The role of human papillomaviruses in cancer progression

Pinar Tulay, Nedime Serakinci

Department of Medical Genetics, Faculty of Medicine, Near East University, 999058 Nicosia, Cyprus.

Correspondence to: Dr. Nedime Serakinci, Department of Medical Genetics, Faculty of Medicine, Near East University, 999058 Nicosia, Cyprus.
E-mail: nedimeserakinci@gmail.com

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 infect 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 HPV's 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.[8,16-17]

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

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: service@oaepublish.com

How to cite this article: Tulay P, Serakinci N. The role of human papillomaviruses in cancer progression. J Cancer Metastas Treat 2016;2:201-13.

Received: 31-08-2015; Accepted: 17-03-2016.
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 I genes and changing the antigen production.[39] High risk HPV types continue to
express the E6 and E7 oncoproteins that leads to genomic

<table>
<thead>
<tr>
<th>HPV proteins</th>
<th>Function</th>
</tr>
</thead>
</table>
| E1 | Viral DNA replication
| | Repressive agent in transcription
| | Inhibition of DNA replication[24,199]
| | DNA replication
| | Functions with E1, especially in HPV6, 11 and 16[26]
| | Responsible for coding proteins regulating viral DNA transcription[199] |
| E2 | Cell transformation, initiating and inhibiting apoptosis, transcriptional regulation, and in the modulation of the immortalizing and transformation potential of HPV[24]
| | When inactive, it promotes E6 and E7 expression and influence tumor lesion development
| | When active, it inhibits E6 and E7 transcription leading to increased p53 expression and apoptosis of infected cells[199] |
| E4 | 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]
| | Maintains the viral replication
| E6 | 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]
| | Maintains the viral replication
| E7 | 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
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,[59] 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. HPV interferes 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.\[81,82\] 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.\[9\] 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 vivo.\[72\] 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. 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 HPVs 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. Therefore, these neoplasias causes cancer. HPV16 is associated with vulvar intraepithelial neoplasia, however only half of the cases with CIN2 and CIN3 have high risk HPV infections and the deregulation of E6 and E7 expression. In clinical vaccine trials it was shown that young women can have CIN2+ soon after infection with high risk HPV infections such as 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. It is also possible that the initial deregulation leads to decreased expression of E7 and E6 and that the virus may not contribute to cancer progression. In CIN2/ CIN3+, the viral deregulation assists the viral episome into the host cell chromosome.

In this scheme, flat warts can be regarded as CIN1 lesions, however the proliferation level of the cell is lower in the basal and parabasal layers. 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 with high risk HPV infections such as 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. It is also possible that the initial deregulation leads to decreased expression of E7 and E6 and that the virus may not contribute to cancer progression. In CIN2/ CIN3+, the viral deregulation assists the viral episome into the host cell chromosome.

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. 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, electrofulguration and cryotherapy.

The other lower genital cancers include vulvar and vaginal cancers. Majority of the vulvar and vaginal cancers are squamous cell carcinomas. 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%). 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. 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. 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. The prevalence of HPV DNA in head and neck cancers depends on the cancer site, geography and ethnicity. 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. 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. Overall the prevalence of these cancers are higher in men compared to women. 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. HPV positive oropharyngeal cancers are mainly associated with oral sex and rare p53 mutation. Interestingly HPV infection was shown to improve the prognosis of OPC with better survival is reported in HPV positive OPCs and therefore these patients may have a chance to benefit from a less intense treatment strategy. Chemotherapy using paclitaxel, cisplatin on centuximab; followed by concurrent radiation has been used in treatment of OPC patients. With the increasing number of HPV associated OPC patients, the use of antiviral and immunotherapeutic strategies show an improved outcome. 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. HPV is also associated with potential malignant disorders, such as erythroplakia, oral leukoplakia and oral lichen planus. Erythroplakia has the highest risk of malignant transformation. Half of the cases with erythroplakias alone is associated with HPV infection 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[126,130] 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 of 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.[14,152] 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.[166,167] The controversy continues with the inverted papilloma of the urinary tract and urothelial carcinomas. In some reports HPV is associated with inverted papilloma of the urinary bladder[168] and urothelial carcinomas,[169,170] 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[152,177-179] 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.[178] Mainly HPV16 (69%) and HPV18 (13%) play a role in the development of penile squamous cell carcinomas.[179] 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 perineally.[180] HPV16 and HPV18 are also associated with Erythroplasia 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 HPV's, HPV6 and HPV 11.[182,183] Additionally, in both males and females, approximately 85-95% of the anal cancers are HPV DNA positive.[192,196] Of these, HPV16 (75%) and HPV18 (3%) are the causes for almost all the cases of anal cancers.[182,184]

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.[186,187] Genetic susceptibility to HPV is demonstrated with epidermodysplasia verruciformis; however, HPV infection alone is not enough to develop cancerogenesis in epidermodysplasia verruciformis.[191] Mainly, these tumors are induced by sun explosion and ultraviolet radiation. Cells with HPV5 and HPV8 E6 proteins disturb DNA double strand break repair[191] and reduces the efficiency of base excision repair pathway[190] 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.[196] 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 has 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 HPV 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 penis 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 HPV's 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.

Financial support and sponsorship
Near East University, Center of Excellence research fund (www.neu.edu.tr).

Conflicts of interest
There are no conflicts of interest.
REFERENCES


38. Kanodia S, Fahey LM, Kast WM. Mechanisms used by human


