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Genital Human Papillomavirus (HPV) Infections in Men as a Factor for the Development of Cervical Cancer

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Abstract

The prevalence of human papillomavirus (HPV) infection in males is comparable to females, although in men it is largely unknown. HPV infections may be connected with the development of carcinomas and other dermoepithelial changes such as intraepithelial neoplasia. Multidirectional studies have shown that chronic HPV infection is a necessary, though insufficient factor for the development of cervical cancer. Although men are regarded as the dominant vector of HPV transmission to their female sexual partners, they do not develop clinically significant HPV-related lesions and are usually asymptomatic during relatively short infections.

Analysis of data from a multicenter, clinical preventive trial was to estimate the incidence of type-specific genital infection among men and HPV transmission dynamics. The routine clinical examination included a peniscopy and detection of HPV DNA in smears using hybrid capture and in biopsy material using PCR.

It is necessary to establish prevention strategies for HPV infection in men whose female sexual partners have cervical cancer. Cervical cancer prevention strategies are likewise needed and should include the use of prophylactic HPV vaccines.

Keywords: human papillomavirus, genital infection, sexually transmitted disease, cervical cancer, HPV free

1. Introduction

Numerous infectious, inflammatory, and neoplastic diseases arise in male sexual organs. Infection of the genitalia with human papillomavirus (HPV) is worldwide and is currently

the most frequent sexually transmitted infection [1]. For unknown reasons, clinical changes are absent in most infected individuals as the virus remains in a latent phase until spontaneous elimination occurs by unknown mechanisms. On the other hand, immunosuppressed individuals frequently present with the clinical changes caused by HPV. Their clinical course is more severe, and their therapy is impeded since the immune system is compromised. Furthermore, genital HPV infections in women and subclinical changes of various degrees of cervical intraepithelial neoplasia (CIN 1–3) that can pave the way for the development of cervical cancer are relatively well understood. However, little is known about the subclinical infections in men that cause penile intraepithelial neoplasia (PIN). The significance of PIN is clear, since men who are carriers of HPV can be frequently undiscovered sources of infection for their female sexual partners [2, 3].

2. The risk of HPV infections

HPV is known for its characteristic heterogeneity, and the viral infection can run its course asymptomatically, subclinically, or symptomatically. Thanks to the polymerase chain reaction (PCR), over 200 types of HPV have been identified and subsequently classified according to changes induced, that is high risk (e.g., types 16, 18, 31, and 33) and low risk (e.g., 6 and 11) [2, 4]. Infection with HPV types 16 and 18 carries a large risk of precancerous and cancerous changes, while the appearance of genital warts caused by HPV types 6 and 11 is accompanied by a small risk of cancer development. Evaluation of risk and detection of HPV infection when clinical symptoms are absent is possible with a number of investigations, which include peniscopy, hybrid capture II (HC2), and PCR. The results of tested specimens, however, are variable and largely depend on anatomic sampling site and method of investigation [5, 6]. For instance, HPV DNA was found around the glans penis and external prepuce in 24% of individuals studied, while in 44% it was found on the inner (mucosal) prepuce where low-risk HPV types predominated. When material was collected using a brush, 70–92% of obtained samples were positive and 33% of which were high-risk types [6]. Furthermore, the results of a peniscopy only suggest the probability of HPV infection, since the presence of HPV DNA was not confirmed in 57% of positive peniscopy results [5, 7]. Nonetheless, peniscopy is necessary for gross identification of lesions, and the biopsy allows for histopathologic assessment of character to differentiate inflammatory changes (e.g., lichen sclerosus) from neoplastic changes of low- and high-grade PIN. PCR and HC2 examinations together with peniscopy allow for evaluation of the infection and defining its risk group. Also, positive findings upon acetowhitening, PCR, and HC2 are sufficient to establish diagnosis [7].

3. The risk of HPV infection transmission to partners depending on type of changes

3.1. Genital warts

HPV DNA is detected in approximately 5–11% of sexually active and healthy men aged 16–35 years [8]. The HPV types responsible for the development of genital warts (mainly types 6 and 11) are the predominant cause of infection. Other viral types are strongly associated with cancer of the cervix and are therefore termed “high-risk” types, and they include 16, 18, 31, 33, 39, 42, and 51–54 [9]. HPV viruses 16 and 18 are diagnosed most often in infections running subclinical courses in genital cancer patients. The risk of infecting sexual partners is estimated at 60%. However, although the peak of infection detection is in the age of 18–25 years, peak incidence of cervical cancer occurs around the fifth decade of life. Thus, the process of tumor progression is slow, and additional factors, so-called cocarcinogens, are necessary for the development of the cancer [10, 11].

Warts are most often multifocal. The following are three main types affecting the genital region:

1. genital warts (condyloma acuminata) are the most infectious lesions; they are pedunculated with a cauliflower-like appearance; depending on location and degree of irritation, they can be flesh-colored or various shades of red; and in uncircumcised men, they are localized on the inner (mucosal) prepuce, but can also be found on the glans penis, coronal sulcus, frenulum, external prepuce, shaft of penis, and scrotum [12].
2. papular, flesh-colored warts, and
3. flat warts—flattened papules of various colors such as red, pink on red, and brown [8, 13].

Warts may also occur at the urethral meatus or navicular fossa, where they are diagnosed in approximately 28% of patients [8]. In men who use condoms, warts are often localized in the suprapubic area. Interestingly, apart from prevention, condoms may accelerate the regression of flat warts on the penis [14]. In addition, they prevent reinfection and formation of new growths on the penis, but only when the same type of HPV occurs in partners. When different HPV types are present in the female partner, condoms do not protect against infection [15]. Condoms minimize the risk of so-called neoplasm transmission because they block the transmission of oncogenic HPV [16]. By minimizing the risk of penile cancer formation, the risk of cervical cancer is significantly limited. Moreover, with circumcision, the risk of penile cancer is decreased from 19.6 to 5.5% and subsequently the risk of cervical cancer formation in female sexual partners is also decreased [17, 18].

In a study of a large number of patients and a group of healthy controls, HPV DNA was found in 25% of men whose female partners had been diagnosed with CIN. HPV DNA was found in 6% of healthy women, but there was often discord with the results

in their partners. Consequently, it has been proposed that no investigations are required in the absence of clinical changes in the partner of a woman with diagnosed CIN. It is also emphasized that HPV DNA results be assessed diligently because HPV DNA was not found in 25% of positive acetowhitening and 57% of those diagnosed with peniscopy [19]. In addition, up to 30% of warts have been found to regress spontaneously over the course of 3 months owing to immune system functions dominated by a cell-mediated response [10].

The treatment of warts includes the use of podofilox in 0.5% gel or solution, dichloroacetic acid or trichloroacetic acid, 5% imiquimod cream, cryotherapy with liquid nitrogen, destruction of tissue with electrofulguration, and laser ablation [20].

3.2. Buschke-Lowenstein tumor

Large warts resembling tumors were first described in 1925 by Buschke and Lowenstein—the Buschke and Lowenstein tumor [21]. This rare wart variant is associated with HPV infection types 6 and 11 and is characterized by deep rooting into the stroma that results in damage to deep-lying tissues. Its aggressive growth produces tumors of large dimensions. Histopathologically, typically mild warts are found alternating in coexistence with foci of atypical epithelial cells or cells of highly differentiated squamous cell carcinoma. Patient history is positive for inflammation or ulceration and phimosis of the glans penis. The warts may ulcerate or cause fistulation. Diagnosis of this tumor may require multiple biopsies or imaging studies that include computed tomography (CT) and magnetic resonance imaging (MRI) [22].

3.3. Changes in female partners of men having intraepithelial neoplasia

Intraepithelial neoplasia may involve both male and female genitalia—penile intraepithelial neoplasia (PIN), cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), and vaginal intraepithelial neoplasia (VaIN), respectively. Additionally, the anus may be involved in either gender—anal intraepithelial neoplasia (AIN). The changes can have a character of bowenoid papulosis or Bowen's disease. Moreover, female sexual partners of men with diagnosed PIN can have changes corresponding to CIN, VIN, or VaIN in various degrees of advancement. They require long-term observation over several months because these changes often resolve spontaneously. Fortunately, neoplastic transformation of PIN is very rare [23]. Although the infection status of female partners of men with subclinical infection of the penis is not determined, it has been accepted that subclinical changes and latent infections do not require treatment, which would be ineffective in such cases.

3.4. Risk of bowenoid papulosis (BP) development in sexual partners

Bowenoid papulosis (BP), also described as Bowen's atypia, is an advanced phase of intraepithelial changes with features of PIN. These warts are generally numerous and tend to form clusters on the penile shaft and scrotum [22]. In young men, BP resolves spontaneously, but in the elderly it can maintain itself for years with a tendency to progression. Progression to squamous cell carcinoma is marked. BP characterizes itself with the occurrence of flat warts

(papulae) of skin color, but they may also be pink or sometimes brown. In men, it mainly occurs on the glans, while in women on the labia, groin, and around the anus. It is evoked by HPV 16, but other types (e.g., 18 and 31) may be culprits. The threat to infected women is the development of cervical cancer; for men, it is that they can infect their female partners and in doing so predispose them to cervical cancer [24]. Since the presence of BP is entwined with great risk of cancer development, treatment is considered crucial; excision of the change is most effective. Cryoablation with liquid nitrogen or laser ablation is also used. Recurrence should be taken into consideration since it has been estimated as high as 33% [20].

3.5. Erythroplasia of Queyrat

Erythroplasia of the glans penis is a form of carcinoma *in situ* occurring in uncircumcised men. Macroscopically, the change is erythematous, well demarcated, and slightly raised above the level of the skin on the glans penis or on the internal (mucosal) prepuce.

Histologically, it resembles Bowen's disease; it occurs on mucosal surfaces. The changes are singular or multiple and painless. Their surface tends to be smooth, scaly, or verrucous. The most frequent patient complaints are itching and bleeding with difficulties in retracting the prepuce. Diagnosis is made on the basis of biopsy specimen evaluation. Transformation of erythroplasia into penile squamous cell carcinoma occurs in 10–33% of patients [25]. Treatment of choice is surgical excision of the lesions.

3.6. Bowen's disease

Bowen's disease is most often observed as a solitary focus that is demarcated, flat, and reddish in color. Histopathological assessment reveals a squamous cell carcinoma *in situ* (corresponding to changes of PIN 3 and VIN 3). The disease is mainly caused by HPV 16 and 18, but sometimes also by HPV 31, 33, 45, and other oncogenic types. It occurs less often in women, growing slowly over years though it does not resolve spontaneously. The possibility of progression to invasive cancer should be considered when induration of the base, ulceration, or bleeding occurs, or the lesions increase in size. Changes on the vulva classified as intraepithelial neoplasia VIN 1–3 occur particularly in young women. The possible risk of progression of VIN3 to invasive cancer should be considered during therapy [22, 26]. In men who are partners of women with CIN 1–3 or VIN 1–3, changes consistent with PIN 1–3 are relatively frequent (up to 40%) in comparison with partners of women with genital warts (approximately 5%) [22]. Advanced changes corresponding to PIN 3 are diagnosed more often in older men in comparison with PIN 1–2. Clinical observations show that BP occurs more often than Bowen's disease in younger men [22].

3.7. Penile cancer

Penile cancer is not analogous to cervical cancer. While the detection of HPV DNA approaches 100% in cervical cancer cases, it is found in approximately 40% of penile cancer cases. Differences in frequency of finding HPV DNA (50–70%) exist and it depends on the type of cancer. HPV DNA is diagnosed most often in early premalignant changes corresponding to PIN 3,

and in warts undergoing malignant transformation. For female sexual partners, infectivity is greater in cases with PIN 2 and 3 than in those with invasive cancers. The risk of infecting male partners of women with invasive cancer is not greater than when compared to women with CIN 2 [27].

Penile cancer is a rarely diagnosed neoplasm (<1% of neoplasms in men) occurring mainly in older individuals. In recent years, however, this cancer is being diagnosed in younger men. It predominantly arises on preexisting PIN 3, but, in addition to infection with high-risk oncogenic HPV types, other factors play a significant role: tobacco smoking, poor hygiene, phimosis, and changes consistent with lichen sclerosus [28, 29]. When PIN lesions are sustained, circumcision should be performed for its protective effect.

Chronic infection with oncogenic HPV types, specifically 16 and 18, is the most significant factor favoring penile cancer. Depending on the method used, HPV DNA is found in up to 90% of penile cancer in such cases. The risk of developing cervical cancer is increased in female partners of men having penile cancer [30]. As in women, an association between lichen sclerosus and cancer of genital organs has also been described in men [29, 31]. In one study, it was shown that neoplastic changes of the penis occur in approximately 8% of men with lichen sclerosus localized there for 10–23 years [32]. In subsequent studies, it was concluded that lesions consistent with lichen sclerosus coexisted or preceded penile squamous cell carcinoma in eight of 20 cases [33]. The etiopathogenesis of lichen sclerosus is unknown, but genetic, immunologic, infectious (bacteria such as *Borrelia*), or environmental factors may be possible. The disease is chronic in character. An association between lichen sclerosus and squamous cell carcinoma, which is diagnosed in 6% of patients with lesions on the labia, exists in women. Lichen sclerosus is an inflammatory disease in which involved tissues are affected by atrophic changes and indurations. Secondary phimosis or induration of the urethral meatus may be observed in men [31, 33]. In a study of 86 uncircumcised men affected by lichen sclerosus (the disease most often concerns the uncircumcision of middle age), malignant changes occurred in five (6%) [32]. The presence of HPV 16 was found in PCR studies while another study found histologic features of lichen sclerosus in 10 of 20 patients with diagnosed penile squamous cell carcinoma [33]. A significant role is attributed to genital HPV types. Men affected by lichen sclerosus report to physicians due to itching and burning sensations, they have painful erections and difficulties retracting the prepuce, and also they complain of voiding symptoms. If lichenification involves the glans penis, there is often bleeding, ulceration, and fistulas, and hemorrhagic bullae may also occur. Progression of changes often expands to involve the glans penis and prepuce, as well as the frenulum. An indurated white ring around the rim of the prepuce is a significant finding. It can present with strangulation of the prepuce (paraphimosis) or phimosis [34, 35]. Genital HPV types are regarded as dominating in the development of cancer on preexisting lichen sclerosus [36]. It is possible that the long-term inflammation favors proliferation of epidermal cells and causes activation of the HPV life cycle. Another favoring factor is local immunosuppression caused by use of preparations containing potent corticosteroids [36]. Due to the risk of phimosis, especially in young men, circumcision is most often performed following diagnosis of lichen sclerosus.

Since HPV is a proliferating virus, it should be remembered that it multiplies only in proliferating cells. Therefore, an underlying inflammatory state or irritation in the genital region increases the proliferation of epidermis, which in this way supports infection and multiplication of the virus. Significantly more often, infections with genital HPV types occur in immunosuppressed patients, such as those undergoing treatment with cytostatic agents, those after organ transplant, and also women during pregnancy [37–39]. The clinical course of HPV infection in patients infected with HIV is very aggressive [40]. The changes caused by HPV are more extensive in such cases. The risk of progression of preneoplastic lesions into invasive cancer increases, and the changes occur rapidly. The risk of neoplasm development increases fivefold in patients after organ transplant [41, 42]. This is linked to HPV infection and impairment of T lymphocyte and natural killer (NK) cell function by the immunosuppressive preparations. T lymphocytes and NK cells are responsible for elimination of neoplastic cells in early oncogenesis [43].

4. Discussion

Most men infected with HPV are naive, either because they have no signs and symptoms or because the signs and symptoms are so mild that they persist unrecognized or ignored. Men with HPV infection are a frequent source of infection for their female sexual partners who are at great risk of death resulting from the development of cervical cancer. Identification of infected men may reduce transmission and subsequent preneoplastic and neoplastic changes; however, numerous factors reduce the plausibility of testing men. Unlike the consistent sampling site in women (the cervix), the sampling site in men varies from anus and perianal area to the scrotum up to the urethral meatus and into the navicular fossa. Incomplete anogenital sampling is a major factor contributing to the variability in HPV prevalence estimates [44]. This variability together with spontaneous elimination of the virus will pose difficulties for recommendations regarding duration of abstinence and frequency of follow-up. It has been suggested that for optimal detection, scrotal, perianal, or anal samples should be included together with the minimum protocol of penile shaft, glans penis, and coronal sulcus [44].

Surely, we may infer that the knowledge of the presence of HPV infection in the man may reduce the incidence of cervical cancer in woman by reducing transmission resulting from proper condom use or sexual abstinence until the virus is eradicated. However, how can the man be inspired to do comply with such recommendations and what findings can be used to determine when the man is HPV free and allowed to resume unrestricted coitus? For what duration and frequency should the man be tested to determine the continued presence of HPV after the initial positive result? When and for how long should he be tested after changing partners? This can be considered a serious issue since HPV can be deadly for the woman who contracts HPV from the unsuspecting man and develops cervical cancer as a result. Yearly PAP testing for women is already a standard of care in many countries, but what can be done in developing and underdeveloped countries? How can illiterate populations be educated about the risks of HPV infection and consequences, and also how they can avoid it? What

solutions can we implement in poor communities, whose women may not visit their gynecologists yearly, or ever? HPV is currently the leading sexually transmitted infection. In countries where resources are limited or women must travel hours or days by foot to visit their physician, the implications of late diagnosis may be deadly.

5. Conclusion

In summary, it must be stated that chronic immunosuppression favors HPV infection, allows for its self-preservation, and also favors activation of the viral life cycle, which is a primary factor triggering proliferative changes on genital organs. The therapeutic options for HPV-related changes are numerous (superficial preparations, cryotherapy, laser therapy, surgical excision) but are unfortunately burdened with recurrence and complications to a large degree. The changes caused by genital HPV types in the region of the sexual organs demand elimination of coexisting inflammatory states and treatment of sexual partners when indicated. It also appears that using a polyvalent HPV vaccine may prove effective in preventing benign and malignant changes, especially in groups of patients at increased risk [45]. Vaccination strategies, however, may be met with difficulties given geographic (e.g., access to facilities), cultural (e.g., core beliefs), and socio-demographic limitations (e.g., access to information) [46].

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