

# REVIEW ARTICLE

## Oral Cancer and Viruses: A Comprehensive Review

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### ABSTRACT:

One of the most common malignant tumours of oral cavity is Oral squamous cell carcinoma (OSCC). The aetiology of epithelial cancer of the head and neck is considered to be a multifactorial, sequential process. DNA viruses are found in many different cancers and are also capable of transforming cells to a malignant phenotype. Human Papilloma Virus (HPV) has been proposed as risk factors in OSCC development and HPV type 16 is the most important subtype. Hence, in the present review, we aim to highlight the association of viruses in causation of oral cancer.

**Key words:** Oral Cancer, Review, Viruses.

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### INTRODUCTION

Oral cancer is generally classified as head and neck cancer, and head and neck squamous cell carcinoma (HNSCC) is the sixth to ninth most common malignancy in the world. Some authors have classified oral cancer as oropharyngeal cancer (OPC), and oropharyngeal squamous cell carcinoma (OPSCC) has been confused with oral squamous cell carcinoma (OSCC). In our previous report on the incidence of oral cancer in Korea<sup>1</sup>, we identified oral and maxillofacial cancer according to anatomic site, dividing it into 10 areas of the lip, tongue, mouth, salivary glands, tonsil, oropharynx, nasopharynx, hypopharynx, pharynx unspecified, and nose and sinuses.<sup>1-3</sup>

Cervical cancer is the second most frequent cancer in women worldwide, and human papilloma virus (HPV) infection causes most cervical cancers and a variable proportion of certain non-cervical malignancies, including vulvar, vaginal, penile, anal, and OPC. More than 150 different subtypes of HPV have been reported globally, and types 16 and 18 are associated with the onset of 70% of cervical cancers worldwide. Smoking and alcohol are well known risk factors of oral cancer, as is HPV infection, and the relationships between these known factors warrant closer examination.<sup>4-6</sup>

Link between high-risk human papilloma viruses, cell cycle and oral squamous cell carcinomas

In a normal keratinocyte, DNA damage induces p53 expression that in turn up-regulates p21 expression. P21

binds with proliferative cell nuclear antigen (PCNA), deactivates it and thus blocks the phosphorylation of the retinoblastoma gene (pRb). Thus hypo-phosphorylated pRb binds and deactivates E2f, a transcription factor. PCNA and E2f inactivity inhibits DNA replication and oral keratinocyte division. DNA damage may result in apoptosis of oral keratinocyte.<sup>7-9</sup>

The relevance of the role of HPV infection in cervical and anal cancer is well established and, by way of analogy, oncogenic HPV viruses might play a role in malignant transformation of squamous epithelia in any body region. Although still controversial, such evidence implies that carcinogenesis by environmental chemical carcinogens is not the only cause of OSCC.<sup>10-13</sup>

Syrjanen et al. were the first to provide, in 1983, evidence on HPV as an etiological factor in OSCC when cytopathic effects of HPV (koilocytosis) were noted on light microscopy of oral carcinomas and the presence of HPV antigens in 40 oral carcinomas were analyzed using immunohistochemistry. Of the 40 lesions, 16 (40%) showed HPV suggestive changes on light microscopy, and of those, 8 of 16 expressed HPV structural proteins.<sup>12</sup> A few years later in 1990, these biopsies were examined by Chang et al. for the presence of HPV DNA using in situ hybridization (ISH) and polymerase chain reaction (PCR), and 12 of 40 disclosed the presence of HPV 11, 16 or 18 DNA.<sup>14, 15</sup>

### THE HERPESVIRUS FAMILY

Herpesviruses have a double-stranded DNA genome and are among the largest and most complex human viruses. There are eight members of the human herpesvirus (HHV) family (Table 2). The more common, as to oral health problems, are the two herpes simplex viruses (HSV-1 and -2), which cause recurrent herpetic ulcerations referred to as cold sores. These ulcers typically occur on the lips, but the viruses can also cause similar lesions in the mucosa, such as in the case of gingivostomatitis. The mucosal affection is normally associated with a primary herpes infection in children, and is accompanied by bodily symptoms such as fever and malaise. Both HSV-1 and -2 may be involved in oral manifestations, although the latter is primarily associated with the genitals.<sup>3-5</sup>

Epstein-Barr virus (EBV) and cytomegaloviruses (CMV) are present in the vast majority of adults, but in most cases probably without ever causing any overt disease. Both can, however, cause mononucleosis; EBV being responsible for most of the cases. Mononucleosis is also known as 'kissing disease', suggesting that the virus spread through direct mouth-to-mouth contact. The condition is common at puberty, and is considered a consequence of the host not having been in contact with the virus earlier in life. EBV's potential for affecting the mouth is further underlined by oral hairy leukoplakia, i.e. white patches typically on the side of the tongue with a hairy appearance, a rare condition restricted to immunosuppressed patients.<sup>7,8</sup>

Varicella-Zoster virus (VZV) is associated with chicken pox, as a primary infection, and with herpes zoster if reactivated later in life. The vesicular rash formed occurs primarily in the skin, but may also affect the mucosa. The three remaining human herpesviruses (HHV-6, -7 and -8) rarely cause serious disease, but the former two are responsible for a particular type of rash (roseola) with associated fever in infants. HHV-8 is presumably responsible for Kaposi's sarcoma, a rare form of skin cancer seen in immunosuppressed patients.<sup>10-14</sup>

#### SYSTEMATIC META-ANALYSIS ON ASSOCIATION OF HUMAN PAPILLOMA VIRUS AND ORAL CANCER

Oral cancer is a disease with complex etiology. There is a strong evidence for the role of smoking, alcohol, genetic susceptibility, and indications that DNA viruses could also be involved in oral cancer. Recognized initially as sexually transmitted agent, human papilloma virus (HPV) is now considered a human carcinogen. Papilloma viruses are epitheliotropic viruses. A strong association of cervical cancer has been implicated with high-risk HPV16 and HPV18 infections, establishing the viral pathogenesis of the carcinoma. The etiopathogenesis is still unclear referring mainly to conflicting evidences in the detection of such viruses in oral carcinoma in spite of few studies suggesting their positive correlation. Their systematic meta-analysis aimed to provide evidence-based analysis of literature relating oral cancer and HPV, along with identification of reliable diagnostic methodology for identifying HPV in oral and

oropharyngeal cancer. A systematic review was performed using PubMed (from the year 1995 to 2015), Medline, Cochrane, ScienceDirect, and the Internet search. Reviewed literature included randomized control trials, cross sectional and cohort studies. Pooled data were analyzed by calculating relative risk and odds ratios (ORs), using a binary random-effects model. Out of 1497 cases, 588 patients were positive for HPV DNA, detected by various methods. About 39.27% of case samples were positive for HPV DNA. The calculated OR was 2.82 and 95% confidence interval, which showed significantly an increased risk of HPV among case group when compared to that of controls. Their meta-analysis suggested a potentially significant casual relation between HPV and oral and oropharyngeal cancers.<sup>16</sup>

#### CONCLUSION

Various oncogenic virus species have been proposed to be involved in oral carcinogenesis. However, still lots of research are required for finding of substantial evidence in relation to the role of viruses in causation of cancer.

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