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Review

Human papillomavirus infection in oral potentially malignant disorders and cancer

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ABSTRACT

Human papillomavirus (HPV) infects keratinocytes in the mucosa or skin, and persistent infection with HPV may lead to premalignant lesions and invasive cancer, especially cervical cancer. It has also been hypothesized that HPV infection is an etiological factor of oral squamous cell carcinoma and oral precancerous disorders such as lichen planus, leukoplakia, and erythroplakia. A high percentage of HPV in oral lesions supports the possible viral contribution, but an association of HPV infection with these lesions remains to be established. The current paper will update the latest progress of HPV infection in several oral potentially malignant disorders and oral squamous cell carcinoma and discuss the impact of HPV infection on the progression of oral potentially malignant disorders.

Human papillomavirus (HPV) is a kind of small circular DNA virus infecting epithelial cells of the skin or mucosa. HPV infections are usually asymptomatic, but infections in some people will cause benign papillomas and premalignant lesions that will drive to cancers (Stanley, Winder, Sterling, & Goon, 2012). Over 170 types of HPV have been reported (Ghittoni, Accardi, Chiocca, & Tommasino, 2015). Out of them, HPV 6 and 11 infections are believed to develop genital warts. Sustained infection with high-risk HPV may develop precancerous disorders and invasive cancer (zur Hausen, 2002). In fact, the majority of cervical cancers are caused with high-risk HPV infection. Around 70% cervical cancers are specially caused by HPV16 and 18 (Ghittoni et al., 2015).

The HPV genome consists of the early genes (E) and the late genes (L). The early genes encode proteins E1 to E7 and the late genes encode viral capsid proteins L1 and L2 (Rautava & Syrjanen, 2012). E6 and E7 are important viral oncoproteins associated with cell malignant transformation. E6 directly binds to E6-associated protein, an ubiquitin ligase, targeting p53 for degradation. E6 protein also binds to several other cellular targets, leading to genomic instability (Rautava & Syrjanen, 2012). E7 binds to the retinoblastoma protein (pRb) and prevents the association of pRb with transcription factor E2F (Sritippho, Chotjumlong, & Iamaroon, 2015). Consequent E2F activation induces cell cycle progression and promotes transcription of the p16INK4A (p16) gene. p16 is a cell-cycle inhibitor, binding to cyclin-dependent kinase 4 (CDK4)/CDK6 and preventing the phosphorylation and subsequent inactivation of pRb (Kalof & Cooper, 2006). The expression of p16 was frequently down-regulated during carcinogenesis (Leversha, Fielding, Watson, Gosney, & Field, 2003; Makitie et al., 2003). However, the HPV E7 could bind to and inactivate pRb, which facilitates the production of p16 via a negative feedback mechanism (Klaes et al., 2002). Thus, p16 is a surrogate marker of high-risk HPV infection (Halloush, Akpolat, Jim Zhai, Schwartz, & Mody, 2008).

Accumulating evidence demonstrates a pathogenic role of HPV in oral carcinoma and a number of oral potentially malignant disorders including lichen planus, leukoplakia, and erythroplakia (Dalla Torre et al., 2015; Gorsky & Epstein, 2011; Mattila, Rautava, & Syrjanen, 2012; Szarka et al., 2009). HPV infection has been proposed to be an etiological factor of these diseases. The viruses may inactivate tumor suppressors and induce abnormal cellular signaling pathway leading to disease development (Brand et al., 2017; Rampias et al., 2010; Schiffman et al., 2016). A high percentage of HPV in oral lesions supports the possible viral contribution as shown by immunohistochemistry (Campisi et al., 2004; OFlatharta, Flint, Toner, Butler, & Mabruk, 2003) and polymerase chain reaction (Pol, Ghige, & Gosavi, 2015; Yildirim, Senguven, & Demir, 2011) or Southern blot hybridization (Table 1) (Khanna et al., 2009; Ostwald et al., 2003). However, whether HPV infection is a coincident event or an etiological factor of these diseases is still controversial (Marini, Wagenmann, Ting, & Hengge, 2007). In this article, based on the published literatures and data in the PubMed, we will summarize the association of HPV infection with several oral potentially malignant disorders and oral squamous cell carcinoma and discuss the effects of HPV infection on the

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Table 1
HPV infection in oral potentially malignant disorders and oral squamous cell carcinoma.

Method and references	OSCC[a]	OLP	OL	OSMF	Normal
PCR/Southern (Ostwald et al., 2003)	43.2% (118) HPV; 34.7% (118) HPV 16/18	15.4% (65) HPV; 9.2% (65) HPV 16/18	22.2% (72) HPV; 16.7% (72) HPV 16/18		
PCR (Khovidhunkit, Buajeeb, Sanguansin, Poomsawat, & Weerapradist, 2008)	3.1% (32) HPV	0% (16) HPV	5.9% (17) HPV		
PCR (Szarka et al., 2009)	47.7% (65) HPV	32.8% (119) HPV	40.9% (44) HPV		
PCR (Llamas-Martinez et al., 2008)	39.4% (33) HPV; 33.3% (33) HPV 16	45.7% (35) HPV; 40% (35) HPV 16			23.3% (30) HPV; 0% (30) HPV 16
PCR/sequencing (Jalouli et al., 2010)	24% (62) HPV; 16% (62) HPV 16/18			67% (12) HPV 16/18	
PCR/HC-II (Chaudhary, Pandya, Mehrotra, Bharti, & Singh, 2010)	32.4% (222) HPV 16 by PCR; 31.4% (222) HPV 16 by HC-II			26% (208) HPV 16 by PCR; 27.4% (208) HPV 16 by HC-II	
PCR (Mathew et al., 2011)	73.3% (45) HPV 16; 71.1% (45) HPV 18; 57.7% (45) HPV 16/18		58.3% (20) HPV 18; 50% (20) HPV 16/18		
Southern (Khanna et al., 2009)	64.5% (45) HPV 16/18		40%(30) HPV 16/18		20% (45) HPV 16/18
Flow-through hybridization and gene chip (Chen et al., 2016)	14.04% HPV; 10.67% HPV 18				3.17% HPV; 2.12% HPV 18
PCR/sequencing (Campisi et al., 2004)		19.7% (71) HPV	17.6% (68) HPV		5.6% (90) HPV
PCR (OFlatharta et al., 2003)		26.3% (38) HPV 16			0% (20) HPV 16
PCR (Razavi, Ghalayani, Salehi, Attarzadeh, & Shahmoradi, 2009)		31.0% (29) HPV 18			7.1% (14) HPV 18
PCR (Arirachakaran et al., 2013)		2.7% (37) HPV			
IHC (Yildirim et al., 2011)		21% (65) HPV			
Microassay (Mattila et al., 2012)		15.9% (82) HPV			
PCR/sequencing (Sikka & Sikka, 2014)			45% (91) HPV 16		23% (100) HPV 16
HC-II (Mehrotra, Chaudhary, Pandya, Debnath, & Singh, 2010)				31.4% (105) high-risk HPV	

HC-II, Hybrid Capture II assay; HPV, human papillomavirus; IHC, immunohistochemistry; Normal, normal mucosal control; OL, oral erythroplakia; OLP, oral lichen planus; OSMF, oral submucous fibrosis; PCR: polymerase chain reaction; Southern: Southern blot.

[a] Detection rates (cases).