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Human papillomavirus and oral disease – emerging evidence: a review

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ABSTRACT

Human papillomavirus (HPV) infections have received considerable attention in recent years. Of the 120 or so known types of the virus, some cause a variety of benign wart-like lesions of the skin and genital and oral mucosae, whilst others are aetiologically associated with cervical and anogenital cancers. Recent epidemiologic evidence suggests that HPV may also be an independent risk factor for oropharyngeal cancer. In this context it has been suggested that HPV virus may modulate the process of carcinogenesis in some tobacco and alcohol induced oropharyngeal cancers and act as the primary oncogenic agent for inducing carcinogenesis among non-smokers. Dental practitioners have a major role in detecting all lesions of the oral mucosa caused, or possibly caused, by HPV. This paper briefly reviews the current state of knowledge of molecular and clinical aspects of HPV infections of the oral mucosa.

Keywords: Human papillomavirus, oral conditions, oral potentially malignant disorders, oral cancer.

Abbreviations and acronyms: CIN = cervical intra-epithelial; CMV = cytomegalovirus; EBV = Epstein–Barr virus; EV = epidermodysplasia verruciformis; FEH = focal epithelial hyperplasia; HIV = human immunodeficiency virus; HPV = human papillomavirus; HR-HPV = high risk HPV; HSV = herpes simplex virus; LP = lichen planus; LR-HPV = low risk HPV; OHL = oral hairy leukoplakia; OLP = oral lichen planus; OPMD = oral potentially malignant disorder; ORF = open reading frames; OVC = oral verrucous carcinoma; PCR = polymerase chain reaction; PVL = proliferative verrucous leukoplakia; VLP = virus-like particles.

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INTRODUCTION

Worldwide human papillomavirus (HPV) infection is the most common sexually transmitted viral infection.[1] Over 120 types of HPVs have been identified to date.[2] Based on their biological behaviour, HPVs are divided into low risk and high risk groups. Low risk HPVs cause wart-like lesions of the skin and anogenital region and the oral mucosa. High risk HPVs are aetiologically associated with cervical and anogenital cancers.[1,3] Recent studies have shown that oral infection with human papillomaviruses is associated with a significant risk of developing oropharyngeal cancer and oral potentially malignant disorders (OPMDs).[1,3,4] In this paper biological aspects of HPVs and their role in the development of a range of oral mucosal lesions are briefly reviewed for the purpose of updating oral health professionals and raising the awareness of emerging relationships being established between HPVs and some oral diseases including oral cancer.

The human papillomavirus

The human papillomaviruses belong to the *Papillomavaviridiae* family of viruses.[5] They are capable of infecting mucosal and cutaneous epithelia in a species specific manner and inducing cellular proliferation.[5] Transmission of HPV from non-primates to humans is not known to occur.[5,6]

The HPVs are small, non-enveloped DNA viruses with a diameter of 52–55 nm.[1] The HPV genome contains a double-stranded DNA molecule that is bound to cellular histones and contained in a protein capsid.[1–6] The HPV-DNA genome encodes approximately eight open reading frames (ORFs).[1–6] The ORF is divided into three functional parts: the early (E) region, the late (L) region and a long control region (LCR). The early region is necessary for replication, cellular transformation and for the control of viral transcription while the late (L) region encodes the structural proteins (L1-L2) that take part in virion assembly.[1–6] The long control region (LCR) is

necessary for viral DNA replication and transcription.[1–6]

The early (E) region of the ORF encodes seven proteins: E1, E2, E3, E4, E5, E6 and E7. E1 is necessary for viral DNA replication. E2 has a role in viral gene transcription and replication.[1–6] The function of E3 is still not understood. E4 protein interacts with the keratin cytoskeleton and intermediate filaments and also facilitates virus assembly and release. E5 protein interacts with the receptors of growth factors and stimulates cellular proliferation and inhibits apoptosis. E6 induces DNA synthesis, prevents cell differentiation, interacts with tumour suppressor proteins and repair factors; and E7 induces cell proliferation and interacts with negative regulators of cell cycle and tumour suppressor proteins.[1–6] E6 and E7 proteins act as oncogenes which are causally associated with carcinogenesis.[1–6] L1 is a major capsid protein which interacts with cell receptors whereas L2 is a minor capsid protein which interacts with DNA. It facilitates virion assembly.[1–6] The capsid contains two structural proteins: late (L) 1 and L2. Virus-like particles (VLPs) can be produced by the expression of L1, alone or by both L1 and L2.

Based on their oncogenic potential, HPVs have been divided into high risk (HR-HPV) and low risk (LR-HPV) groups.[1–6] High risk HPVs are associated with an elevated risk of development of cancer and are often referred to as 'cancer associated' or 'oncogenic' types.[1–6] Examples of high risk HPVs include: HPV 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59, 68, 73 and 82.[1–6] HPV types 16 and 18 types in particular are responsible for the development of cervical carcinomas.[1–6] Some high risk HPVs are also associated with anogenital and oropharyngeal cancers.[1–6] Low risk HPVs on the other hand are associated with benign wart-like epithelial lesions. These HPV types include HPV 6, 11, 42, 43 and 44.[1–7]

Transmission of HPV infection

HPVs are prevalent worldwide and infection with cutaneous HPV is ubiquitous.[7] The common mode of transmission and acquisition of HPV is by horizontal transmission consequent to sexual activity.[8–11] Occasionally, HPV may be transmitted through modes other than sexual activity. These routes include vertical transmission (mother to child), fomites and skin contact.[10–12] Most HPV infections are transient and become undetectable by sensitive PCR assays within 1–2 years.[13] Persistence of HPV for a long duration is uncommon. Viral DNA persists for a median of approximately one year, and HR-HPV types persist longer than low risk types.[14] The prevalence of HPV tends to peak after an individual's first sexual intercourse (i.e. 'sexual debut') and remains high with each new sexual partner among all age groups.[15] Prevalence sites of HPVs include the epithelium of the vagina, vulva, penis, anal canal, cervix, perianal region, crypts of the tonsils and oropharynx.[7] Ninety per cent of HPV infections are usually cleared by the body within two years.[16] Persistence of HPV infection is essential for the development of cervical precancerous lesions and cancer.[17] This may take a long time, usually a decade or more after the initial infection.[18]

Although HPV transmission usually occurs via direct contact, normal intact skin or mucosa is resistant to inoculation by the virus.[1–6,19,20] Through breaks in the epithelial layers, HPVs could gain entry and infect the basal epithelial cell layers where the virus is maintained in the nuclei of the infected cells.[19,20] However, confirmatory evidence supporting this hypothesis is lacking. HPVs do not kill infected epithelial cells. As the basal cells of the infected epithelium divide and progress into squamous cells, HPV is carried within them. HPV needs terminally differentiated epithelial cells, such as the squamous cells for replication. In the squamous cells, the virus replicates and retains a high copy number.[19,20] In these cells, the viral genes are expressed and progeny viruses are produced, which are subsequently shed into the environment.[19,20]

Pathology of HPV infection

HPV infections can cause a range of pathological lesions of the female cervix, male and female anogenital tract, upper respiratory tract, oral cavity and conjunctiva.[14] HPV associated lesions include: genital warts, epidermodysplasia verruciformis (EV) of the skin, cervical intra-epithelial neoplasia (CIN), invasive cervical carcinoma, vaginal intra-epithelial neoplasia, vaginal carcinoma, vulvar intra-epithelial neoplasia (also known as Bowenoid papulosis and erythroplasia of Queyrat), vulvar carcinoma, penile carcinoma and anal and perianal carcinoma.[1–6] HPVs are also associated with oropharyngeal carcinoma and oesophageal carcinoma.[6,21]

HPV as a carcinogenic agent

Of the 120 types known, nearly 45 types of HPV have been found to be associated with cervical premalignant and malignant lesions.[21] The role of HPVs in the causation of cervical cancers has been established by the regular presence of HPV DNA in tumour biopsy specimens and by the identification of viral oncogene (E6 and E7) expression in the tumour material.[1–6,22] HPV produces keratinocyte immortality for which integration of the viral genome into the host genome is a prerequisite. The integration of HPV genome disrupts the E2 protein of the ORF leading to the loss of E2

repressing function.[1–6,22] This event permits free transactivation of E6 and E7 proteins and results in the increased expression of E6 and E7 oncoproteins. E6 and E7 proteins play an important role in increased cell proliferation and extended cell survival in HPV associated malignancies by altering the cell cycle regulatory factors.[22] When integration of the viral genome into the host cell genome takes place, key functions of tumour suppressor genes such as p53 and pRb are rendered useless.[1–6,22] This leads to abnormalities in apoptosis, DNA repair mechanisms, cell cycle regulation and finally to cellular immortalization, thus inducing and maintaining a malignant cell phenotype.[22]

In carcinogenesis of the cervix, interactions between HPV and environmental factors have been extensively studied. These environmental factors include biological agents, hormonal contraceptive use, nutrients and tobacco smoke.[23,24]

Of the biological agents, the role of herpes simplex virus (HSV-2) as a co-factor in HPV carcinogenesis has attracted considerable attention. However, epidemiological and laboratory studies are not consistent with regard to a possible interaction of HSV-2 in HPV carcinogenesis and have provided conflicting results for a possible association of HSV-2 with cervical cancer.[23] Other viruses studied in relation to HPV carcinogenesis include cytomegalovirus (CMV), human herpes virus (HHV), Epstein–Barr virus (EBV) and human immunodeficiency virus (HIV). These studies have not yet provided convincing evidence of a contributory role in HPV associated cervical cancer.[23]

Among other microbial agents, the possible role of *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae* and *Candida albicans* in cervical carcinogenesis have also been extensively studied. Epidemiological studies have demonstrated a consistent association between *C. trachomatis* and cervical cancer. However, other studies have suggested that *C. trachomatis* does not have a direct effect on host DNA or on the transcription of HPV genes but it may increase the risk for cervical cancer by its anti-apoptotic effects on cells.[23]

Studies conducted on the role of nutrients such as vitamins A, C and E, folate and zinc did not provide statistically significant evidence to suggest a contributory role of these nutrients in HPV associated cervical cancers.[23] Studies have suggested an association between hormonal contraceptives with formulations of oestrogen and progesterone and the risk for preneoplastic lesions of the uterine cervix.[24] Oestrogen and progesterone may mediate changes in the immune status of the cervical mucosa and have effects on the HPV expression.[24] Use of tobacco has been found to be associated with a significant increase in the risk for cervical cancer.[25]

HPV and the mouth

Oral transmission of HPV

HPV is known to contaminate the oral cavity of healthy individuals. The normal oral mucosa may act as a reservoir for new HPV infections and/or as a source of recurring HPV associated lesions. The prevalence of HPV in normal oral mucosa ranges from 0.6% to 81%.[26,27] The HPV detection rate in normal oral mucosa shows variation depending upon whether buccal scrapings, biopsies or mouthwash specimens are collected and which of the molecular detection methods is used. HPV-DNA has been detected in exfoliated oral squames from clinically healthy individuals.[28] HPV detection methods in use include immunoperoxidase, immunofluorescence, *in situ* hybridization, Southern blot, Dot blot, Reverse blot hybridization and polymerase chain reaction (PCR). PCR is considered to be of the highest sensitivity and can detect even a single copy of viral DNA per infected cell.[29] It is clear that the different molecular methods used in various studies contribute at least in part to disparities in the reported prevalence of HPV in tissues.

Multiple pathways for HPV transmission to the oral cavity can exist. These include sexual transmission, autoinfection and rarely through perinatal transmission of the neonate during its passage through an infected birth canal of the mother.[8,30,31] Oral sex is a well recognized mode of transmission of HPV to the oral cavity.[26,27] Oral HPV acquisition was found to be more positively associated with number of recent oral sex and open mouth kissing partners than with the number of vaginal sex partners.[26] Reports also indicate that men who have sex with men (MSM) have a high risk of developing oral HPV infection.[26] However, there is no evidence to suggest that the virus is transmitted from person to person through saliva.

HPV and oral lesions

Human papillomavirus presence in the oral mucosa appears to be closely associated with a range of benign papillomatous lesions. These include oral squamous papilloma, oral verruca vulgaris, oral codyloma accuminatum and focal epithelial hyperplasia. It is unclear whether normal oral epithelium has a similar HPV prevalence to these lesions. A brief review of these lesions follows.

HPV and oral squamous cell papilloma

Oral squamous papilloma is the common benign epithelial neoplasm of the oral cavity. Oral squamous papilloma is a painless lesion which can occur at any intraoral site but most commonly it is seen on the

tongue, lips, cheek mucosa and hard and soft palates.[32,34,35] Most papillomas are single. The wart-like lesion shows numerous projections and tends to be pedunculated. The papillary projections may be pointed and finger-like or rounded and cauliflower-like in appearance.[32,34,35] If excessive keratinization is present, the lesion appears white and less keratinized lesions are often raspberry-like and pink in colour. Squamous papillomas are usually single and less than 1 cm in size. Clinically, squamous papilloma is often indistinguishable from the common wart (verruca vulgaris) which is a common lesion found on the skin and occasionally on the keratinized regions of the oral mucosa such as the vermilion aspect of the lips, hard palate and gingivae.[32,34,35]

Oral squamous cell papilloma is caused by human papillomaviruses.[32,33] Viral particles closely resembling HPV were first reported in squamous papillomas in 1967.[34] The most prevalent HPV types associated with oral squamous papillomas are HPV 6 and 11.[35] Oral squamous papillomas are not known to turn into malignant lesions if left untreated. Surgical excision is the treatment of choice. Once surgically removed, oral squamous papillomas usually do not recur.

HPV and oral condyloma accuminatum

Condyloma accuminatum, also known as venereal wart is a sexually transmitted disease. Condyloma accuminatum is predominantly seen on the skin and mucosal surfaces of the anogenital tract.[36] Oral condyloma accuminatum lesions occur as a result of oral sex or from autoinoculation of the virus in adults.[37]

The presence of oral condyloma accuminatum in young children may also be due to sexual abuse.[38,39] Oral condylomas develop at the site of orogenital sexual contact.[37,40] Common oral sites include the tongue, gingiva, soft palate and lips. Lesions are multiple and confluent and generally larger than squamous papillomas.[41] They present as a broad based (sessile) pink or white mass with blunt projections producing a cauliflower-like or mulberry-like appearance.[41] Patients with genital condyloma have a high incidence of HPV induced oral condylomas with up to 50% of individuals with genital condylomas having oral condylomas.[40] Oral condylomas are also frequently encountered in HIV affected persons.[42] HPV types 6, 11 and 16 are found in oral condyloma lesions.[43,44] Cryotherapy, surgical excision, laser treatment and topical 5-fluorouracil are the treatment modalities available for oral condylomas.

HPV and focal epithelial hyperplasia (Heck's disease)

Focal epithelial hyperplasia (FEH), also known as Heck's disease, is a relatively rare disease of the oral mucosa. It is predominantly a childhood disease first described by Archard *et al*. in 1965 from observations of multiple soft painless papular or sessile raised lesions of the buccal mucosa in Navajo, Chavante Indian and Alaskan Eskimo children.[45] Though FEH was once thought to be exclusively confined to South American Indian children, several reports of cases of FEH have been published from other parts of the world in recent times.[46–48]

FEH commonly occurs in children but may occur in young adults. FEH has no gender predilection but genetic predisposition seems to be an important factor.[49] FEH lesions are multiple asymptomatic lesions of normal mucosal colour. They are well demarcated round to ovoid, flat lesions measuring 1–10 mm in diameter. Lesions are sessile. When clustered, these lesions present a cobblestone appearance. Any part of the mucosa may be involved but frequent sites in order of frequency include lower labial mucosa, buccal mucosa, labial commissures, upper labial mucosa, tongue, gingivae, alveolar mucosa and palatal mucosa.[50]

The aetiologic agent of FEH was first identified in 1983 and was designated as HPV 13.[51] HPV 32 was identified with the disease in 1987.[52]

Generally, FEH does not pose any diagnostic challenge. Since this is a contagious disease, history should include information on sharing of food and personal objects. Clinically, condyloma accuminatum lesions resemble FEH, but lesions of FEH are flatter and more numerous.[32–54] Lesions of FEH heal spontaneously. Therefore, treatment is not necessary except in cases of functional or aesthetic impairment. When treatment becomes necessary, available options include surgical excision, laser ablation, cryotherapy, cauterization, topical treatment with retinoic acids or interferon.[53]

HPV and verruca vulgaris

Verruca vulgaris is a skin wart that affects fingers, the back of hands and feet, face, eyelids and mucocutaneous surfaces of the genito-anal region.[32] Oral involvement is uncommon. Preferred oral sites include the labial mucosa of the lower lip and the vermilion border of lips. Oral lesions generally result from autoinoculation of the virus from lesions on the fingers. Lesions are painless and appear as sessile, papillomatous, exophytic hyperkeratotic lesions.[32,54] Verruca vulgaris lesions are predominantly seen in children. When oral lesions are found, a search for skin lesions should be carried out. Generally, oral lesions result from autoinoculation of the virus from lesions on the fingers. Verruca vulgaris is caused by HPV 2 and 4.[44] Oral verruca vulgaris lesions are treated with surgical removal. Recurrence is uncommon.

HPV and oral potentially malignant disorders

There is ample evidence available which suggests that a significant number of oral cancers are preceded by visible clinical changes that occur in the oral mucosa in the form of chronic white or red patches.[55,56] Some of these lesions and conditions carry malignant potential and until recently were listed as premalignant. At a WHO sponsored international workshop held in 2005, the expert panel recommended that the distinction between oral premalignant lesions and conditions be abandoned and that the term 'oral potentially malignant disorders' (OPMDs) be used.[57,58]

Based on the recommendations of the panel, oral leukoplakia, oral erythroplakia, oral proliferative verrucous leukoplakia, oral submucous fibrosis, oral lichen planus and actinic cheilitis have been grouped as OPMDs.[57,58] The global prevalence of OPMDs ranges from 1% to 5%.[59] However, wide geographical variation of OPMDs exists with much higher rates reported from South-East Asian countries pointing to differences in socio-demographic characteristics and type and pattern of tobacco use.[60] In recent investigations however a significant HPV detection rate was noted in some of the OPMDs.[61] Studies have reported prevalence rates of HPV association with OPMDs ranging from 0% to 85%.[62,63] In the following paragraphs, the current state of knowledge of the association of HPV with each of the oral potentially malignant disorders is reviewed.

HPV and oral leukoplakia

The term leukoplakia essentially means a white patch. Not all oral white patches are potentially malignant. A mucosal white patch (leukoplakia) that histologically exhibits a varying degree of epithelial dysplasia can be considered a potentially malignant lesion; 3–6% of 'dysplastic' white patches show malignant transformation.[64] Oral leukoplakia carrying malignant potential can present a varied clinical appearance. It is seen as a well demarcated white/grey keratotic patch which may appear flat, smooth, fissured, granular or nodular in appearance. Sometimes a red and white mixed plaque (called erythroleukoplakia or speckled leukoplakia) may be seen. Known aetiologic factors of oral leukoplakia include long-term use of tobacco and/or alcohol, chronic friction, electro-galvanic reaction caused by two dissimilar metallic restorative materials and ultraviolet radiation from chronic sun exposure. It should be noted that oral hairy leukoplakia (OHL) induced by Epstein–Barr virus as seen on the lateral tongue borders of HIV infected individuals is not a potentially malignant lesion and should not be confused with leukoplakias with malignant potential that are aetiologically associated with the risk factors mentioned above. In recent years HPV has received considerable attention as a risk factor for oral leukoplakia. HPV type 16 and 18 have been identified in leukoplakia lesions by several investigators.[65,66] In a meta analysis, Miller and Johnstone showed an association of HPV in 22% of oral leukoplakia lesions.[67] Analysing 90 oral leukoplakia cases, Campisi *et al.* studied exfoliated lesional cells by nested PCR and found HPV DNA in 25.5% of cases.[68]

HPV and proliferative verrucous leukoplakia

Proliferative verrucous leukoplakia (PVL) is a distinct form of oral leukoplakia.[69] Gingiva and alveolar ridges are the favoured sites of PVL. It is a slow growing hyperkeratotic lesion that tends to spread and become multifocal, and develops as a wart-like lesion over time.[69] PVL has a higher rate of malignant transformation.[69] PVL is of unknown aetiology. An association with HPV has been suggested by some investigators.[69,70] Available literature reveals a 0–89% range for the association of HPV with PVL.[69–71]

HPV and oral lichen planus

Lichen planus (LP) is a chronic mucocutaneous disorder which is immunologically mediated. Often it involves only the oral mucosa with white hyperkeratotic or red erosive lesion patterns. Oral lichen planus (OLP), particularly of the erosive variant has been considered as a potentially malignant disorder with less than 2% of OLP lesions showing malignant transformation over a period of 10 years.[72] Although considered to be an immunologically derived disorder, many aspects of its aetiopathogenesis are not yet clear. Among other factors, viral aetiology of LP has been proposed in recent years. Ostwald *et al.* reported the presence of HPV DNA in 15.4% of OLP lesions.[73]

HPV and oral squamous cell carcinoma

Head and neck cancers include cancers of the oral cavity, oropharynx, hypopharynx, larynx, sinonasal tract and nasopharynx. Collectively, they are the sixth most common types of cancer worldwide.[64,73] More than 90% of these cancers are squamous cell carcinomas of the mucous membranes of the mouth and oropharynx.[75] Current theory holds that oral carcinogenesis involves the interaction of risk factors such as age, gender, ethnicity, life style, genetic background and exposure to one or more carcinogenic factors.[75–77] Nearly 75% of oral cancers have been attributed to smoking and alcohol consumption.[64,75,78] However, 15–20% of head and neck cancers have no known tobacco or alcohol exposure.[79] Nevertheless, despite the recent evidence of declining rates of tobacco and alcohol associated oral cancers, the overall incidence of oropharyngeal cancers, particularly of the base of the tongue and tonsils, is increasing.[80,81] These findings reflect a possible role of

risk factors other than tobacco and alcohol in the causation of oropharyngeal cancer. In this context, HPVs have received considerable attention in recent years.[82,83] Oral infection with high risk HPV has been found to be associated with a significant increased risk of developing oropharyngeal cancer when adjusted for tobacco use and alcohol consumption.[84]

Data on HPVs association with oral cancer range from 0% to 100%.[85–87] The role of HPV in oral cancer is supported by findings of HPV in tumour tissues.[88] In a review of head and neck carcinoma samples, HPV was detected by PCR method in 34.5%; by *in situ* hybridization method in 15.8%; and by Southern blot method in 24.5% of cases.[89] In a multicentre case control study of cancer of the oral cavity and oropharynx carried out in nine countries (Italy, Spain, Northern Ireland, Poland, India, Cuba, Canada, Australia and Sudan), the investigators concluded that HPV appears to play an aetiologic role in many cancers of the oropharynx and possibly in a small subgroup of cancers of the oral cavity.[90] The group identified HPV 16 as the most common HPV type in these cancers.[90] In most HPV-related oral cancers, HPV oncogenes act synergistically with chemical carcinogens in alcohol, tobacco and betel quid resulting in malignant transformation of oral keratinocytes.[78] On the other hand, a small number of HPV-related oral cancers may result from HPV E6 and E7 activity in the absence of chemical carcinogens.[78,79] *In vitro* studies on squamous cell carcinoma cell lines showed HPV 16 DNA sequences suggesting that HPV may have a 'hit and run' function in oral carcinogenesis.[78] HPV has been identified aetiologically with cancers of the tonsils and base of the tongue.[91] It has also been observed that HPV-associated base of tongue-tonsillar squamous cell carcinomas are poorly differentiated, HPV 16 positive are radiosensitive and have a better prognosis.[91]

There is evidence to suggest that the risk factors for HPV positive head and neck cancers increases with increasing numbers of both oral and vaginal sexual partners, a history of genital warts and a younger age at first intercourse.[92,93] Studies also suggest that development of oropharyngeal cancer is associated with a high lifetime number of vaginal and oral sex partners.[94] A recent study has also found that the risk of developing an HPV-16 positive head and neck cancers increased with increasing numbers of oral sex partners, as well as with increased marijuana use.[95]

HPV and oral verrucous carcinoma

Oral verrucous carcinoma (OVC), also known as Ackerman's tumour, is a variant of oral squamous cell carcinoma. OVC presents as an exophytic, soft, fungating, painless, slow growing and locally aggressive tumour.[96] A strong aetiological association with tobacco and alcohol has been reported for the development of OVC. HPV DNA types 6, 11, 16 and 18 have also been shown to be associated with OVC by some investigators.[97,98] OVC responds well to surgical management but recurrences are common.

Prevention of HPV positive oral lesions

Early detection of HPV positive oral lesions

The early detection of any oral lesion that shows clinical characteristics of malignancy or carries malignant potential is important. Detection of such lesions can be carried out by combining HPV typing with exfoliative cytology. As chemical carcinogens in tobacco and alcohol appear to enhance HPV transforming activity, patients with positive oral cytology should be strongly advised to reduce or discontinue their use.[78] Patient education on risk factors for oral cancer and OPMDs, which among other things include oral HPV transmission, should also be a part of an oral cancer preventive strategy.

HPV vaccination programmes all over the world have been targeted primarily at females, but studies reveal that the vaccines also elicit a strong humoral immune response in males.[99,100] Commercial vaccines currently available are quadrivalent Gardasil® (Merk & Co, USA) and bivalent Cervarix® (GlaxoSmithKine Group of Companies, Australia). These vaccines prevent infection with HPV types 16, 18, 6 and 11, and are primarily designed for the prevention of cervical cancer and genital warts. They do not cure HPV infection or cervical cancer. Vaccines are recommended for females aged 9–25 who have not been exposed to HPV. It is possible that currently available HPV vaccines designed to prevent cervical cancers and genital warts will also contribute to the reduction in the incidence of HPV related oral cancers. Therapeutic HPV vaccines which are being developed for cervical cancer may also be of benefit in the management of HPV related oral cancer.

CONCLUSIONS

It is evident that our knowledge of the relationships between the HPV family of viruses and oral conditions is expanding. Of particular significance is the emerging evidence of a causal relationship between some cases of oral cancer and HPV-16. This is especially so for oral cancer cases occurring in the base of the tongue, tonsillar region and possibly for oral cancers occurring in (younger) patients where there is no history of exposure to the usual risk factors such as tobacco smoking and alcohol. From the dental practitioners' point of view, where appropriate, patient education with regard to oral transmission of HPV and its possible role in the causation of a range of oral lesions including oral cancer should be included in preventive strategies.

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