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內文：

1. Introduction:

- Worldwide human papillomavirus (HPV) infection is the most common sexually transmitted viral infection
- Based on their biological behavior, 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.
- Recent studies have shown that oral infection with human papilloma viruses is associated with a significant risk of developing oropharyngeal cancer and oral potentially malignant disorders (OP- MDs)

2. The human papilloma virus

- The human papilloma viruses belong to the Papilloma vaviridae family of viruses.
- They are capable of infecting mucosal and cutaneous(皮膚)epithelia in a species specific manner and inducing cellular proliferation.

3. Transmission of HPV infection

- HPVs are prevalent worldwide and infection with cutaneous HPV is everywhere
- The common mode of transmission and acquisition of HPV is by horizontal transmission consequent to sexual activity. Occasionally, HPV may be transmitted through vertical transmission (mother to child), fomites (污染物) and skin contact.
- Most HPV infections are transient and become undetectable by sensitive PCR assays within 1–2 years.¹³
- Viral DNA persists for a median (媒介) of approximately one year, and HR-HPV types persist longer than low risk types
- Ninety percent of HPV infections are usually cleared by the body within two

years. Persistence (持續) of HPV infection is essential for the development of cervical pre-cancerous lesions and cancer.

4. 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.
- 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. HPVs are also associated with oropharyngeal carcinoma and oesophageal(食道) carcinoma.

5. HPV as a carcinogenic agent

- The role of HPVs in the causation of cervical cancers has been established by the regular presence of HPV DNA in tumor biopsy specimens and by the identification of HPV viral oncogene (E6 and E7) expression in the tumor material.
- HPV produces keratinocyte immortality for which integration of the viral genome into the host genome is a pre-requisite(首要條件)
- E6 and E7 proteins play an important role in increased cell proliferation (增生) and extended cell survival in HPV associated malignancies (altering the cell cycle regulatory factors) .
- In carcinogenesis (致癌機轉) of the cervix, interactions between HPV and environmental factors have been extensively studied. These environmental factors include biological agents (HSV) , hormonal contraceptive use, nutrients and tobacco smoke.
- Studies have suggested an association between hormonal contraceptives (避孕藥) with formulations of estrogen (雌激素) and progesterone (黃體激素) and the risk for pre-neoplastic (癌前) lesions of the uterine cervix.

6. Oral transmission of HPV

- 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%. The HPV detection rate in normal oral mucosa shows variation depending upon whether buccal scrapings (刮下來碎屑), biopsies or mouthwash specimens are collected and which of the molecular detection methods is used.

- HPV detection methods in use include immunoperoxidase(免疫過氧化酶), immunofluorescence(免疫螢光酶), in situ hybridization(原位配種), Southern blot, (南方點墨) Dot blot (打點法), Reverse blot hybridization and polymerase chain reaction (PCR) (聚合酶連鎖反應) .
- PCR is considered to be of the highest sensitivity and can detect even a single copy of viral DNA per infected cell.
- 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.
- 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.

7. HPV and oral lesions

- Human papilloma virus presence in the oral mucosa appears to be closely associated with a range of benign papillomatous lesions.
- These include oral squamous papilloma (口腔鱗狀上皮乳突瘤), oral verruca vulgaris (口尋常瘤), oral condyloma acuminatum (菜花) and focal epithelial hyperplasia (局部上皮增生) .
- HPV and oral squamous cell papilloma
- Oral squamous papilloma is the common benign epithelial neoplasm (瘤) 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.
- The wart-like (疣狀) lesion shows numerous projections and tends to be pedunculated (有梗的). The papillary projections may be finger-like or rounded and cauliflower-like in appearance.
- The most prevalent HPV types associated with oral squamous papillomas are HPV 6 and 11. 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 acuminatum
- Condyloma acuminatum is predominantly seen on the skin and mucosal surfaces of the anogenital tract. Oral condyloma acuminatum lesions occur as a result of oral sex or from autoinoculation (自體傳染) of the virus in adults.

- Lesions are multiple and confluent (融合) and generally larger than squamous papillomas. They present as a broad based (sessile) 無柄 pink or white mass with blunt projections producing a cauliflower-like or mulberry-like appearance.
- Oral condylomas are also frequently encountered in HIV affected persons. HPV types 6, 11 and 16 are found in oral condyloma lesions.
- Cryotherapy (冷凍療法), surgical excision, laser treatment and topical 5-fluorouracil (毒殺癌細胞) 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
 - FEH commonly occurs in children but may occur in young adults. FEH has no gender predilection but genetic predisposition (傾向) seems to be an important factor.
 - They are well demarcated round to ovoid, flat lesions measuring 1–10 mm in diameter. Lesions are sessile. (無柄) When clustered (聚集), 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, gingiva, alveolar mucosa and palatal mucosa
 - Clinically, condyloma accuminatum lesions resemble FEH, but lesions of FEH are flatter and more numerous. Lesions of FEH heal spontaneously
 - When treatment becomes necessary, available options include surgical excision, laser ablation, cryotherapy (冷凍), cauterization(燒灼), topical treatment with retinoic acids or interferon (干擾素).
- HPV and verruca vulgaris
 - Verruca vulgaris is a skin wart(疣) that affects fingers, the back of hands and feet, face, eyelids and muco- cutaneous surfaces of the genito-anal region.
 - Oral involvement is uncommon. Preferred oral sites include the labial mucosa of the lower lip and the vermilion border of lips. When oral lesions are found, a search for skin lesions should be carried out. Generally, oral lesions result from autoinoculation (自體感染) of the virus from lesions on the fingers.
 - Lesions are painless and appear as sessile (無柄), papillomatous, exophytic (外生性) hyperkeratosis (過度角化) lesions. Verruca vulgaris lesions are predominantly seen in children
 - Oral verruca vulgaris lesions are treated with surgical removal. Recurrence is uncommon

8. HPV and oral potentially malignant disorders

- 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.
- Based on the recommendations of the panel, oral leukoplakia(白斑), oral erythroplakia, oral proliferative verrucous leukoplakia (增生性疣狀白斑), oral submucous fibrosis(粘膜下纖維化), oral lichen planus (扁平苔蘚)and actinic cheilitis (光化性嘴角炎) have been grouped as OPMDs.
- In recent investigations however a significant HPV detection rate was noted in some of the OPMDs. Studies have reported prevalence rates of HPV association with OPMDs ranging from 0% to 85%
- HPV and oral leukoplakia
 - A mucosal white patch (leukoplakia) that histologically exhibits a varying degree of epithelial dysplasia (表皮增生) can be considered a potentially malignant lesion
 - 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.
 - In recent years HPV has received considerable attention as a risk factor for oral leukoplakia. HPV type 16 and 18 has been identified in leukoplakia lesions by several investigators.
- HPV and proliferative verrucous leukoplakia
 - Proliferative verrucous leukoplakia (PVL) is a distinct form of oral leukoplakia. Gingiva and alveolar ridges are the favored 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. PVL has a higher rate of malignant transformation.
 - Available literature reveals a 0–89% range for the association of HPV with PVL.
- HPV and oral lichen planus
 - Often it involves only the oral mucosa with white hyperkeratotic or red erosive (

腐蝕性) lesion patterns.

- Although considered to be an immunologically derived disorder(免疫缺乏), many aspects of its aetiopathogenesis (致病原因) are not yet clear. Ostwald et al. reported the presence of HPV DNA in 15.4% of OLP lesions
- HPV and oral squamous cell carcinoma
- Oral infection with high risk HPV has been found to be associated with a significant increased risk of developing oropharyngeal cancer
- 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.
- A small number of HPV-related oral cancers may result from HPV E6 and E7 activity in the absence of chemical carcinogens.
- 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.
- HPV and oral verrucous carcinoma
- Oral verrucous carcinoma (OVC), also known as Ackerman's tumour, is a variant (變形) of oral squamous cell carcinoma.
- OVC presents as an exophytic, soft, fungating, painless, slow growing and locally aggressive tumour.
- HPV DNA types 6, 11, 16 and 18 have also been shown to be associated with OVC by some investigators. OVC responds well to surgical management but recurrences are common.

9. Early detection of HPV positive oral lesions

- As chemical carcinogens in tobacco and alcohol appear to enhance HPV transforming activity, patients should be strongly advised to reduce or discontinue their use
- 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
- These vaccines prevent infection with HPV types 16, 18, 6 and 11, and are primarily designed for the prevention of cervical cancer and genital wart
- 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.

10. Conclusion

- 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.
- 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.

題號	題目
1	下列何者不是與人類乳頭瘤病毒(human papillomavirus, HPV)有關的人類疾病? (A) 疣狀黃瘤(verruciform xanthoma) (B) 口腔鱗狀細胞乳突瘤(oral squamous cell papilloma) (C) 腳掌疣(verruca plantaris) (D) 尖形濕疣(condyloma acuminatum)
答案 (A)	出處：A此篇paper.口病課本P. 362~366
題號	題目
2	與鱗狀上皮癌(squamous cell carcinoma)最密切相關之致病因子為? (A) HPV type 6, 11 (B) HPV type16,18 (C) Herpes simplex virus (D) Enterovirus
答案 (B)	出處：此篇paper,口病課本P. 409~422