HPV infections in heterosexual couples: mechanisms and covariates of virus transmission

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Abstract

Sexual intercourse is regarded as the primary route of HPV transmission. Reported rates of the genotype-specific genital concordance of human papillomavirus (HPV) infection among heterosexual partners vary. Most studies have evaluated only male/female genital transmission but lately oral region has grown its interest because of rising trend of HPV-associated oropharyngeal cancer. Risk factors for type-specific concordance have been reported as an increasing number of younger couples, persistent HPV infection, higher frequency of sexual intercourse, rising number of spouse's lifetime sexual partners and sexual relations with prostitutes. However, the concordance of the same genital HPV genotype does not absolutely mean that it has been transmitted by the current partner. There are also other possible non-sexual transmission routes. The detected HPV infection may also be a reactivation of a previous infection. The high complexity of HPV transmission dynamics within an individual him/herself as well as within sexual couples is discussed with this article.

There are no reliable means to detect the first human papillomavirus (HPV) infection. The challenge grows with the fact that most HPV infections are asymptomatic and clear in months [1-3]. In addition, it is crucial to understand the complexity of the natural course of HPV infection, including also the plausible reactivation of the latent virus for example by a mucosal trauma, for not to interpret an old infection as a new one (transmitted by a current partner). However, sexual intercourse is regarded as the primary route of HPV transmission at some point of life [4] and therefore studies of the marital/long-term sexual couples have been considered to best reveal the mechanisms and covariates of the HPV transmission of the couples.

HPV status and concordance in heterosexual couples

The median probability of transmission of HPV per sex act is 40% (range 5 – 100%) calculated by transmission model studies [4]. According to previous studies, genotype-specific concordance rates of HPV infection among sexual partners vary. Meta-analysis by Reiter and coworkers [1] showed genotype-specific concordance of α-HPV genotypes of HPV6, 11, 16 and 18 in 25.5% of the couples (30 studies, 2972 couples). Among these, type-specific concordance of at least one genotype was 63.2% (95% CI: 49.1%-75.3%). The reported concordance was greater than could be expected by chance. The concordance has been shown to be higher among female partners of men with HPV infections than among the male partners of the HPV infected women [5].

Since meta-analysis of Reiter et al. [1], 16 studies have been published of HPV concordance and/or transmission in heterosexual couples (Table 1). In addition to α – HPVs, first study has evaluated β and ϒ-HPV concordance [6]. Concordance of 0-87.5% has been reported in genital sites when 6-37 different genotypes have been detected. In addition to genital concordance, oral mucosal concordance (either oral-genital or oral-oral) has been included in four studies. Study by Vogt et al., [7] reported oral HPV prevalence of 4%, one couple having oral-oral concordance. Beder Ribeiro et al., [8] consisting of 31 couples showed HPV DNA in 54.8% of the female oral samples and total of 16 couples were concordant in penis - vagina/ uterine cervix /oral region. Two studies reported oral sampling but did not disclose the results.

HPV transmission in heterosexual couples

Men have been suggested to be reservoirs of HPV to their female partners [1]. Transmission from man to woman or woman to man has been evaluated in six of these recent studies shown in Table 1. Three of the studies have detected that transmission of α-HPV is more likely from man to woman [4, 19, 20] and two from woman to man [16, 17]. The only study detecting β- and ϒ-HPV infection with six-week follow-up, so far, did not find difference in transmission between sexes [6]. Interestingly, in African settings there is evidence that auto-inoculation may play role between woman's genital and oral transmission [23]. This highlights the complexity

of HPV transmission dynamics within individual as well as sexual couples.

Risk factors for HPV concordance in heterosexual couples

Viral load of HPV infection has been studied in one concordance study. It shows that higher viral load of both high-risk and low-risk HPV infection was associated with the risk of new detection of a specific genotype in the other partner [21]. In addition to actual transmission studies, cervical HPV infection in men's female sexual partner has been found as a risk for man's genital HPV infection [24]. Other risk factors for type-specific concordance were 1) an increasing number of younger couples, 2) persistent HPV infection, 3) higher frequency of sexual intercourse, 4) rising number of spouse's lifetime sexual partners as well as 5) sexual relations with prostitutes [9, 14, 19, 25]. A recent systematic review evaluated the risk of cancer among spouses of patients with HPV-related cancer [25]. According to 13 case-reports or case-series and nine larger population based retrospective studies, a small trend of increased risk was found (1-3%). Higher concordance rates have also been related to short abstinence times before sampling [6, 16].

Sexual partners living in a stable relationship share the same environment and are exposed to one another's risky sexual behavior, should such occur. A study has implicated that a stable marital relationship protects against oral and genital HPV. Changing the sexual partner (OR=15.00, p=0.028) and marital status (especially divorce) (p=0.001) increases the risk of incident genital HPV infections. [26]

Study variations

There is great variation between studies and at present, conclusions should be made with caution. To start with, the definition of stable sexual relationship (a couple) differs from three months to marriage. Studies from African continent include both monogamous and polygamous marriages. Burcell and co-workers [4] studied especially new sexual relationships. Of the 179 disconcordant couples at baseline, 73 showed transmission during the follow-up. Studies differed also on whether the cohort consists of healthy individuals or with participants with known HPV infection/disease. The recent studies are shown in Table 1. Eleven studies included healthy participants, two healthy but with known HPV infection of other spouse and three studies with HPV-related mucosal benign or malignant changes of the partner. Additionally, most studies were cross-sectional studies with only one point sampling data while the others had generally follow-up from six weeks to only two years. Today, Finnish family HPV study has the longest follow-up of six years. Different from other studies, the female spouse in Finnish Family HPV study were pregnant [11]. Albeit the used sampling and HPV detection techniques vary in different studies, significance of the methods used is most likely low since the same HPV genotypes have been detected in different anatomical sites and documented in separate studies.

At this point, more studies and longer follow-up periods with multiple follow up - points are needed to elucidate the transmission of HPV between sexual couples.

Other transmission routes should be evaluated with the future investigations as well. Importantly, concordance of the same HPV genotype does not necessarily mean that it has been transmitted by the current partner. HPV DNA can be detected also during periods of abstinence from sexual intercourse [16]. This most likely reflects the natural course of HPV infection meaning reactivation of the latent infection [27]. In an ideal future study, the HPV status of the study participants should be known starting from the birth and at latest before any sexual contact. The study should also have long follow-up with multiple sampling from multiple anatomical sites.

Other possible transmission routes of HPV infection

The HPV transmission requires skin-skin, skin-mucosa or mucosa-mucosa contact. However, it does not necessarily require the contact to be sexual [28, 29]. HPV seropositivity is found already in children and teenagers, implicating that non-sexual transmission early in life may be a significant way of acquiring the infection [30, 31]. Vertical transmission from mother to neonate during and after pregnancy has been reported [32-34]. HPV is found already in the placenta [35-37]. Children of HPV-positive mothers had a 33% higher risk of becoming infected than children of HPV-negative mothers. The risk was 45% when only HR-HPV infection was considered. [33]. A recent meta-analysis calculated that the pooled percentage of antenatal vertical HPV transmission was 4.936% (95% CI 1.651-9.849) [38]. Thus, the literature implies that the mother is playing a significant role as the main transmitter

of HPV infection to her child. It seems that perinatal transmission occurs also in 15% of the children born by ceasarean section [39]. A HERITAGE study in Canada will provide better understanding of perinatal HPV [40]. The role of the father and other care-givers as a transmitter is not clear. Semen may be a vector for HPV transmission, as well [41-43].

As previously shortly mentioned, transmission of the HPV may be transmitted between anatomic sites of the same individual as autoinoculation. HPV infection in the anal region of women may serve as a reservoir for the uterine cervix and vice versa. [44] The vaginal discharge may spread to the perineum. HPV infection can also be transmitted via manual-to-genital or oral-to-genital routes (heteroinoculation) [45]. However, so far factors possibly related to auto/hetero-inoculation such as masturbation, fingernail biting and current genital warts have not been found as risk factors for HPV infection [46].

For the future

The above is a reflection of the fact that HPV concordance among couples is highly variable. More attention should be taken to the factors before sexual debut. There is growing evidence that many of us actually have the first HPV infection before starting our sexual life, maybe already perinatally. There is no doubt that sexual transmission is important, particularly for genital regions. The reported risk factors of sexual behavior have been highly consistent according to earlier studies. However, as

discussed above, the concordance of the same genital HPV genotype does not absolutely mean that it has been transmitted by the current partner. Moreover, from incident and prevalent infections there is need to understand which infections become persistent and what are the reasons that could explain the risk of the infection to persist. Fundamental issues might be linked with immune responses and diverse responses of the genders. Also, difference between the anatomical sites and their immunological respond is not yet completely understood, low-risk HPV infection may act differently between the sites [47] and may have impact on the natural course of HPV infection. Furthermore, the role other than α-HPV genotypes may influence the infection [6]. Fortunately, we already have interventions to prevent a part of HPV infections. As shown with this review, vaccinations are needed to protect both women and men.

Disclosure statement

The authors have no conflicts of interest to declare.

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