

# PHP-NUKE

## **Communication: Epidemiology and transmission of HPV infection: vaccination for H**

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Human papillomavirus (HPV) is commonly sexually transmitted. Oral and oropharyngeal HPV infections occur most frequently in persons who commence sexual activity at a young age, who have numerous sexual partners, and who practise orogenital sex. There is a definite association between nearly all squamous cell carcinomata of the uterine cervix and persistent high-risk HPV infections. The same association prevails in about 50% of cases of HPV-cytopositive oropharyngeal squamous cell carcinoma; but in the case of oral squamous cell carcinoma such an association can be demonstrated in only a few cases.

In the light of the irrefutable evidence of the rôle of HPV in the pathogenesis of premalignant and malignant diseases of the uterine cervix, prophylactic vaccination of young women against high-risk HPV genotypes before they start sexual activity is likely to reduce the overall incidence of HPV-associated squamous cell carcinoma, both in women and in men. In order to gain the full benefit of such a program of prophylactic HPV vaccination, young men should also be vaccinated.

In South Africa the prevalence of genital HPV infection and associated diseases including carcinoma is high, but it appears from the available published evidence that the frequency of oral HPV infection and related squamous cell carcinoma is low.

**Key words:** HPV, uterine cervical infection, oral mucosa, HPV transmission

## Introduction

Human papillomavirus (HPV) is usually sexually transmitted within the first few years of sexual activity<sup>1</sup>: it is one of the most common sexually transmitted diseases<sup>2</sup>, but can also be transmitted by close personal contact.<sup>3</sup> The prevalence of HPV infection is lower in the oral mucosa than in the genital mucosa.<sup>4,5</sup>

Normal-looking skin, oral and oropharyngeal mucosa, and genital mucosa are not infrequently infected with HPV, and the virus exists in a latent form or replicates in small numbers, is shielded from the immune system by reason of its intracellular location, and is asymptomatic.<sup>6,7</sup> In the skin, sunlight, immunosuppression (drug induced, HIV infection etc.) or incidental epithelial proliferative conditions can convert latent infection into high-level productive infection.<sup>6</sup> The cause of HPV-reactivation in oral, in oropharyngeal or in anogenital mucosae is unknown.

In the oral mucosa, symptomatic HPV infection manifests as benign oral warts: oral squamous cell papilloma, verruca vulgaris, condyloma acuminatum, and focal epithelial hyperplasia.<sup>8,9</sup> Although HPV is not infrequently detected in keratinocytes of potentially malignant oral lesions and of oral squamous cell carcinoma<sup>10</sup>, there is only a weak causal association between HPV infection and these lesions.<sup>11</sup> On the other hand, in a subset of subjects with HPV-cytopositive oropharyngeal squamous cell carcinoma, a causal relationship between high-risk HPV-16 and the malignancy has been established.<sup>11,12</sup> Although HPV infection is usually sexually transmitted, it is possible that HPV is acquired early in life, and may be part of the commensal viral microflora of the skin, anogenital mucosa, and perhaps of the oral and the oropharyngeal mucosae. Intermittent reactivation of this common latent intracellular viral resident resulting either in subclinical infection or in symptomatic infection is unusual, and is dependent on the host immune status and on other ill-defined factors.<sup>6</sup>

## HPV transmission

HPV is highly contagious. HPV infection is mainly transmitted sexually, is the most common sexually transmitted disease, and usually occurs within the first few years of sexual activity.<sup>1,2</sup> About two out of three persons having sex with an infected partner will become infected. The incubation period of HPV infection is thought to be 3 months.<sup>13</sup> Beginning sexual activity at a younger age and having multiple sexual partners are factors associated with increased frequencies of persistent HPV infection.<sup>14</sup>

Oral and oropharyngeal HPV infections are acquired by oro-ge-nital contact with an infected sexual partner or possibly by mouth-to-mouth contact, or by autoinoculation from another infected site.<sup>11,12</sup> Oropharyngeal infection may also be acquired by spread of virally infected squames from the mouth.<sup>9</sup>

Peri-natal HPV transmission from mother to foetus probably occurs when the foetus passes through the infected birth canal; and HPV infection ascending via the genital tract and crossing the placental barrier, can infect the foetus.<sup>3,15</sup>

## Epidemiology of HPV infection

### Genital HPV infection

The prevalence of asymptomatic genital HPV infection in women may reach 44%.<sup>16</sup> Infection with multiple HPV types is common.<sup>6</sup> The risk of new infection in women who are already infected with one or more HPV types is higher than in uninfected women.<sup>17</sup> The life-time risk for genital infection with one or more HPV types is around 80%<sup>13</sup>, but about 40% of cervical infections are cleared spontaneously within 1-2 years, probably by the immune system.<sup>18,19</sup> Only about 10% of HPV infected women will develop persistent uterine cervical infection which in a minority of cases will progress to premalignant and eventually to malignant lesions over a period of 12-15 years.<sup>16,18,19</sup>

The use of an oral contraceptive probably does not affect the risk of acquiring HPV infection, but women infected with high-risk HPV and using oral contraceptives have a four

times greater risk of developing genital squamous cell carcinoma (SCC) than women infected with high-risk HPV who do not use oral contraceptives.<sup>6</sup> Women with HPV infection who have other concurrent sexually transmitted diseases (e.g. *C. trachomatis* infection, herpes simplex virus-2 infection) have a greater risk of developing cervical SCC than do HPV positive women without any concurrent sexually transmitted diseases. This could be because high-risk HPV has an increased potential for carcinogenesis in the presence of any chronic cervical inflammation.<sup>6</sup>

The prevalence of genital HPV infection increases between the ages of 14 and 24, and thereafter declines until the age of 59. HPV infection is associated with a variety of benign, premalignant and malignant epithelial lesions.<sup>16</sup> Benign genital warts are common and occur most frequently in women aged 20 to 24 years.<sup>2</sup>

Anogenital HPV infection in men is as common as it is in women, and most of the infections are asymptomatic. Genital warts in men are more common in the 25 to 29 year old age group, and a small but significant number of HPV infections in men will give rise to premalignancy and malignancy. As in women, HPV infection in men is positively correlated to high-risk sexual practices.<sup>2,13</sup>

There is a high rate of transmission of HPV infection from infected men to their sexual partners, contributing to the development of HPV-induced benign, premalignant and malignant genital lesions in women.<sup>2</sup> This 'male factor' not only is a major cause of HPV infection in women but may also influence the course of HPV-associated diseases in these women by continuous reinfection.<sup>6</sup>

In South Africa, the prevalence of cervical HPV infection and related diseases is high. In black women and in women of mixed-race (coloured) in the Western Cape Province, the overall prevalence of cervical HPV infection is 26%. Among women younger than 30 years of age the prevalence is about 42%; in women aged 45-49 years it is about 19%; and in all women with normal cervical cytology it is about 20%.<sup>20,21</sup>

HIV-seropositive subjects, both women and men, have a greater risk of persistent genital HPV-infection and related premalignant and malignant diseases than do HIV-seronegative subjects.<sup>22,23</sup> In South Africa, the prevalence of clinical HPV infection in HIV-seropositive women is between 80% and 97%.<sup>5,23</sup> In these HPV cervical infections, the frequency of detection of a high-risk HPV genotypes varies from 77% to 79%<sup>5,23</sup>; cervical infection with multiple HPV genotypes occurs in 78% to 93%<sup>5,23</sup>; and about 50% of HIV-seropositive women have cytological abnormalities as evident on Pap smear.<sup>5,24</sup>

### **Oral and oropharyngeal squamous cell carcinoma**

Epidemiological data on oral and oropharyngeal SCC varies considerably among different populations depending on their ethni-city and geographic locations.<sup>25</sup> Males are more frequently affected than females (male-to-female ratio is 3:1) and the median age at diagnosis is 60 to 65 years.<sup>26</sup> The 5-year overall survival rate for people with oropharyngeal SCC is 40%.<sup>25</sup>

Tobacco or alcohol or a combination of both are the most important risk factors, and about 80% of oral and oropharyngeal SCC are related to these factors. The cancer risk is positively correlated to the duration and amount of smoking, and tobacco and alcohol used concurrently are synergistic factors in carcinogenesis.<sup>25</sup>

Only a few people who smoke and drink, or do both, develop oral or oropharyngeal SCC. In the case of the majority who do not develop it, it is possible that as yet unknown protective factors exist. In the minority who develop cancer, the possibilities are either that the tobacco or the alcohol, singly or together, constitutes the aetiology; or there may be other co-factors such as oncogenic viruses, diet, persistent inflammatory processes and genetic or epigenetic predisposition which, acting synergistically with tobacco/alcohol, precipitate the malignancy. One should not lose sight of the fact that there are also persons who will develop the cancer who neither drink nor smoke nor have any other discoverable risk factors.<sup>12,27</sup>

Although the number of smokers in the western world has declined in recent decades, the

incidence and prevalence of oral SCC has remained unchanged and that of oropharyngeal SCC has actually increased. This is most probably owing to an increase in the prevalence of high-risk HPV oral and oropharyngeal infections associated with changes in conventional morality and in sexual mores.<sup>25</sup>

The reported rates of detection of HPV in oral and oropharyngeal SCC and in oral potentially malignant lesions range from 0% to 100%.<sup>11,12,27-33</sup> This extreme variation is owing to differences in geographic location, in ethnicity and in sample size of the subjects examined; and to differences in methods of tissue collection and methods of detection of HPV DNA.<sup>10,28,34-37</sup> Furthermore, in some reports SCC of the soft palate and of the base of the tongue are erroneously assigned to oral mucosa instead of to oropharyngeal mucosa.<sup>26,36</sup> In a systematic review of 60 studies including 5046 cases of SCC of the head and neck from 26 countries, Kreimer *et al* (2005) determined that the likelihood of HPV being detected in oropharyngeal SCC is 35.6% and in oral SCC is 23.5%. HPV-16 is the most frequently detected HPV type.<sup>34</sup> In a meta-analysis of data of 4580 specimens from 94 studies, Miller and Johnson (2001) found that the likelihood of HPV being detected in normal mucosa is 10%, in non-dysplastic leukoplakias is 20.2%, in dysplastic leukoplakia and other precancerous intra-epithelial oral lesions is 26.2%, and in oral SCC is 46.5%.<sup>10</sup> Taken together, these data suggest that HPV may play a rôle in the pathogenesis of some potentially malignant lesions of the oral and oropharyngeal regions and their progression to malignancy.<sup>11,36</sup>

The prevalence of HPV in oral SCC in North America and in Europe is similar (~16%) but is much greater in Asia (~33%), while the prevalence of oropharyngeal SCC it is higher in North America and in Asia (~47%) than in Europe (~28%).<sup>34</sup> In South Africa a low prevalence of HPV (0%-12%) in oral SCC has been reported.<sup>31-33,35</sup> This suggests that in South Africa HPV plays only a minor rôle in the aetiopathogenesis of oral SCC.<sup>33,35</sup> The mere presence of HPV DNA, even of high-risk HPV oncogenes in SCC of the mouth and the oropharynx is not proof of a causal relationship between the HPV and the malignancy. The virus may well have infected the established tumour or may have been present during, but may not have contributed to the development of the malignancy. On the other hand, absence of HPV DNA from a SCC does not negate a possible rôle of HPV in the initiation of the malignancy. After playing a part in the initial cell transformation, the HPV DNA may have been lost from the transformed cells.<sup>11,12,35,38-40</sup>

If the cancerous HPV-cytopositive cells show high viral loads (>1 copy per cell), express transcriptionally active E6/E7 mRNA, and demonstrate viral integration within the cellular genome the likelihood of a causal association between HPV and SCC is very high.<sup>11</sup> In oral SCC there is in fact only a weak causal association with HPV as is apparent from the low viral load, the infrequent transcription of high-risk HPV E6/E7 mRNA, and the infrequent viral integration in HPV-cytopositive oral premalignant lesions and oral SCC.<sup>41,42</sup>

On the other hand, HPV-16 can be causally associated with HPV-16 cytopositive oropharyngeal SCC in a subset of subjects who, in comparison to subjects with oral SCC mentioned in the previous paragraph, typically are younger, on average do not use as much tobacco or alcohol, have higher HPV-16 antibody titres, have a better rate of survival, and their cancerous HPV-cytopositive cells show high viral loads, express transcriptionally active mRNA, and demonstrate viral integration within the cellular genome.<sup>43-49</sup> Furthermore, subjects with oropharyngeal SCC caused by HPV have usually had a greater number of life-time sexual partners, have started sexual activity early, and have practised orogenital sex more often than subjects with HPV-cytonegative oropharyngeal SCC.<sup>43</sup> Although the prevalence of oral HPV infection and of HPV cytopositive oral SCC reportedly is low in black South Africans,<sup>5,31-33</sup> the prevalence of genital HPV infection is high.<sup>20,21,23,24</sup> It might be that the practice of orogenital sex is less common among rural black South Africans than among populations in western or westernized countries.

Supportive of this notion is the fact that only 20% of HIV-seropositive black women with genital HPV infection have concurrent oral HPV infection, and in only half of this 20% can the genital HPV genotypes be detected in the oral mucosa.<sup>5</sup>

### **HPV vaccination**

As acquisition of oral and oropharyngeal HPV infection and development of HPV-related diseases are associated with high-risk sexual activity<sup>43,48-51</sup>, and perhaps more specifically with orogenital sexual practices, the encouragement of responsible sexual behaviour may promote a decrease in the prevalence of persistent HPV infection.<sup>12</sup>

Decreasing the frequency of HPV infection can be achieved by education aimed at delaying the commencement of sexual activity, at having fewer sexual partners, at promoting the use of condoms and at acceptance of prophylactic HPV vaccination, preferably before the commencement of sexual activity.<sup>14</sup>

Although the increased use of condoms has brought about a decrease in the prevalence of persistent cervical HPV infection in recent years, the increase in orogenital sexual practices among adolescents and young adults in North America, and probably in other westernized populations, may be the cause of the increase in the prevalence of HPV-associated oral and oropharyngeal infections and oropharyngeal HPV-related malignancies.<sup>50</sup>

Prophylactic vaccines against HPV infection are synthetic DNA-free, virus-like particles (VLPs), with microstructural similarities to natural HPV. The HPV VLPs generate a high-titre of neutralizing antibody against HPV.<sup>52,53</sup> HPV VLPs induce seroconversion in about 99% of vaccinated subjects.<sup>17</sup> The seroconversion is HPV type-specific, develops rapidly, and the antibodies persist for about 5 years.<sup>14</sup>

In contrast, serological responses to natural HPV 16/18 infections as identified by capsid specific antibodies occur in only about 50% of subjects with HPV 16/18 infections and develop slowly over about 6 months.<sup>6</sup>

Results of clinical trials have demonstrated that the synthetic quadrivalent HPV-6/11/16/18 L1 vaccine is safe, is highly immunogenic and is effective against infection with the corresponding HPV types. For optimum protection the vaccine must be given in 3 doses over a period of 6 months. Vaccination of women aged 15 to 26 years who have not previously been infected with HPV 6/11/16/18 imparts substantial protection against infection with these viruses and against diseases that they cause.<sup>54</sup> The quadrivalent vaccine has an efficacy of 98% in preventing HPV-16 or HPV-18 related high-grade cervical intraepithelial neoplasia.<sup>17</sup> However, in vaccinated women some of whom had and some of whom had not already been infected with HPV 16/18 at the time of vaccination with the quadrivalent HPV-6/11/16/18, the quadrivalent vaccine had an efficacy of 44% only.<sup>17</sup>

Therefore it is clear that the vaccine is most beneficial when it is administered to young women before they acquire cervical HPV infection, and therefore by implication, before the commencement of sexual activity.<sup>2,55</sup>

It is still to be seen if, as a result of the vaccination, a selective growth advantage will be conferred on other strains of HPV which may then emerge as oncogenic types.<sup>55,56</sup> It is also unclear what benefit the vaccine will have for women engaged in high-risk sexual activity or how the vaccine will influence the prevalence of premalignant lesions caused by HPV types not covered by the quadrivalent vaccine.<sup>55</sup>

In time, the effect of vaccination of young women should be a decrease in the prevalence of high-risk HPV infections and associated diseases, not only in the vaccinated female population but also in their male partners. A further significant benefit might be the prevention of HPV-associated oropharyngeal SCC that is more frequent in males.<sup>50</sup>

However, without vaccination of young men as well, the HPV vaccination of women would only gradually have an impact on the population as a whole. In order to have a maximal effect on the prevention of HPV infections in the public health context, young men should also be vaccinated before commencement of sexual activity.<sup>50</sup>

Mathematical models predict that implementation of HPV vaccination of the young

population, as a planned governmental and private health initiative will result in a substantial reduction of the prevalence of HPV 16/18 infections and associated diseases and in a reduction of the mortality of persons with HPV-associated cancer.<sup>14</sup>

### Comments

HPV vaccination would benefit all populations, but most of all those where the medical infrastructure is poor and where there is a high incidence of HPV-associated cancers.<sup>6</sup> In South Africa where HIV infection is pandemic and consequently owing to HIV-induced immunosuppression the prevalence of genital HPV infection and related premalignant and malignant diseases is high, the importance of the implementation of a large-scale program of HPV vaccination cannot be overemphasized.

However, because of the high cost of HPV vaccines, at present neither the medical aid companies nor the provincial departments of health can provide mass vaccination.

Furthermore, the vast majority of South Africans cannot afford a private service of HPV vaccination. Regrettably therefore, the South African population is likely to continue to be burdened with HPV infection and associated diseases.

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