillner J. Seroreactivity to cutaneous human papillomaviruses among patients with nonmelanoma skin cancer or benign skin lesions. *Cancer Epidemiol Biomarkers Prev* 2008;17:189-95.
192. Scarbrough Lefebvre CD, Van Kriekinge G, Gonçalves MA, de Sanjose S. Appraisal of the burden of genital warts from a healthcare and individual patient perspective. *Public Health* 2011;125:464-75.
193. Grce M, Husnjak K, Skerlev M, Lipozencić J, Pavelić K. Detection and typing of human papillomaviruses by means of polymerase chain reaction and fragment length polymorphism in male genital lesions. *Anticancer Res* 2000;20:2097-102.
194. Bhatia N, Lynde C, Vender R, Bourcier M. Understanding genital warts: epidemiology, pathogenesis, and burden of disease of human papillomavirus. *J Cutan Med Surg* 2013;17 Suppl 2:S47-54.
195. Ling MR. Therapy of genital human papillomavirus infections. Part I: Indications for and justification of therapy. *Int J Dermatol* 1992;31:682-6.
196. Lacey CJ, Lowndes CM, Shah KV. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. *Vaccine* 2006;24 Suppl 3:S3/35-41.
197. Ljubojevic S, M Skerlev. HPV-associated diseases. *Clin Dermatol* 2014;32:227-34.
198. Fathi R, Tsoukas MM. Genital warts and other HPV infections: established and novel therapies. *Clin Dermatol* 2014;32:299-306.
199. Gnanamony M, Peedicayil A, Abraham P. An overview of human papillomaviruses and current vaccine strategies. *Indian J Med Microbiol* 2007;25:10-7.
200. Remy-Ziller C, Germain C, Spindler A, Hoffmann C, Silvestre N, Rooke R, Bonnefoy JY, Préville X. Immunological characterization of a modified vaccinia virus Ankara vector expressing the human papillomavirus 16 E1 protein. *Clin Vaccine Immunol* 2014;21:147-55.