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## HPV studies in sexual couples: prevalence, pathology and intervention

Hogewoning, C.J.A.

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## Summary

High-risk Human papillomavirus (hr-HPV) is involved in many anogenital cancers, cervical carcinoma and its precursor lesions being the most important, with hr HPV detected in virtual all cases. Infection with HPV is the most common sexually transmitted disease with a lifetime risk of 80% in women.

Although there are at least three pathways in the carcinogenesis of penile cancer, HPV is causal in 40% of the cases. Precursor lesions like Bowenoid papulosis, Bowens disease, erythroplasia of Querat and high-grade intraepithelial neoplasia (PIN 3) are all related to hrHPV and although they have separate histological and dermatological features they all belong to the same clinical entity. However the prevalence of these penile lesions is very low.

In the introduction, **chapter 1**, we present basic information about biological aspects and detection methods of HPV. We then review the role of hrHPV and genital carcinogenesis.

In the last part of the introduction arguments are presented regarding HPV infection in men and the evident role of the male sexual partner.

There is abundant epidemiological evidence of this role, male sexual partners being the vector and the reservoir of the virus. The wide spread of genital hrHPV infections in women and men and the very low prevalence of hrHPV related precursor of penile cancer suggested other HPV related penile lesions as carrier and vector. In order to clarify the biological course of male genital hrHPV infections we started penoscopic examinations of male sexual partners of women with CIN, in the knowledge that CIN lesions are in more than 90% hrHPV positive and thus expecting to find penile HPV related lesions too. Penoscopy was performed like colposcopy with application of an acetic acid solution of 3% before the procedure. Our penoscopic findings were classified after careful evaluation of photographs taken, with the help of an experienced dermatologist (TS) In the end we indentified flat penile lesions, papular lesions, pearly penile papules and condylomata acuminata. We concluded that flat penile lesions are the most present lesions during an HPV infection and that they are strongly HPV-related (60%) and producing HPV themselves. These findings, presented in **chapter 2** were in accordance with other investigators looking at the same category of men (Barasso, Hippelainen).

Pearly Penile Papules (PPP's), who in the beginning were thought to be related to HPV were studied separately. The results of this study are presented in **chapter 3**. We proved PPP's to be a normal physiological skin formation of the penile corona and sulcus, being present in 34% of the 238 men studied in our partner study.

Like the PPP's papular lesions had no association with HPV, while condylomata acuminata were related to low-risk HPV only.

Flat lesions are normally subclinical lesions, ie not to be seen on the penile skin in normal conditions. Only after application of acetic acid they show up, most of them located in the inner

part of the foreskin, the frenulum and around the coronal sulcus. They present themselves as well-demarcated, slightly elevated areas with punctuation or mosaic, in analogy with cervical acetowhite lesions, this aspect caused by vascular patterns of capillary loops. They are multifocal, ranging between 1 and 10, their size varying from 1 mm to >2 mm.

Although other penile lesions, caused by inflammation, traumatic micro-abrasions or chronic skin disease are also acetowhite after staining their appearance is normally different and punctuation absent.

In histology flat penile lesions show squamous hyperplasia or low-grade PIN. Although high-grade PIN is described (Barasso, Campion) this was exceptional in our study.

Penoscopic follow-up showed a benign course with a median regression of 12.4 months and a cumulative regression of >90% after 5 years. This regression time was HPV dependent, being much shorter in HPV negative men than in HPV positive ones.

In order to evaluate the clinical significance of flat penile lesions we studied the prevalence of HPV and HPV associated penile lesions in a male hospital population with non-STD complaints. This study is presented in **chapter 4**. Using the same penoscopic approach as in the male sexual partners of women with cervical intraepithelial neoplasia we found a prevalence of flat lesions of 17%, this is in accordance with earlier studies regarding men with partners without CIN. The lesions as described by us in these men were not only less prevalent but also smaller in size than in the men described in the partner study. We also found for HPV 16, the most prevalent HPV type, higher viral loads in the men of the partner study. The differences between these 2 groups of male sexual partners strongly suggest that flat penile lesions are related to the transmission of HPV and form a reservoir of hrHPV in men.

Recent studies suggest that not the presence of viral DNA per sé, but the amount of viral DNA in a cervical scraping (*i.e.* viral load) would be a potentially relevant determinant for risk assessment of  $\geq$ CIN 2. In **chapter 5** we present our study results regarding viral load and CIN. It has been demonstrated for HPV 16 infections that increased viral loads would be associated with an increased risk of  $\geq$ CIN 2 whereas reduced amounts of viral DNA reflects the absence of CIN lesions or viral clearance, which is associated with regression of CIN lesions. Viral load assessing seeming therefore helpful in the elucidation of the clinical/biological course of hrHPV related cervical lesions led us to evaluate the viral load assessments of high-risk types 16, 18, 31 and 33 in women with diverse CIN grades and we could demonstrate a relation between viral load numbers per cell and CIN grade for all types investigated. We used viral load assessments of the most common hrHPV types, *i.e.* HPV 16, 18, 31, and 33 in women with normal cytology participating in a population-based cervical screening trial (the POBASCAM study) to calculate clinical relevant thresholds to evaluate women with abnormal cytology having an hrHPV infection of one of these types in order to rule out the presence or the development of high grade CIN ( $\geq$ CIN2) In this way, in analogy with male sexual partners of women with and without CIN, we

were able to discern clinical relevant infections from infections that will not lead to high-grade CIN. As a consequence remaining hrHPV positive women with normal cytology having viral load values below the threshold values set in this study could be referred back to the screening program. This would lead to the exclusion of almost 25% of hrHPV positive women from follow-up, which results in a significant increase in the specificity and the positive predictive value of hrHPV testing for  $\geq$ CIN 3 in cervical screening programs.

We evaluated HPV type concordance in sexually active couples. Predominantly high-risk HPV types were found in persons of both sexes, but infections with multiple and non-high-risk HPV types were more common in men. HPV was detected in 73% of the penile scrapes, confirming the high prevalence in male sexual partners of women with CIN. In these men 80% of the HPV infections proved to be of an high-risk type. Of the HPV-positive couples, 57.8% of the men had the same HPV type as their partners; this rate was significantly higher than that expected by chance. HPV-concordant men had higher penile scrape viral loads than did the non-HPV-concordant men. For HPV type 16-positive women, higher cervical viral loads were predictive of presence of HPV type 16 in their sexual partners. In our view these data give substantial biological support for HPV transmission between sexual partners. As a consequence this led to the wish to evaluate the possible effectiveness of condom use as a block for the transmission of HPV, for which we used randomised use of condoms for at least three months for couples in the partner study (**chapter 6 and 7**).

With the help of this prospective randomised clinical trial we evaluated the transmission of HPV between partners and were able to demonstrate the influence of condom use on the clinical course of an HPV infection and related penile or cervical lesions in both sexual partners and so indirectly established facts concerning reinfection by the sexual partners and the consequences of it. We could demonstrate a significantly faster healing in time of flat penile lesions and clearance of HPV in the male partners as well as a faster regression of CIN 1 and CIN 2 and clearance of HPV in the female partners.

As a last step for the confirmation of our condom blocking viral transmission model we examined whether the effect of condom use on the regression of flat penile lesions depended on the presence of human papillomavirus (HPV) type concordance in sexual couples. We concluded that condom use was only effective blocking sexual HPV transmission in HPV concordant couples, but not in nonconcordant couples. This confirmed our hypothesis that condom use can prevent reinfection and development of new penile lesions in men who are susceptible to the same type as present in their female partner.

Male sexual behaviour is one of the most important determinants in the incidence of cervical carcinoma. Blocking the transmission of men infected with hrHPV to women would therefore lead to the decrease of the incidence of cervical carcinoma. The other way around would blocking the transmission of hrHPV from infected women to male sexual partners limit the

reservoir of hrHPV in men and thus the risks for other future female sexual partners and the risk for penile lesions, developing to penile (pre)cancer. In the discussion, **chapter 8**, all results are evaluated regarding the natural course of HPV and penile and cervical carcinogenesis.

The three issues, the relationship between HPV and the prevalence of penile lesions in men, the relationship between viral load and the presence of penile lesions in men and CIN lesions in women, and the effect of condom use on the regression of penile and cervical lesions are presented in relation to epidemiology, clinical aspects and virology. Intervention in relation to current knowledge regarding condom use, male circumcision and vaccination is also covered.