

# The Role of Human Papillomavirus in Oral Disease

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## KEYWORDS

- Human papillomavirus • Squamous papilloma • Condyloma acuminatum
- Oral squamous cell carcinoma • Multifocal epithelial hyperplasia • Verruca vulgaris

## KEY POINTS

- A wide range of low-risk and high-risk human papillomavirus (HPV) genotypes have been detected in oral mucosa after infection. Clinical infections with low-risk genotypes manifest as squamous papilloma, condyloma acuminatum, verruca vulgaris, or multifocal epithelial hyperplasia.
- Clinical infections with high-risk genotypes have been associated with malignant lesions. The most common genotype isolated from subclinical infection is HPV-16.
- Unlike oropharyngeal carcinoma, a causal role for HPV in carcinogenesis of oral squamous carcinoma is minimal, with greater influence in a small subset of nonsmokers.
- Ongoing vaccination against HPV types 6, 11, 16, and 18 is expected to decrease spread of infection and decrease the carcinogenic potential of HPV-16 in the oropharynx and oral cavity.

## INTRODUCTION

Human papillomavirus (HPV) is the cause of benign cutaneous and anogenital warts (condyloma acuminatum). HPV is also firmly established as an etiologic agent in cervical, vulvar, penile, and anal intraepithelial neoplasia (dysplasia) and carcinoma.<sup>1,2</sup> Low-risk and high-risk anogenital HPV genotypes are spread by sexual contact. The same viral genotypes have been identified in oral condylomata, squamous papillomas, and head and neck squamous cell carcinomas.<sup>3,4</sup> The same viral genotypes have also been detected in exfoliated cells of the oral cavity<sup>5,6</sup> or brushings of normal oral mucosa<sup>7-9</sup> in 6% to 30% of study populations; HPV-16, the high-risk genotype most commonly associated with cervical and genital carcinomas, is also the most common oral genotype<sup>5,8,9</sup> identified. Although the incidence of oral squamous carcinoma in the United States, largely as a result of environmental carcinogens derived from tobacco, alcohol, and areca nut use has remained relatively

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stable, the incidence of oropharyngeal squamous carcinoma, strongly associated with HPV-16, has been increasing rapidly.<sup>10-12</sup>

## THE VIRUS

HPVs constitute several species within 5 genera of the Papillomaviridae family. All HPVs share the same basic structure: a nonenveloped virus, 55 nm in diameter, with an icosahedral protein capsid consisting of 72 capsomeres. The viral genome is circular double-stranded DNA, approximately 7900 bp in length. All putative coding sequences are located on only 1 DNA strand.<sup>1,2</sup>

The HPV genome consists of 3 functional regions.<sup>13-15</sup> Soon after infection, early genes (E1-E7) are transcribed, and their protein products control viral replication and gene transcription and modulate epithelial cell growth and proliferation. The E2 gene product is a transcriptional repressor that inhibits transcription of oncogenic E6 and E7 proteins. Genes expressed later (L1 and L2) code for the capsid proteins and are transcribed before the final assembly of virions. An upstream regulatory region of the viral genome is noncoding and controls viral DNA replication and transcription of the early and late genes. Sequence analysis of the L1 major capsid protein gene derived from DNA isolated from various benign and malignant lesions has shown that considerable genomic variation exists in this gene. Less than 90% homology between L1 genes defines different HPV genotypes, and there are more than 120 well-characterized genotypes, with many more recognized (Table 1).

Much of the recent literature relating HPV genotypes with disease has focused on HPV in the cause of anogenital warts and dysplasia and cancer of the uterine cervix. At least 40 HPV genotypes can infect genital skin and mucosae.<sup>1,2</sup> HPV genotypes associated with high-grade dysplasia and carcinoma of cervical, vaginal, vulvar, penile, and anal epithelium are subclassified as high risk, whereas those genotypes associated with low-grade dysplasia, condylomata, and other warts are described

<b>Genotypes</b>	<b>Lesion</b>
1, 2, 4, 26, 27, 57	Verruca vulgaris
3, 10, 26, 27, 75	Verruca plana
1, 2, 4, 63	Plantar warts
13, 32	Multifocal epithelial hyperplasia
6, 11, can also harbor high-risk genotypes	Condyloma acuminatum
6, 11, can also harbor high-risk genotypes	Oral squamous papilloma
6, 11, can also harbor high-risk genotypes	Recurrent respiratory papillomatosis
6, 11, can also harbor high-risk genotypes	Anogenital low-grade intraepithelial neoplasia
16, 18, 31, 33, 51, 52, 66 and other high-risk genotypes	Anogenital high-grade intraepithelial neoplasia
16, 18, 31, 33, 35, 51, 66, 73, 82 and other high-risk genotypes	Anogenital and cervical carcinoma
16, 33, 31, 18, 52 and other high-risk genotypes	Head and neck squamous cell carcinoma

The table lists the more common genotypes associated with the disease, as well as a small representative number of other genotypes. This list is not exhaustive; many other genotypes are also potentially involved in the various lesions listed.

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