Institut Pasteur
Microbes and Infection 16 (2014) 371–378
www.elsevier.com/locate/micinf

Review

# Viruses and oral cancer. Is there a link?

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Received 22 November 2013; accepted 24 February 2014
Available online 5 March 2014

**Abstract**

Oral squamous cell carcinoma (OSCC) is the most common malignant tumour of the oral cavity. 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. Other oncogenic virus species i.e., Epstein–Barr Virus and Herpes Simplex Virus Type 1 have been proposed to be involved in oral carcinogenesis. However, no convincing evidence exist that they are an established risk factor in OSCC. Therefore more studies are needed in order to clarify the different aspects of virus involvement. Here, we review the existing literature on viral involvement in oral cancer.


*Keywords:* Oral cancer; Human Papilloma Virus; Epstein–Barr Virus; Human herpes simplex virus type 1

## 1. Introduction

Oral squamous cell carcinoma (OSCC) is the most common epithelial malignancy of the oral cavity. OSCCs and their variants constitute over 90% of oral malignancies, and the disease is associated with poor prognosis. OSCC is a complex malignancy where environmental factors, viral infections, and genetic alterations most likely interact, and thus give rise to the malignant condition.

Viral causes of cancer have been studied since the beginning of the 20th century, when an infective agent, which later was shown to be a virus that had the ability to induce tumours in chickens, was isolated [1,2]. During the 1930s, Richard Shope was able to transfer a papillomavirus, by using cell-free medium, to rabbits [3]. Groupe et al. showed in various studies that leukaemia and sarcoma could be induced in mice through an infectious virus [4]. Another major step was made when two research groups successfully transformed cells which were infected with Rous sarcoma virus, into mice [4,5]. It was thereby possible to identify specific viral oncogenes that could transform normal cells into cancer cells.

Viral involvement in the development of OSCC has been proposed in many studies. The most frequently studied virus species are Human Papilloma Virus (HPV), Epstein–Barr Virus and Herpes Simplex Virus Type 1 (HSV-1). Some authors have confirmed a clear connection, while other authors have not been able to find any convincing evidence. Co-infection by two or more virus species has been suggested as an increased risk factor for cancer development in general [6], but also in OSCC [7–10].

There now seems to be a consensus that HPV has oncogenic capacity not only in cervix cancer but also in oral, as well as head and neck cancer. Regarding the other oncogenic viruses, the situation is more doubtful.

In this article, we review available literature regarding viral involvement in the development of OSCC.

## 2. Oral cancer

Oral cancer is usually defined as a neoplastic disorder in the oral cavity, which includes the following areas: lip, buccal

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http://dx.doi.org/10.1016/j.micinf.2014.02.009
1286-4579/

mucosa, lower and upper alveolar ridges, retromolar gingiva, floor of the mouth, hard palate, and the anterior two-thirds of the tongue. By gross morphologic examination, one sees exophytic, ulcerative, or verrucous types.

Squamous cell carcinoma (SCC) constitute 90% of epithelial malignancy in the oral cavity and over 50% of the tumours have an apparent "precancerous" state, often preceded by potentially malignant disorders such as leukoplakia, oral lichen planus and oral submucous fibrosis [11–13].

The aetiology of epithelial cancer of the head and neck is considered to be a multifactorial, sequential process. The continuum of SCC progress from individual epithelial cell changes (atypia) to a generalized disturbance of the epithelium (dysplasia), and then to carcinoma in situ, and finally to invasive SCC. The malignant tumour, consisting of strands of malignant epithelial cells infiltrating subepithelially, may resemble any or all of the layers of stratified squamous cell epithelium. The two major aetiological factors in SCC of the oral cavity are the social habits of tobacco use and alcohol consumption [14,15].

Different groups of genes are involved in the multiple genetic events of malignant cell transformation: oncogenes, tumour-suppressor genes, DNA repair genes, and DNA sequences that control apoptosis. The normal function of the p53 tumour-suppressor gene, located on the short arm of chromosome 17, is that of "guardian of the genome". Damage to DNA is associated with nuclear accumulation of the p53 protein, presumably inducing growth arrest for repair or the induction of apoptotic cell death [16]. Mutation in the p53 gene is frequently found in human cancer, and also in SCC of the head and neck. These mutations likely result from carcinogen-induced DNA damage. In patients with head and neck SCC, using high amount of tabacco and alcohol, elevated p53 expression has been detected [17,18]. Elevated p53 has also been associated with HPV-infection [19].

OSCC is treated with surgery, radiotherapy, chemotherapy or a combination of these three modalities. The main prognostic factors are tumour size/stage, presence of locoregional metastasis and sub site and the 5-year survival rate is approximately 50% and has not improved much over the last decades. HPV-infected OSCC, however, seems to have a slightly better prognosis [20].

## 3. Oncogenic viruses and oral cancer

### *3.1. Human Papilloma Virus (HPV)*

#### *3.1.1. Historical background*

Papillomavirus infection in the oral mucosa was first demonstrated in animals by DeMonbreun et al., in 1932 [21]. Yet not until 1967 did Frithiof et al. present the first ultra structural evidence of the presence of papillomavirus in human oral papillomas, and Praetorius-Clausen et al., in 1971, demonstrated particles compatible with papovavirus in oral focal epithelial hyperplasia [22]. Jenson et al. were first to detect HPV antigen in oral verrucae, multiple papillomas, and condylomata [23]. Later, after the development of hybridization techniques, especially the very sensitive polymerase chain reaction (PCR), numerous investigations have detected different types of HPV in different oral lesions, as well as in normal oral mucosa.

#### *3.1.2. HPV characteristics*

The papillomaviruses, which replicate in the nucleus of squamous epithelial cells, belong to the papovavirus group, and are small, non-enveloped DNA viruses of a symmetrical icosahedral shape. Papillomavirus particles (52–55 nm in diameter) consist of a single molecule of double-stranded, circular DNA with approximately 8000 bp, contained in a capsid (spherical protein coat) composed of 72 capsomeres (repeating subunits of the capsid) [24]. In a virus, only the genome is present, with no cellular machinery for replicating the genome or manufacturing the capsid. The host cell must supply the necessary ingredients for the assembly of the viral components. When cellular death does not occur during viral reproduction, chronic infection can probably succeed. HPV is a very large and heterogenous group of DNA viruses and over 100 types have already been identified. Based on the clinical behaviour of HPV infections, HPV viruses can be grouped into high-risk (HR) and low-risk (LR) HPV types. HR-HPVs are associated with lesions that have a propensity to undergo carcinogenesis, and these viruses include types 16, 18, 31, 33, 35, 39, 45, and 52.

#### *3.1.3. Carcinogenesis of HPV*

Initially, HPV infects undifferentiated proliferative basal cells, which are capable of dividing. Once inside the host cell, viral DNA localizes into the nucleus and establishes itself as an episome with a low copy number (some 10–200 copies per cell). At this stage, the viral proteins E1, E2, E6, and E7 transcribed from the early promotor are expressed at a low level [25]. Mainly E6 and E7 may disturb the normal terminal differentiation by stimulating cellular proliferation and DNA synthesis. After the onset of genome amplification, the capsid proteins L1 and L2 accumulate in the mature epithelial cells. The assembly of infectious virions takes place in terminally differentiated cells of the upper epithelial layers, and the virions are shed to the environment, as the cells are lost through desquamation. In addition to active replication, HPV infection can result in latency and malignant transformation through interactions of viral E6 and E7 proteins with p53 and pRB [26]. The tumour suppressor p53 can dictate cellular fate by initiating cell cycle arrest, promoting DNA repair, triggering apoptosis, and inducing growth arrest/senescence. Thus a direct mutation can alter or inactivate p53, and interactions with the oncogene products of HPV (e.g., E6) can also cause aberrations in p53 regulation [27]. The viral E7 protein binds and inactivates a human tumour suppressor gene product, the retinoblastoma protein (pRB) and the viral E6 protein binds p53 and earmarks it for destruction by the ubiquitin pathway. In malignant tumours, including SCC of the head and neck, somatic mutations in the p53 gene, or in other cellular genes that modulate p53 activities, commonly inactivate p53 function. Such E6 elimination of p53 represents a critical step in