

HPV in men

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Summary

Purpose: To collect information about HPV in men and the (possible) correlation with HPV infection in women. **Methods:** Review of the literature. **Results:** An overview of HPV-related penile and anal malignancies in men and the risk factors of acquiring HPV. **Conclusion:** In men HPV is also partially responsible for anogenital malignancies. Although the prevalence of HPV-related malignancies in men is much lower than in women, it is useful to gain more knowledge. Especially knowing if men are really the HPV reservoir and transmitters for women can make a difference in deciding whether men should also be screened for HPV and if they are good candidates for vaccination.

Key words: HPV; Male; Penile lesions; Anal lesions; Screening.

Introduction

Human papilloma virus (HPV) infection is a sexually transmitted disease (STD) that mostly follows a self-limiting transient course for both sexes. Persisting infection causes clinical lesions, depending on the subtype of HPV. Low-risk types (6, 11) cause benign but bothersome lesions such as anogenital warts. High-risk types (16, 18, 31, 35, 45, 51, 52, 56, 58, 66) are associated with high-grade dysplasia and anogenital cancers. HPV infection is a necessary cofactor in causing cervical cancer, with the types 16 and 18 being responsible for more than 70% of the cervical cancers, killing 250,000 women a year worldwide. Because of this, research has mainly focused on women and screening methods, and treatments for women are well developed. Because of the low prevalence of HPV-related disease in men, the nature of the infection in men is less understood and a male screening/treatment organogram does not exist. More knowledge on HPV in men would be useful for women because men are believed to be the carriers and transmitters of the virus to women.

Overview

Men and HPV - clinical consequences

Anogenital HPV infection is found mostly in young men, with a peak incidence in their second and third decade. The incidence is higher in homosexual men [1, 2]. The incubating period varies from three weeks to nine months after sexual intercourse with an infected partner [3]. Of men who test negative for HPV at baseline, up to 13.8% screen positive during follow-up [4]. The risk of persisting HPV infection is associated with the detection of more than one HPV type at baseline screening [4]. Most common low-risk type is HPV 6; most common high-risk type is HPV 16. Penile cancer is mostly of squamous epithelial origin, differentiated in *in situ* carcinomas (Bowen disease and erythroplasia of Queyrat) and invasive car-

cinomas (squamous cell carcinoma (SCC) and verrucous carcinoma). HPV subtypes are found in patients with Bowen disease [5], erythroplasia of Queyrat [6], bowenoid papulosis [7, 8] and penile lichen sclerosus [9]. Bowenoid papulosis remains mostly a benign condition and will only rarely evolve to an invasive cancer. It is mostly found in young, circumcised men with a rather active sexual life [10]. Erythroplasia of Queyrat (10 to 30%) [11] can progress to invasive SCC. Ulceration of the original lesions is most of the time suggestive of malign evolution. Both are observed in elderly uncircumcised white men [11, 12]. Penile lichen sclerosus is a chronic inflammatory disorder of unknown origin that may lead to meatal stenosis or phimosis [9]. Non-healing wounds are the first sign of malignancy – a process that can take up to 34 years. The incidence of penile cancer is 1/100,000 with penile squamous cell carcinoma (SCC) representing 95%. High-risk HPVs are detected with polymerase chain reaction (PCR) in 17% to 82% of the cases. HPV 6 and 11 are mostly associated with verrucous carcinoma: invasive growth is mostly associated with HPV 16, 18 and 54 [7]. The prevalence of HPV in patients with anal intraepithelial neoplasia is up to 85% [13].

Men and HPV – risk factors

HPV-infection: The degree to which HPV infection plays a necessary causative role in men remains a matter of debate. Men with a history of anogenital warts have a 5- to 6-fold risk of penile SCC [14]. Some cases of penile SCC and many of verrucous carcinoma are negative for HPV-DNA testing. In the latter, when HPV is found it is most often low-risk HPV 6 and 11, showing that other cofactors must be involved [15]. Probably there are two pathways involved in penile carcinogenesis. One with sexual activity as a route for oncogenic HPV-transmission and the other as a result of synergistic effects of cofactors unrelated to HPV-infection in the patient or the patient's partner [15]. Patients with lichen sclerosus have a significantly higher rate of oncogenic high-risk HPV than a control group (17.4 vs 8.7%) [16]. When lichen sclerosus is associated with low-risk HPV infection, the development to cancer is probably unrelated to the HPV infection.

HPV transmission: Sexual transmission is the predominant mode of HPV acquisition. In men having anal receptive intercourse, the virus acts in the same way as in the cervix with the dentate line in the rectum being similar to the squamous colum-

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nar junction-zone of the cervix. This leads to a massive increase of anal cancer in homosexual men [13]. Additional risk factors are the same in both genders: early age at first sexual contact, a high lifetime number of sexual partners [17, 18], and being uncircumcised. Independent risk factors are anal intercourse with men [13] and having had more than three sexual partners [4].

The incidence (59%) of HPV-related lesions in the male sexual partners of women with cervical carcinoma [19] may feed the assumption that penile infections are a source of female reinfection. Bleeker *et al.* detected 22.7% of partners in a heterosexual relationship being infected with the same HPV type [19]. However, specific HPV concordance between sexual partners is not found in every study [17]. When ignoring type-specificity, both partners in 76% of couples are HPV-DNA positive [20].

HIV: In areas where HIV infection is widespread, the incidence of penile SCC has not increased [21]. The incidence of verrucous carcinoma did increase among HIV patients, and was probably related to immune suppression [22].

Condom use: Occasional use of condoms reduces the risk of HPV infection [4], and consistent use of condoms significantly reduces the risk [23]. The sites that have the highest chance of harboring the virus are covered when the condom is properly used. Other areas such as the proximal shaft, scrotum, and inguinal and anal area, can harbor HPV but will not be protected with the condom. Condom use will decrease the risk of low-risk HPV infection when used during anal sex [23].

Circumcision: The protective effect of circumcision has been proven for HIV-infection [24]. A recent meta-analysis study did not support the claim that this is also true for genital HPV infection [25]. Equally low HPV-rates are found in uncircumcised men who practice good hygiene. Penile SCC is only rare in men circumcised at birth; late or adult circumcision is ineffective [2].

Others: Cigarette smoking is without doubt a risk factor for acquiring HPV, independently of the presence of phimosis or genital infection [26].

Men and HPV-screening: Samples are taken by rotating a swab or brush, which may be dry or moist. By means of polymerase chain reaction (PCR), HPV-DNA can be amplified and typed. Sample adequacy is checked by evaluation of B-globin. Using a saline-moistened sterile Dacron swab after having rubbed the sampling site with a piece of emery paper was [27] superior in one study. In regions where continuity of medical care is not available, it would be useful if patients (women as well as men) could sample themselves. One study found that self-collection results in more adequate samples than physician-collected samples [28]. Anatomical sites, most expected to harbor HPV are the scrotum, penile shaft, glans, corona and the prepuce. Studies of the corona and glans show a prevalence up to 50% [20, 27-29]. The prevalence on the prepuce lies between 24-50% [20, 27, 28]. Studies sampling the penile shaft report a prevalence between 5.6 and 51.5% [27-29]. The distal urethra samples reveal 8.7 to 50% of HPV infections [20, 30, 31]. The anal region has up to 32.8% of HPV positive samples [46, 30]. Also the scrotum has up to 46.2% of HPV positive samples [20, 27-29, 31]. HPV has also been found in semen (41.3%) [20, 32] and in urine (< 7%) [27, 29, 30, 32]. Our own study, comparing urine with urethro-glandular swabs, shows that swabbing the urethra and glans is a highly reliable method to collect sufficient cells for HPV-typing [33].

Discussion

Regular screening programs are important to prevent HPV-related cancers, since HPV infection precedes the development of cancer by several years. The prevalence

of malign consequences of HPV infection in women and men in Western countries is rather low: 10/100,000 for cervical cancer, 1/100,000 for penile cancer and 1.5/100,000 for anal cancer. In the third world where there is a lack of good sexual education, standard screening programs and good medical care, the incidences are higher, except for anal cancer; respectively 44.1/100,000, 4.4/100,000, and 0.7/100,000 [34]. The best anatomical sites for HPV sampling in men are the glans, corona, prepuce and the shaft of the penis. The prepuce is probably the best single site for HPV detection. Screening and treatment of female patients is clear. Many governments are looking into if and how to include the vaccination in the routine vaccination program. HPV-vaccine is especially important for the third world; the highest reduction in mortality rate is to be expected from prevention, since screening and treatment are suboptimal. Should men be screened and vaccinated? At this time there is no current indication for testing men. First of all, HPV infection is very common, but finding HPV infection does not equal an increased risk of disease or cancer in these men or in their sexual partners. Furthermore, there is no standard test available and in addition, there is no therapy for eradicating the HPV infection. One considers that men will profit from the "herd"- effect, if all women should be vaccinated. The future will tell if maybe a subpopulation of men should be screened: men with promiscuous sexual behavior (sex workers), men with anal receptive intercourse, and male partners of women with CIN.

Conclusion

Since the last review in 2004 [35] research has focused more on men and HPV. The natural history of HPV in men is still mainly unknown. Although at this time there is a consensus that general screening of men is useless, especially because there is no real treatment, the number of reports on this subject is increasing.

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