Human papilloma viruses (HPVs), members of the papillomaviridae family, infect squamous epithelial cells of cervix, lower genitalia, and oral cavity. The association of HPV with oropharyngeal carcinogenesis is well documented. The incidence of oral cancer ranks second in Karachi South in both genders according to World Health Organization (WHO) statistics. This is attributed to the popularity of chewable tobacco products among the general population. Studies on Gutka-eaters in a set population of Karachi showed high frequency of HPV (17%) and high prevalence of HPV in squamous cell carcinoma in Pakistani patients (68%). The exposure of oral mucosa to chewable tobacco causes abrasions making it susceptible to HPV. This review strives to summarise the role of HPV in chewable tobacco-related precancerous and cancerous lesions. The literature of about a decade was retrieved from Google and PubMed with the under mentioned key words. It was found that the use of chewable tobacco products, especially Gutka, may increase the risk of oral squamous cell carcinoma (OSCC).

**Keywords:** HPV, Gutka, Squamous cell carcinoma.

**Introduction**

Human papilloma viruses (HPVs) are members of the papillomaviridae family that infect epithelial cells exclusively. The most common sites are squamous epithelium of skin, lower genitalia, and oral cavity. Within the genome is similar in all papillomavirus types and partly overlapping ORFs are arranged on a sole DNA strand. The genome can be divided into three regions: the long control region (LCR) without coding potential; the region of early proteins (E1-E8), and the region of late proteins L1 & L2. Among all different viral proteins, it is found that E6 and E7 are necessary for HPV-induced malignancy.

**Invasion of Oral Cavity**

The invasion and transformation of oral epithelium by HPV, causing multiple lesions is attributed to the histology of the oral cavity which is lined by a mucous membrane consisting of a stratified squamous epithelium and lamina propria made up of dense connective tissue. The mechanism of development of infection by HPV is shown in Figure-2. The lining of the gingiva, hard palate and the dorsum of the tongue are completely keratinised with a superficial horny layer, whereas in the lip, cheek, vestibular fornix, alveolar mucosa, floor of mouth and soft palate, the epithelium is non-keratinised. The histology of oral mucosa resembles that of the uterine cervix, other lower genital tract or skin, depending on the anatomic site. On the basis of these morphological similarities, one can anticipate the presence of both the mucosal and cutaneous HPV types in different squamous cell lesions of the oral mucosa. Such benign oral lesions include squamous cell papilloma (SCP), condyloma, verruca and focal epithelial hyperplasi (FEH) which are linked with HPV.

**Structure of Human Papilloma Virus**

The HPV, a double-stranded diribonucleic acid (DNA) molecule, consists of eight kilobase (8kb) nucleotides genome with 72-capsomere capsid. Capsomers are composed of two structural proteins: the 57kD late protein L1, which accounts for 80% of the viral particle, and the 43-53kD minor capsid protein L2 (Figure-1). Arrangement of the 8-10 open reading frames (ORFs) among all different viral proteins, it is found that E6 and E7 are necessary for HPV-induced malignancy.

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Figure-1: The circular organization of HPV DNA episome.\textsuperscript{1-5}

HPV: Human Papilloma Virus. DNA: Deoxyribonucleic acid. ORF: Open reading frames.

Figure-2: The Association of HPV infection.
display greatest susceptibility to HPV due to the easy exposure of the basal cells to HPV infection. Oral mucosa, especially oropharyngeal mucosa, is similar histologically to cervical mucosa. The presence of HPV in oral mucosa suggests that, as in cervical cancer, HPV infection may also play a similar role in the transformation of oral epithelium. HPVs have a strong affinity for squamous epithelial cells and are associated with a wide range of proliferative epithelial lesions.\textsuperscript{10,11}

**Interrelationship among Gutka, HPV and Oral Cancer**

In Western populations, tobacco and alcohol use are the major etiologic factors associated with oral cancers. In developing countries of Asia and the South Pacific, oral cancer is increasingly associated with the chewing of betel nut. As the population of Asia and the South Pacific immigrants, head and neck surgeons in North America are likely to see more patients with oral carcinoma induced by betel nut chewing.\textsuperscript{12} The quid (Gutka) habit has a major social and cultural role in communities throughout the Indian subcontinent, Southeast Asia and locations in the western Pacific.\textsuperscript{13} In Pakistan, an 8.5 to 10 times increase in the risk of oral cancers has been reported due to an increase in tobacco chewers.\textsuperscript{14} Gutka (betel, areca, lime and tobacco concoction), marketed locally since 1975, is one of several smokeless tobacco formulations, and the cause of the worst recognisable oral lesions. This habit has now incorporated into the cultural setup of South Asians, especially the strong inclination of children toward chewable tobacco products, which warrants vital action.\textsuperscript{15} Several studies have shown a link between the use of Gutka and oral submucosal fibrosis, oral cavity cancers, leukoplakias and other head and neck malignancies.\textsuperscript{14,16,17} It has been estimated that 58% of the total worldwide head and neck cancers occur alone in South and Southeast Asia.\textsuperscript{17} In Pakistan, 40% of the adolescent and adult population of squatter settlement in Karachi has been reported to be using at least one product of chewable tobacco every day.\textsuperscript{18}

A variety of betel/areca nut/tobacco habits have been reviewed and categorised because of their causal association with oral cancer, oral precancerous lesions, and their widespread utilisation in different parts of the world. At a recent workshop in Kuala Lumpur it was proposed that quid-related lesions should be classified into two categories: first are diffusely outlined, and second confined to the quid placement site. Elaborate guidelines were proposed to recognise lesions such as chewer’s mucosa, areca nut chewer’s lesion, oral submucous fibrosis and other quid-related lesions. A new clinical entity, betel-qid lichenoid lesion, was also proposed to demonstrate an oral lichen planus-like lesion associated with the betel qid habit.\textsuperscript{19,20} In chronic chewers a condition known as betel chewer’s mucosa, a discoloured areca nut-encrusted change, is often found where the quid particles are retained. Areca nut chewing is implicated in oral leukoplakia and submucous fibrosis, which are potentially malignant conditions. Oral cancer often arises from precancerous changes in Asian populations.\textsuperscript{21-23}

HPV was positive approximately in 18% to 25% of subjects with ulceration, leukoplakia, burning sensation and erythroplakia respectively. Some symptoms such as rough mucosa were found to have the highest frequency, Abrasions like white patches, swelling, sub-mucosal fibrosis (SMF), pain, trismus, cuts, sepsis are due to continuous exposure of oral mucosa to Gutka, making this mucosal surface more vulnerable to viruses like HPV (Figure-3). Sub-mucosal fibrosis was present in 24% of Gutka eaters. Oral lesions caused by constant exposure to Gutka are associated with high frequency of HPV infection, which may be a risk factor for squamous cell carcinoma of the oral cavity.\textsuperscript{24,25} The frequency of HPV in oral cavity was found high in subjects with trismus in a recent study suggesting risk of oral squamous cell carcinoma.\textsuperscript{28}

**Conclusion**

Persistent HPV infection in the oral mucosa might increase the risk of developing oral cancer in a population younger
than that typically affected by HPV-independent oral cancer. The use of chewable tobacco products, especially Gutka, may increase the risk of oral squamous cell carcinoma.

References


2. Chen JJ. Cell cycle checkpoints, genomic instability, and apoptosis in cells expressing papillomavirus oncogenes. (Online) (Cited 2009 June, 28). Available from URL: http://www.umassmed.edu/faculty/show.cfm?start=0&facul


