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REVIEW ARTICLE

Human papillomavirus-associated diseases and cancers*

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Abstract

Human papillomaviruses (HPVs) have been detected in cervical cancer cells and skin papilloma cells, which have a variety of types, including low-risk and high-risk types. HPV genome replication requires the host cell's DNA synthesis machinery, and HPVs encode proteins that maintain differentiated epithelial cells in a replication-competent state. HPV types are tissue-specific and generally produce different types of lesions, either benign or malignant. This review examines different HPV types and their associated diseases and presents therapeutic options for the treatment of HPV-positive diseases.

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Human papillomaviruses (HPVs) are classified according to the International Committee on Taxonomy of Viruses (ICTV) into the *Papillomaviridae* family and group I viruses (Baltimore), which are small, non-enveloped double-stranded DNA viruses with sizes close to 8000 nucleotides. HPV infection is associated with many benign and malignant tumors, which may activate specific anti-apoptotic, proliferative, and malignant cellular responses that also may be intensified in combination with the effects of other risk factors [1].

HPVs have been classified based on their DNA sequence similarities with some biological and medical properties [2–5]. HPV subtypes are defined based on homology differences of 2%–10%, or less than 2% [6]. More than 120 different HPV types have been identified and characterized. All human papillomavirus genomes include 3 general regions: an upstream regulatory region (URR), an early region, which contains open reading frames (ORFs; E1, E2, E4, E5, E6, and E7), and a late region, which codes for the L1 and L2 capsid proteins that form the structure of the virion and facilitate viral DNA packaging and maturation [7]. How does HPV cause benign tumors and cancer? It was reported that non-oncogenic (low-risk) HPV infections may be more transient than oncogenic (high-risk) HPV infections. The virus's DNA integrates into human DNA in the nuclei of healthy cells, and uses the cells' machinery to produce two harmful proteins, E6 and E7. These bind to, and shut down, two important tumor-suppressor proteins, p53 and pRb. Active pRb prevents excessive cell growth; active p53 arrests the cell-division cycle when DNA is damaged, and then either activates DNA repair or initiates cell death. Such carcinogenic mechanisms for the pathogenesis of HPV have been studied in cervical cancer since the late 1980s, and it has been confirmed [8], that E6 and E7 genes from HPV16 and HPV18 are the most frequent types detected in cervical cancer [9]. Subsequently, new insights of HPV carcinogenesis have been revealed, including integration of high-risk HPV [10], and the effect of HPV infection on HPV-E6,E7-induced genomic instability, host cell cycle, apoptosis, and telomerase activity [11–14]. Furthermore, HPV infection has been reported to be a synergistic factor associated with malignant carcinomas, since numerous individuals are infected with HPV, although only a small percentage progress to being classified as malignant over a period of years, often decades [15–16].

The mechanism by which HPV promotes tumorigenesis is similar in cervical, oropharyngeal, and throat cancers. However, identifying the role of HPV in vulvar, esophageal, and other cancers has been inconclusive.

Based on their oncogenicity, HPVs are classified into high-risk and low-risk types. Low-risk HPV subtypes

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cause benign neoplasms, and high-risk types have the ability to induce squamous cell immortalization *in vitro* and can be detected in a subset of malignant neoplasms.

Low-risk HPV subtypes associated with benign diseases

Low-risk HPV subtypes (HPV-1, 2, 3, 4, 6, 7, 10, 11, 12, 13 etc.) have been correlated with urogenital epithelium and benign oral warts in adults as well as children, and they are rarely found in malignant tumors. HPV types 6 and 11, being the most common types detected in benign lesions, are commonly identified in specimens from the oral cavity, pharynx, larynx, and conjunctiva [17–18]. These subtypes are common among sexually active populations. HPV-6 causes cutaneous genital warts [18–19]; HPV-13 and -32 cause focal epithelial hyperplasia of the oral cavity, and neither has been found in genital warts or laryngeal papillomas [4, 20]. HPV-7 was identified in butchers' warts [21–22]. People who professionally handle raw meat and fish may develop warty lesions on their hands that are similar in appearance to common warts (verruca vulgaris) [23]. HPV-6 is the only virus type that has been identified in epidermoid cysts. It most frequently occurs on the weight-bearing plantar surfaces, especially the balls and heels of the feet [24–25]. Verruca vulgaris, including oral verruca vulgaris, verruca plantaris, mosaic warts, and periungual warts, are strongly associated with HPV types 1, 2, and 4 [23, 26–27]. They can affect any skin area, but most commonly affect the hands and feet (plantar warts), and around the nail bed (periungual warts).

High-risk HPV subtypes associated with malignant cancer

At present, approximately 15 HPV subtypes have been classified as "high-risk" types including 16, 18, 30, 31, 35, and others. High-risk HPV is associated with a variety of cancers, including anal and genital tract, head and neck, cervical, vulvar, oropharyngeal, and esophageal cancers [28–31]. The viral oncogenes E6 and E7 play an important role in HPV-related carcinogenesis, abrogating p53 and pRb tumor suppressor functions, respectively [31–32].

High-risk HPV and cervical cancer

HPV is most strongly associated with cervical cancer, as high-risk HPV types 16 and 18 can be detected in more than 90% of cervical cancer lesions. Cervical cancer is considered to be generated by injuries under long-term persistent infection, and expression of viral oncogenes E6 and E7 is a key event [33]. In cervical intraepithelial neoplasia type I (CIN I) and CIN II, the expression levels of E6 and E7 are relatively low, indicating the relative dispersion of viral DNA replication, whereas CIN III and invasive cancer often have a high level of expression of E6 and E7, indicating that the viral DNA has integrated into host cellular genes [34]. Integration of high-risk HPV genes is a critical event in the progression of precancerous cervical injuries to invasive cancer formation [35]. However, Deng *et al* found that low initial HPV viral load may be a poor prognostic factor for cervical cancer patients who have undergone radical hysterectomy [36].

High-risk HPV and vulvar cancer

It was reported that vulvar carcinoma is caused by condyloma or squamous dysplasia [37]. HPV DNA can be detected in most cases of vulvar intraepithelial neoplasia, but it is detected in fewer cases of vulvar cancer [37–38]. The association between HPV infection and vulvar cancer is still unclear. Additionally, the role of HPV in vulvar cancer development, and whether there exists a correlation between HPV and other factors of vulvar carcinoma, remains to be determined.

High-risk HPV and oropharyngeal cancer

Oropharyngeal cancers include two types: HPV-positive, which are related to HPV infection, and HPV-negative, which are usually linked to alcohol or tobacco use. HPV, in particular the 16 subtypes, is a causative agent in about 25% of oropharyngeal cancers, particularly those affecting the lingual and palatine tonsils [37, 39]. However, patients with HPV-positive oropharyngeal cancers have a better prognosis and response to therapy compared to HPV-negative patients. Furthermore, metastases are more likely to occur significantly later in HPV-positive oropharyngeal squamous cell carcinomas compared to HPV-negative tumors [40].

High-risk HPV and esophageal cancer

There have been reports of up to a 500-fold variation in the incidence of esophageal squamous cell carcinoma (ESCC) between low-risk and high-risk regions across the world, with China being one of the highest-risk regions [41]. Even within China, however, there are significant differences in the incidence of ESCC, which are thought to be due to different risk factors such as diet and environmental risk factors; these variations have made it difficult to study the etiology of ESCC [42].

HPV, especially high-risk HPV types 16 and 18, has been suggested as a distinct possible cause of esophageal cancer. It has a specific tropism for squamous epithelium cells where it can cause hyperproliferative lesions, and subsequently carcinogenesis [43]. HPV infection in esophageal cancer was found by Syrjänen in 1982 based on histological observations and detection of HPV DNA in ESCC tissue ranging from 15% to 80% globally [44]. Syrjänen first suggested that HPV may be a risk factor

Table 1 The prevalence of human papillomavirus (HPV) among esophageal squamous cell carcinoma cases in countries

Reference	Region	No. of cases	No. of HPV positive in cases (%)
Ludmir EB, *et al*, 2014 [46]	USA	19	1 (5%)
Yu Q, *et al*, 2014 [47]	China (Shanghai)	307	167 (54%)
Jalilvand S, *et al*, 2014 [48]	Iran	695	161 (23%)
Liu HY, *et al*, 2014 [49]	China (Linzhou in Henan)	78	54 (69%)
Hu J, *et al*, 2012 [50]	China (Xinjiang)	200	82 (41%)
Zhao XY, *et al*, 2009 [51]	China (Hebei)	42	19 (45%)
Shuyama K, *et al*, 2007 [52]	China (Shandong)	59	15 (25%)
Cao B, *et al*, 2005 [53]	China (Anyang in Henan)	265	182 (69%)
Matsha T, *et al*, 2002 [54]	South Africa (Transkei)	50	23 (46%)
Szentirmay Z, *et al*, 2002 [55]	Hungary	82	32 (39%)
Lavergne D, *et al*, 1999 [56]	Germany	11	7 (64%)
Fidalgo PO, *et al*, 1995 [57]	Portugal	8	5 (63%)
Furihata M, *et al*, 1993 [58]	India (Kochi)	71	24 (34%)
Benamouzig R, *et al*, 1992 [59]	France	12	5 (42%)
Toh Y, *et al*, 1992 [60]	Japan	45	3 (7%)

Reference	HPV detection method	HPV subtypes	Types of specimen
Ludmir EB, *et al,* 2014 [46]	ISH	HPV-16, 18	PE
Yu Q, *et al*, 2014 [47]	ELISA	HPV-16	PB
Jalilvand S, *et al*, 2014 [48]	PCR, Real-time PCR	HPV-16, 18	PE, etc.
Liu HY, *et al*, 2014 [49]	PCR	HPV-16, 18, 31	FF/PE
Hu J, *et al*, 2012 [50]	PCR	HPV-16	PE
Zhao XY, *et al*, 2009 [51]	PCR	HPV-16, 18	PE
Shuyama K, *et al*, 2007 [52]	PCR	HPV-16, 18	PE
Cao B, *et al*, 2005 [53]	PCR	HPV-16, 18	PB/PE
Matsha T, *et al*, 2002 [54]	nested PCR	HPV-11, 16, 39, 52	PE
Szentirmay Z, *et al*, 2002 [55]	PCR	HPV-16, 35, 68, 73, etc.	FF/PE
Lavergne D, *et al*, 1999 [56]	PCR	HPV-6, 20, etc.	PE
Fidalgo PO, *et al*, 1995 [57]	PCR	HPV-16, 18	PE
Furihata M, *et al*, 1993 [58]	ISH	HPV-16, 18	PE
Benamouzig R, *et al*, 1992 [59]	ISH, dot blot	HPV-6, 11, 16, 18, 31, 33	PE
Toh Y, *et al*, 1992 [60]	PCR	HPV-16, 18	PE

Abbreviations: PCR, polymerase chain reaction; ISH, *in situ* hybridization; ELISA, enzyme-linked immunosorbent assay; PB, peripheral blood; PE, paraffin-embedded; FF, fresh-frozen

for esophageal squamous cell carcinoma, and in addition confirmed risk factors for ESCC including smoking and alcohol [41, 44]. Subsequently, the correlation between HPV infection and ESCC become a hot research topic for tumor virus etiology. However, the role of HPV in the development of esophageal cancer remains controversial. Koshiol *et al* demonstrated that HPV is not involved in ESCC carcinogenesis in China [45], but the prevalence of HPV infection in esophageal lesions or carcinomas varies largely in different studies and regions [46–60] (Table 1).

Three meta-analyses clearly demonstrated a close relationship between HPV and ESCC [61–63]. Regional and demographic variation may contribute to the differential prevalence in esophageal cancer. Syrjänen *et al* summarized the HPV prevalence of any type in esophageal cancer and reported that the mean prevalence of HPV was 29.0%, ranging from 0% to 78% [64]. Yu *et al* found that HPV-16 serum positivity was increased in ESCC patients who were smokers compared to non-smokers [47, 65]. Researchers in Xingjiang, China, confirmed that HPV infection, especially HPV-16 infection, is closely related to the incidence of Kazakh ESCC in Northwestern Xingjiang in China. HPV-16 virus infection rate in the patients of ethnic Kazakh ESCC was significantly higher than that of the normal ethnic Kazakh population and HPV-16 *E6* gene had some variation [50, 66–67]. Disease status and detection methods have been cited as potential causes of inconsistency. One study reported an infection rate of 100%, as determined by detection of the HPV-16 *E6* and *E7* genes in early cancer cases in a high-risk area using polymerase chain reaction (PCR) and *in situ* hybridization (ISH) [68]. Furthermore, it was reported that the positive rate of HPV detection was associated with the kept time of the paraffin-embedded specimens; more recent specimens were associated with a higher rate of positive HPV detection compared to specimens that had been archived for

longer [69].

The prognostic value of HPV status has also remained controversial in patients with ESCC. Furihata *et al* reported that HPV-positive ESCC patients had poorer prognosis than HPV-negative ESCC patients with overexpression of p53 [58]. Hippeläinen *et al* reported that HPV has no prognostic value in ESCC [70]; other studies have suggested that tumor HPV status is an independent prognostic factor [31]. Still other studies have suggested that patients with HPV-positive ESCC have a better prognosis than HPV-negative patients [71–72]. With the gradual deepening of the study of esophageal cancer etiology, HPV infection has gained increased attention. A better understanding of the pathogenesis and biological characteristics of esophageal cancer and the role of HPV in this disease, will lead to breakthroughs in the prevention of esophageal cancer.

The prevention of HPV infection

Since the first detection of HPV in the 1930s, eradicating this disease has proven to be complex. Vaccines have recently been developed and approved for use against HPV. One of these vaccines is designed against low-risk HPV-6 and -11, which together cause 90% of cutaneous genital warts. The vaccine's efficacy in preventing future persistent genital warts in HPV-negative women is very high, and a decrease in genital warts in young vaccinated women largely contributes to the reduced exposure to these infections in young men [73–74]. For cancers caused by high-risk HPV, in addition to conventional surgery, radiation therapy, and chemotherapy, monitoring HPV and administering intervention treatment are necessary and will reduce tumor recurrence and improve prognosis. One of the recombinant HPV vaccines is a bivalent vaccine, which designed to prevent infection from high-risk HPV-16 and -18 and another vaccine is a quadrivalent vaccine which targets low-risk HPV-6, -11 and high-risk HPV-16, -18. The primary expectation of vaccine efficacy, which is a reduction in precursor lesions by approximately 50% and reduction in cervical cancer by approximately 70%, has been achieved [75].

In combination with surgery, chemotherapy, and radiationtherapy for HPV infection associated carcinoma, immunotherapy can significantly improve survival of patients. Despite cancer having different etiologic factors, we can prevent HPV-related cancer through widespread HPV vaccination. The victory of prophylactic immunization for cervical carcinoma has attracted a lot of interest for preventable HPV-related cancers including vulvar cancer, ESCC, oropharyngeal cancer, and others. HPV vaccination may provide dual disease prevention for both HPV-related oropharyngeal cancer and cervical cancer [76]. However, vaccine efficacy against oropharyngeal HPV infection is still unknown, so the vaccination is not currently recommended for the primary prevention of oropharyngeal cancer [77]. The link between HPV infection and vulvar cancer is unclear, and the association between HPV and ESCC is controversial [44]. Therefore an established association between type-specific HPV infection and vulvar cancer and ESCC are essential for HPV screening and vaccination policies. In addition, since most of the experiments for developing vaccines for HPV infection are performed *in vitro* or in animals *in vivo*, there is a lack of clinical research data, contributing to many problems such as immunization safety and the role of vaccines. However, immunotherapy will play a very important role in the prevention of tumor recurrence and metastasis. According to different tumor characteristics, combined application of a variety of tumor immunotherapy approaches will achieve better results.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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