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Human Papillomavirus Related Head and Neck Cancer: Current Study and Perspective

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Published Date: April 24, 2017

INTRODUCTION

Human Papillomavirus **(HPV)** is reported to be the most sexually transmitted infection worldwide. Approximately 79 million people are currently infected with HPV [1]. It is estimated that 14 million are newly infected each year approximately in the United States [2]. Although 90% of HPV infections are cleared by human immune system naturally, HPV infection is a high risk factor, or viral cause of genital warts and certain cancers [3]. There are more than 150 types of HPV, among which 11 types are classified as high-risk for their potential to induce malignancy [4]. Types 16,18,31, and 33 are the most prevalent of these. Almost all of the cervical cancers are detected positive to HPV, especially for the most common HPV16 and HPV18 accounting for 50% and 20% percent of cervical cancers, respectively.

According to the statistics, HPV is the viral etiology factor for 99% of cervical cancer, part of genital cancer, and head and neck cancer. The dramatic increasing of prevalence of HPV-related head and neck cancer has shed light on the HPV vaccines and put emphasis on treatment.

EPIDEMIOLOGY

Head and neck cancer is the sixth most common cancers worldwide. About 90% of head and neck cancers are squamous cell carcinoma **(HNSCC)**. Traditionally, the most common risk factors for head and neck cancer are tobacco and alcohol use. The relationship between frequency, amount of cigarette smoking or alcohol use and head and neck cancer incidence has been clear proved [5]. In the past decades, traditional head and neck cancer incidence decreased as the efforts made for reducing cigarette use. Whereas, the incidence of HPV-positive head and neck cancer is increasing sharply within the past decades. Approximately 75% of diagnosed oropharyngeal cancers are related with HPV infection and it is estimated the number of HPV-related head and neck cancer will surpass that of HPV-positive cervical cancers in US by the year of 2020 [6]. Although most HPV infections can be cleared by the body's immune system with minimal to no harm within one year, HPV infection accounts for more than 5% of cancers worldwide [7].

HPV-positive HNSCC patients tend to be younger, less exposure to tobacco and alcohol, and higher socioeconomic status and education, compared to HPV-negative patients [8]. HPV16 has been known as a major virtual cause of all cervical cancers and of a part of other anogenital cancers and of oropharyngeal cancers. And HPV16 has been associated with a rapid increase in the incidence of oropharynx cancer in some countries of the world, notably in the United States, Sweden, and Australia, where it is now responsible for more than 50% of cases [9]. Different HPV-associated diseases characteristic different risky HPV types. 11 HPV types (16,18,31,33,35,39,45,51,52,56 and 58) are related with cervical cancer, whereas oral cavity/ oropharyngeal cancers are more susceptible to HPV types of 6,11,16,18,31,33 and 35. HPV types differ from different warts (Table 1).

Table 1: HPV associated diseases.

Disease	HPV Type
Cervical Cancer	16,18,31,33,35,39,45,51,52,56,58
Oral cavity/ Oropharyngeal cancer	6,11,16,18,31,33,35
Laryngeal papillomas	6,11,30
Precancerous changes	16,18,34,39,42,55
Plantar Warts	1,2,4
Common Warts	1,2,4,26,27,29,41,57
Flat Warts	3,10,27,28,41,49
Genital Warts	6,11,30,40-45,51,54

HPV STRUCTURES

HPVs are non-enveloped, double-stranded DNA viruses of the papillomaviridae family of more than 170 members [10]. The 8kb genome encodes 6 early proteins (E1,E2,E4,E5,E6 and E7) and 2 late proteins (L1 and L2). The early proteins interact with cellular gene products and

facilitate viral DNA replication, while the late proteins provide the structural components of the viral capsid and are involved in the packaging of DNA into progeny virions (Figure 1). All these early genes (E1,E2,E4,E5,E6 and E7) and late genes (L1 and L2) are located in open reading frame **(ORF)**, which is a continuous stretch of codons that do not contain a stop codon, like UAA, UAG or UGA. Besides ORF, there is an upstream regulatory region **(URR)**, referring to a non-coding region that includes the origin of replication, E6/E7 gene promoter, enhancers and silencers.

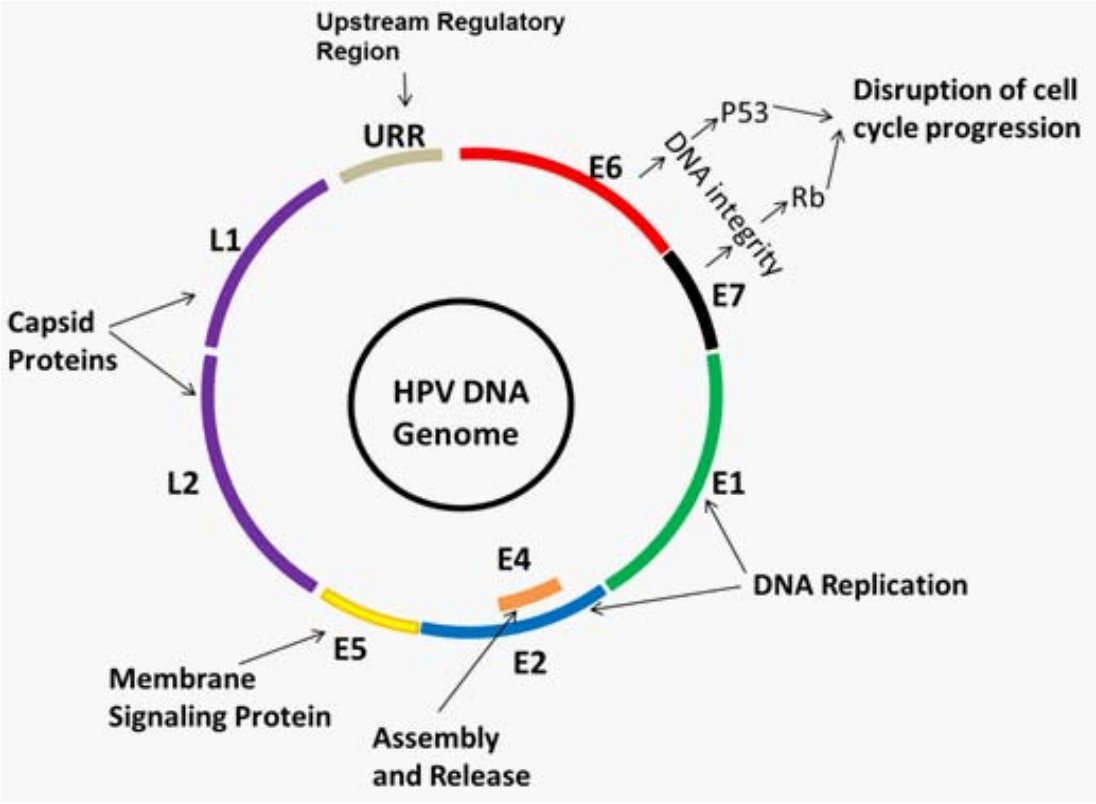

Figure 1: Life cycle of HPV**.** Early proteins: E1,E2,E4,E5,E6 and E7. E1 and E2 regulate DNA replication. E4 controls protein assembly and release. When HPV infects host cells, DNA integrity occurs and E6 and E7 will be left to interrupt cancer suppressor genes p53 and Rb to disrupt cell cycle progression, which leads tumorigenesis. Late proteins: L1 and L2, function as capsid proteins. URR: upstream regulatory region. URR refers to non-coding region that includes the origin of replication, E6/7 promoter, enhancers and silencers.

HOW HPV INDUCE HEAD AND NECK CANCER

Actually, much of our current knowledge regarding HPV-related head and neck cancer is from cervical carcinogenic models. From these models we know the high-risk HPV infects the basal cells of stratified squamous epithelia through micro-abrasions or epithelial wound [11]. Under exposure environment, most sexual activities, infectious viral particles infect host cells

transiently. HPV can live in host cells for years, even decades in latent state. Most of the virus will be erased by human immune system. However, in some cases, typically several years following the initial infection, HPV infected cells can undergo malignant transformation (Figure 2).

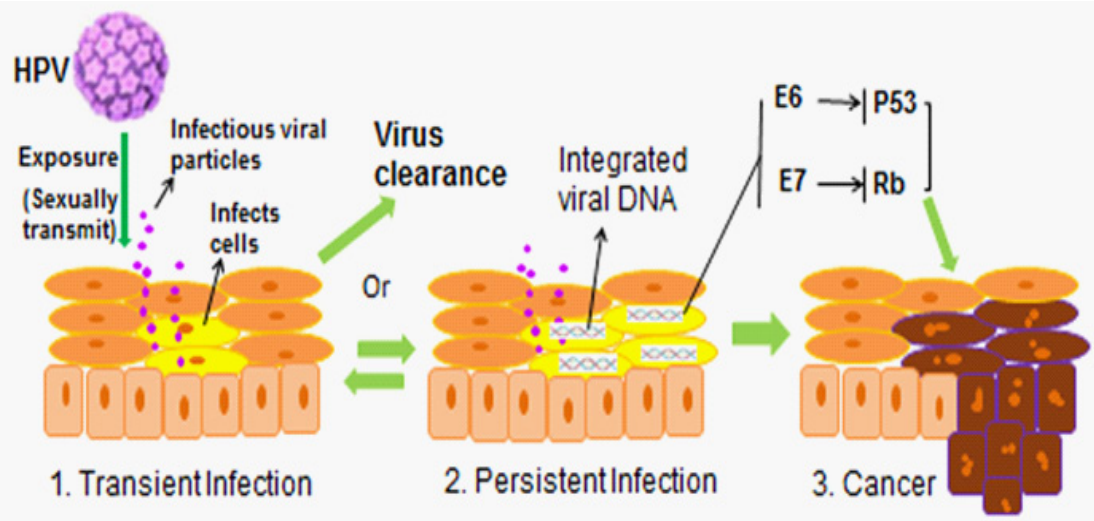

Figure 2: HPV causing cancer process. 1. After HPV exposure, most by sexually transmit, the infectious viral particles caused transient infection of host cells. In most cases, the viral will be cleared by human immune system with 2 years, and it turns back to normal tissue. 2, 3. Some viral DNA integrates with host cell DNA. During the integration, E6 and E7 are left to disrupt the tumor suppressor proteins p53 and Rb, which causes the disruption of cell cycle process and leads cancer.

During the interaction between HPV and host cells, HPV DNA has the potential to integrate into host DNA. In the process of integration, several early genes (E2,E4 and E5) and late genes (L1 and L2) are lost, whereas oncogenes E6 and E7 are left as the primary protein expressed in infected cells [12]. E6 an E7 inactivate cancer suppressor proteins P53 and retinoblastoma **(Rb)** proteins respectively, resulting in the disruption of cell cycle regulation and genomic integrity and contributing to the transformation of HPV infected cells into cancer (Figure 1,2).

TREATMENT OF HPV-RELATED HEAD AND NECK CANCER

No study indicated the differences of treatment of head and neck cancer positive or negative for HPV. Common treatments compose of surgery, radiotherapy or chemotherapy, either alone or combined with each other. Chemotherapy is considered to be conducted in the context of distant metastasis or regional recurrence; or combined with radiotherapy for advanced cancer [13]. About 29% of patients are left with long-term tracheotomy or gastrostomy tube dependence [14]. As HPV-related head and neck cancer always occurs at the oropharyngeal location, including tonsils, tongue root and pharyngeal, open surgery resection could cause higher incidence of

pharyngeal fistula theoretically. Non-surgical approaches, like radiation alone or chemo radiation therapy, would avoid invasive open surgery, but the patients still suffer considerable morbidity for the therapy. Although many retrospective studies exist for these treatments, there is still no prospective randomized clinical trial comparing surgery and non-surgery (radiation or chemo radiotherapy).

Transoral robotic surgery **(TORS)**, as a new minimally invasive surgery, has been proved to be a safe and effective technique to treat head and neck cancers, notably oropharyngeal and selected supraglottic tumors [15,16]. TROS was first reported for supraglottic partial laryngectomy **(SGPL)** in a canine model in 2005 [17], and first applied in patient who underwent radical tonsillectomy in 2007 [18]. US Federal Food and Drug Administration (FDA) approved TROS in 2009. TROS is restricted to benign and malignant tumors of T1-2 according to head and neck TNM (tumor, node and metastasis) staging system. As HPV-related head and neck cancer patients are younger than non-HPV-related head and neck cancer patients, TROS is more recommended to use to decrease the long-term side effects caused by open surgery and radiation.

HPV VACCINATION

Until now, there are three types of HPV vaccine approved by US FDA to be applied on prevention of HPV infection including 2-, 4- and 9-valent HPV vaccines. This results in renewed optimism for prevention of HPV-related cancer. Unexpectedly, the HPV vaccination has not been widely adopted especially for male, as the HPV was first known to be related with cervical cancers. In 2006, the quadrivalent vaccine, Gardasil (Merck) was approved by US FDA for use in girls and women of age 9 to 26 years, which prevents infection with HPV types 6,11,16 and 18. The bivalent vaccine, Cervarix (GlaxoSmithKline) was approved in 2009 and prevents infection with HPV types 16 and 18. A new HPV vaccine, Gardasil 9, 9-valent vaccine was approved in 2014 and prevents against 7 high-risk HPV types of 16,18,31,33,45,52, and 58 associated with cervical, vulvar, vaginal, and anal cancers, and 2 low-risk HPV types of 6 and 11 that cause genital warts [19].

Because the HPV was originally proved to be etiology factor of cervical cancers, HPV vaccine was limited in girls and women at first. As more studies clearly proves HPV is also associated with head and neck cancer, both in male and female, HPV vaccine was recommended to be used in boys and men too. However, the vaccination rate in boy and men is still too low. The HPV-related oropharyngeal cancer incidence is significantly increasing in the last decades. The incidence of oropharyngeal cancer in men has exceeded that of cervical cancer in women in USA. Hence, it is important and urgent to expand the benefits of HPV vaccination to boys and men [20].

In March 2016, one study from US Centers for Disease Control and Prevention compared HPV infection rates before (2003-2006) and after (2009-2014) the vaccination in girls who received at least one dose of the quadrivalent vaccine. In this study, the prevalence of HPV 6,11,16 and 18 decreased by 64% in sexually active girls and women aged 14-19 years and by 34% in those

aged 20-24 years [21]. However, these HPV vaccines can only prevent HPV infections and do not generate therapeutic effects against established HPV infection and HPV-related disease. Thus, the new therapeutic vaccine is in urgent need to treat HPV-related head and neck cancers specifically. To date, several current studies have focused on the therapeutic vaccine by using HPV16 encoded oncoproteins E6 and E7 as the targets of immunotherapy to treat HPV-related cancers, and in clinical trials [22-25]. HPV16.E6/7 long peptide vaccination could induce immune responses against buccal tumors by presenting E7-specific CD8+ cytotoxic T lymphocytes **(CTL)** and CD4+ T cells (regulatory T cells) [1,26].

HPV SCREENING

As it is clear that HPV is positive in 99% of cervical cancer, diagnostic tests are carried out to detect HPV infections when women presented with abnormal cytology on a Papanicolaou **(Pap)** smear or at the age range of 30-65, which was expanded to over 25 years old in 2014 by FDA. Cobas HPV DNA test is the primary screening method for detecting HPV infections. However, there are currently no screening recommendations or standard approaches to detect HPV infections in male and head and neck cancer patients.

Data from a large study showed HPV-positive head and neck cancer patients have a longer survival compared to HPV negative patients. Much more evidence shows that HPV-positive and HPV-negative HNSCCs represent distinct subgroups of HNSCCs with different epidemiological and biological profiles [27-29]. In addition, according to US National Cancer Institute **(NCI)**, HPV status must be included as a stratification factor for clinical trials including oropharynx cancer patients. So HPV testing is strongly recommended for HNSCC patients.

SUMMARY

HPV-related HNSCC has been a significant global burden, which may surpass that of cervical cancer by 2020. Though there have been three prophylactic HPV vaccines approved by FDA to prevent against HPV infection, the vaccination rate, especially in boys and men, is still not satisfied. And no one therapeutic vaccine approved until now to be applied on patients. So it is important and urgent to raise the HPV vaccination rate and develop therapeutic vaccine to lessen the sharply increasing incidence of HPV-related HNSCC. What's more, HPV screening and test is rarely adopted in HPV-related HNSCC patients. Because studies have proved HPV-positive HNSCC patients have better prognosis and longer survival time than HPV-negative HNSCC patients, it is essential and recommended to screen HPV in HNSCC patients. Currently, more and more clinical trials of therapeutic vaccines are in process, which would strengthen our weapons to treat HPV-positive patients. And due to the characteristics of HPV-positive HNSCC patients, younger and better prognosis, optimized therapy strategies, like Transoral Robot Surgery, will be developed to applied on patients to achieve better life quality and longer survival after treatment.

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