# Human papillomavirus infections in the oral mucosa

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Increased awareness of human papillomavirus (HPV) as the causal agent of cervical cancer—and, in the last five years, of oropharyngeal cancer as well—has increased interest in more specific knowledge regarding oral HPV infections. How and when do people acquire oral HPV infection—and when they do, are they at an increased risk of developing a malignancy? The availability of HPV vaccines offers potential protection against HPV oral mucosal infections. In this review article, we provide the latest information regarding HPV and oral HPV infections so that dental professionals can share this knowledge with their patients as part of routine preventive care.

## ABSTRACT

**Background.** Public awareness of human papillomavirus (HPV) as the causal agent of cervical cancer and of the availability of HPV vaccines has increased. As a result, more patients are asking their dentists about oral HPV infection and its prevention by means of vaccination. Parents of pediatric dental patients also may be concerned when their children have HPV-associated oral lesions, because HPV infection still often is considered a purely sexually transmitted disease. In this review, the authors provide the latest information for dental professionals about HPV infection in the oral mucosa and in general.

**Types of Studies Reviewed.** The authors searched PubMed for all studies regarding HPV infection in the oral mucosa, and they reviewed relevant publications focusing exclusively on HPV infections of the oral cavity. In selecting studies for review, the authors made a clear distinction between studies regarding HPV infections in the mouth and those regarding HPV infection in the oropharynx or in other head and neck sites.

**Results.** HPV can infect oral mucosa. A subgroup of oral cancer clearly is associated with HPV. Oral HPV infection is transmitted sexually but also can be transmitted from mouth to mouth and vertically from an infected mother during delivery.

**Conclusions and Clinical Implications.** Persistent HPV infection in the oral mucosa might increase the risk of developing oral cancer. Regular and meticulous clinical examination is the dentist's most important tool in detecting HPV-associated changes in the oral mucosae. HPV-associated oral cancer may affect a population younger than that typically affected by HPV-independent oral cancer. Alcohol and tobacco use increase the risk of developing oral cancer, so good practice includes encouraging patients to avoid these habits. The available HPV vaccines cover the HPV genotypes found most commonly in the oral mucosa, but their protective effect against oral cancer remains to be elucidated.

**Key Words.** Human papillomavirus; oral mucosa; early detection of disease; transmission; warts; oral potentially malignant disorders; oral cancer; risk.

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## THE BASICS OF HUMAN PAPILLOMAVIRUS

**Classification.** Papillomaviruses are small, double-stranded DNA viruses (Figure 1). Humans can be infected only by HPVs, not by papillomaviruses found in animals. The HPV genome contains eight open reading frames (ORFs), which are potential coding sites of six early (E) proteins and two late (L) proteins (Figure 1). The L1 ORF is used to identify new HPV types because it is the most conserved of the eight ORFs within the genome (Figure 1). If the DNA sequences of the L1 ORFs differ more than 10 percent from the closest known HPV type,

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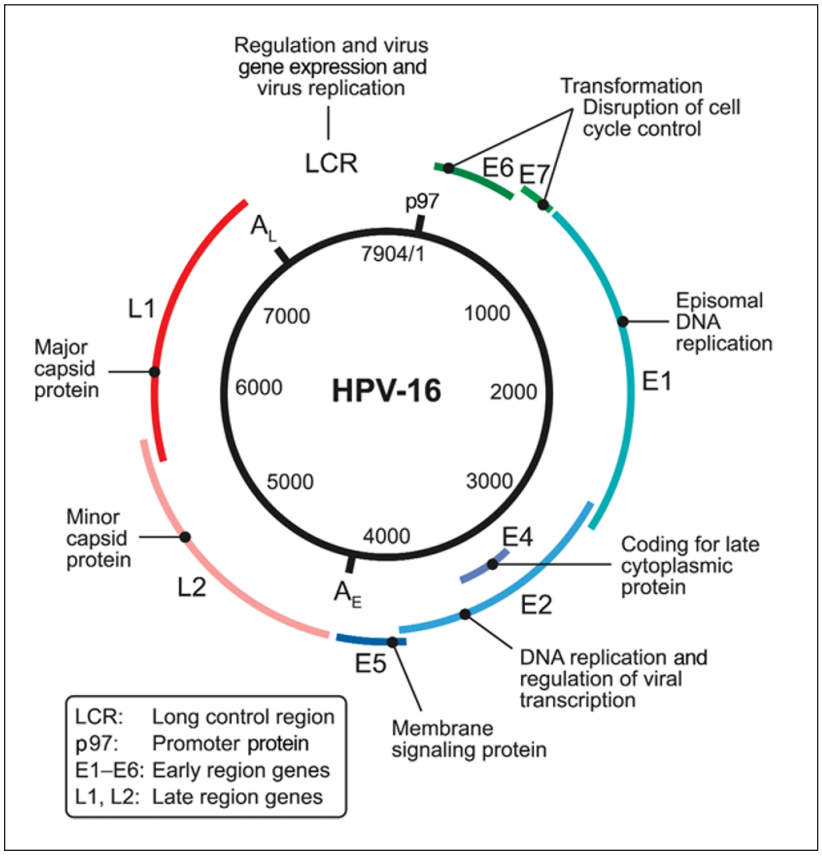


**Figure 1.** The genome of human papillomavirus-16. **$A_E$:** Early polyadenylation. **$A_L$:** Late polyadenylation.

the gene is recognized as a new genotype. The genotypes are numbered in the order of their discovery and characterization. Investigators have described more than 120 different HPV types on the basis of the isolation and sequencing of complete genomes.[1,2] On the basis of nucleotide sequence comparisons of L1, the evolutionary relationships between papillomavirus types can be represented in the form of phylogenetic trees at three taxonomic levels: genus, species and type.[2,3] Most HPVs that infect mucosal sites belong to the alpha papillomaviruses, which consist of 15 species.[2] Information about HPV sequences are available from the Web sites of GenBank, which is the National Institutes of Health's genetic sequence database ("www.ncbi.nlm.nih.gov/genbank"), and the European Nucleotide Archive of the European Bioinformatics Institute ("www.ebi.ac.uk/genomes/virus.html").

HPVs have been classified as cutaneous or mucosal types according to the target site of their infection (Figure 2[1]). Furthermore, classification of HPVs as high-risk types and low-risk types is based on epidemiologic data regarding the behavior of the lesions caused by different HPV types.[2,4] To date, investigators have identified 30 HPV genotypes: 15 high-risk types, three types that probably are high risk and 12 low-risk types (Table 1[5]).

**Viral life cycle.** The life cycle of HPV is linked tightly to the differentiation program of the host keratinocyte (Figure 3[6], page 908). HPV entry into the human body requires epithelial wounding that allows the virus to enter the basal layer of the epithelium.[7] Possible HPV receptors include alpha 6 integrin, extracellular laminin 5 and heparan sulfate proteoglycans.[8-10] After entry, the virus establishes itself in the nucleus as an episome with a low copy number. At this stage, the viral replication is considered to be nonproductive; viral proteins E1, E2, E6 and E7 are expressed at low levels, and no progeny virions are made.[11] After cell division, the infected daughter cells migrate toward the suprabasal region and begin to differentiate, which triggers a coordinated transcriptional cascade of the viral genome. Viral proteins, mainly E6 and E7, retard the normal terminal differentiation by stimulating cellular proliferation and DNA synthesis through interfering with and inhibiting several cell-cycle regulators to allow high-level amplification of the viral genome.[12] In upper layers of the epithelium, the levels of viral proteins necessary for replication (that is, E1, E2, E4 and E5) increase, and capsid proteins (L1 and L2) are produced in

**ABBREVIATION KEY. $A_E$:** Early polyadenylation. **$A_L$:** Late polyadenylation. **E:** Early. **EV:** Epidermodysplasia verruciformis. **FEH:** Focal epithelial hyperplasia. **HIV:** Human immunodeficiency virus. **HNSCC:** Head and neck squamous cell carcinoma. **HPV:** Human papillomavirus. **HR:** High risk. **IHC:** Immunohistochemistry. **ISH:** In situ hybridization. **L:** Late. **LCR:** Long control region. **LR:** Low risk. **mRNA:** Messenger ribonucleic acid. **NB:** Northern blot. **OLP:** Oral lichen planus. **OPMD:** Oral potentially malignant disorder. **ORF:** Open reading frame. **OSCC:** Oral squamous cell carcinoma. **PCR:** Polymerase chain reaction. **p16:** Protein 16. **p53:** Protein 53. **p97:** Protein 97. **pRb:** Retinoblastoma protein. **RT-PCR:** Real-time PCR. **SB:** Southern blot. **WB:** Western blot.