HPV infections and flat penile lesions of the penis in men who have sex with men

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ABSTRACT

Background: Flat penile lesions (FPL) in heterosexual men are thought to play a role in the transmission of HPV. We investigated the association between FPL and penile HPV, and explored determinants of FPL in men who have sex with men (MSM).

Methods: In 2015–2016, MSM were recruited based on HIV and penile HPV status in a previous cohort. MSM self-completed a questionnaire. Peniscopy was performed after application of acetic acid to visualize FPL. Penile physician-collected samples were tested for HPV-DNA using the highly sensitive SPF10-PCR DEIA/Lipa25 system. HPV viral load (VL) was determined using a quantitative type-specific (q)PCR targeting the L1-region. Presence of HPV and HIV, HPV VL and circumcision status were compared between MSM with and without FPL.

Results: We included 116 MSM, of whom 59/116 (51%) MSM were HIV-positive and 54/116 (47%) had FPL. A penile HPV infection was present in 31/54 (57%) MSM with FPL and 34/62 (55%) MSM without FPL (p = 0.8). There was no difference between MSM with and without FPL regarding presence of penile HPV infection, HPV VL, HIV status or circumcision status (p > 0.05 for all).

Conclusion: Among MSM in Amsterdam, we found no association between FPL and penile HPV, HPV VL, HIV status or circumcision status.

1. Introduction

Worldwide, human papillomavirus (HPV) is the most common sexually transmitted virus. HPV can infect epithelial cells of anogenital skin and mucosa [1]. The overall prevalence of any HPV infection of the penis is 45% among men in the United States [2]. Penile HPV infections are mostly transient and asymptomatic [3]. Persistence of some high-risk HPV (hrHPV) subtypes on the penis is associated with a wide range of diseases, from early neoplastic lesions to malignancies like penile cancers [4,5]. Approximately 47% of all penile cancers are attributed to an HPV infection, with HPV 16 and 18 being the most prevalent HPV types [4,6].

Penile HPV infections can be transmitted to the anogenital region or oral cavity of sexual partners via genital-genital or oral-genital contact. Flat penile lesions (FPL) are thought to be important in the transmission of HPV [7]. FPL are also known as flat condylomata, macules or acetowhite or subclinical lesions of the penis [8], and can be made visible by applying a staining solution (acetic acid). Several studies have investigated FPL in heterosexual men [7,9]. The prevalence of FPL ranged between 4% in male partners of women with normal cytology to 60% in male partners of women with cervical intra-epithelial neoplasia (CIN), suggesting an association between FPL and presence of HPV-related conditions in female partners [8,10,11]. Moreover, some studies suggested that presence of FPL is associated with higher HPV viral loads (VL) [8,10,12,13]. Based on these results, Bleeker et al. postulated that identification of FPL could help to distinguish a productive HPV infection from a potentially abortive HPV infection with a low HPV VL or HPV contamination by sex partner(s) when using ultra-sensitive HPV
2. Materials and methods

2.1. Study population

MSM were recruited from the HIV and HPV in MSM (H2M) cohort study. The H2M study recruited HIV-positive and HIV-negative MSM between July 2010 and July 2011 from three sites in Amsterdam, the Netherlands: the Amsterdam Cohort Studies (ACS) among MSM (Public Health Service), a sexually transmitted infection (STI) clinic (Public Health Service), and an infectious diseases outpatient clinic [14]. Data in the H2M study were collected at 6-month intervals during a follow-up period of 24 months, with a maximum of 5 visits per person. Results from the H2M study on the penile shaft HPV status were available, and were used to select MSM for the current study. MSM were selected so that about half of participants had had repeated detection of penile high-risk HPV (hrHPV) and half had had no detection of penile hrHPV at any of the five 6-monthly visits in the original cohort study. Within these two groups, we selected an equal proportion of HIV-positive and HIV-negative MSM for inclusion. A sample size calculation showed that 112 MSM should be included to demonstrate an association between FPL and penile HPV infections in MSM. We also aimed to determine whether presence of FPL is related to a high HPV viral load (VL), and we examined other possible determinants of FPL, such as HIV and circumcision status, in this group.

2.2. Study design

In 2015–2016, selected MSM were invited for study participation by a nurse during their visit to the ACS, or the outpatient clinic, or via telephone or e-mail. Each participant self-completed a computer provided questionnaire about smoking, drug use, sexual behavior, HPV vaccination status and history of STI. Penile samples for HPV testing were physician-obtained from two anatomical sites: (i) shaft and external foreskin tissue, and (ii) glans, coronal sulcus and inner blade of the foreskin. After training by an experienced investigator (MB), the study investigator (AKo) subsequently inspected the penile skin for presence of FPL and condylomata before and after the application of acetic acid solution 3% using a colposcope with a magnification factor ranging from 6 to 16 times (Carl Zeiss, Oberkochen, Germany). Flat penile lesions were defined as flat or slightly elevated, well demarcated, aceto-white lesions with a capillary pattern. Condylomata, or genital warts, were defined as exophytic lesions with an irregular surface. Findings were documented by photographs. In case of uncertainty about presence of penile lesions, findings were reviewed and discussed between two investigators (AKo, MB), blinded to the HPV results.

2.3. HPV testing and classification

Samples were tested for HPV DNA using the highly sensitive SPF10-PCR DEIA/LiPA25 system (version 1). If tested positive for HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and/or 59, we determined the HPV VL by using a previously described quantitative type-specific (q)PCR targeting the L1 region, optimized to approach SPF10-LiPA25 sensitivity levels [16,17]. HPV VLs were corrected for the number of human cells in each sample and expressed as genomes per human cell [16]. qPCRs were performed in 20 μl final volume using LightCycler TaqMan Master on the Roche LightCycler 480 platform (Roche Diagnostics, Almere, the Netherlands). The lower limit of detection varied for each HPV type, ranging from 200 to 920 copies/ml [16,17]. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 were defined as high-risk HPV (hrHPV) and types 6, 11, 34, 40, 42, 43, 44, 45, 53, 54, 66, 68/73, 70 and 74 as low-risk HPV (lhrHPV). HPV VL was categorized in three groups: (1) hrHPV and HPV 6/11 negative, (2) hrHPV and/or HPV 6/11 positive with an undetectable VL, and (3) hrHPV and/or HPV 6/11 positive with a detectable VL. This classification was made to distinguish between possible HPV deposition (group 2) and actual HPV infection (group 3).

2.4. Statistical analysis

HPV status, HPV VL, HIV status and circumcision status were compared between MSM with and without FPL using the Chi-square test for categorical data. Stratified analyses were performed to investigate differences between HIV positive and HIV negative MSM, and between circumcised and uncircumcised MSM. We also performed analyses to assess the association between HPV VL of the glans/foreskin and FPL on the glans/foreskin, and between HPV VL of the shaft and FPL on the shaft. A p-value < 0.05 was considered significant. Analyses were performed using STATA Intercooled 13.1 (STATA Corporation, College Station, Texas, USA).

2.5. Ethical approval and informed consent

The Medical Ethics Committee of the Amsterdam UMC, location Amsterdam Medical Center, the Netherlands, approved the current study (NL49748.018.14). Participation was voluntary and each participant gave informed written consent prior to study enrollment.

3. Results

We included 116 MSM, of whom 59 (51%) were HIV positive. Demographic, health and sexual behavior characteristics are shown in Table 1. Median age was 48 years (interquartile range (IQR) 43–56), and the median number of life-time sexual partners was 250 (IQR 100–850). The majority was not circumcised (98/116, 84%) and not vaccinated against HPV (101/116, 87%). Among HIV-positive MSM, 58/59 (98%) used combination antiretroviral therapy (cART) at time of peniscopy. Their median CD4 count was 660 (IQR 550–810) cells/μL, and 55/59 (93%) had an undetectable HIV viral load.

3.1. HPV status and viral load

In our study, 56 (48%) MSM tested positive for at least one HPV type on the shaft of the penis and 43 (37%) MSM tested HPV positive on the glans/foreskin (Table 2). Twenty-eight (24%) MSM had an hrHPV infection of the shaft, compared to 11 (9%) MSM who had an hrHPV infection of the glans/foreskin. The type-specific HPV VL was determined for 32/116 (28%) MSM who tested positive for one of the hrHPV types and/or HPV type 6 or 11. In 12/32 (38%) MSM no HPV VL was detected, and in 20/32 (63%) MSM at least one detectable HPV VL was found.
3.2. Penile lesions and HPV

Genital warts were detected in 6/116 (5%) MSM during peniscopy. FPL were seen in 54/116 (47%) participants, with predominantly FPL on the foreskin (42/116, 36%) and glans (19/116, 16%) (Table 1). Of MSM with FPL, 31/54 (57%) tested positive for at least one HPV type on the penis, compared to 34/62 (55%) MSM without FPL who tested positive for at least one penile HPV infection (p = 0.8) (Table 3). Among MSM with FPL, 16/54 (30%) had an hrHPV infection and 23/54 (43%) had a lrHPV infection. This did not significantly differ from MSM without FPL (p = 0.5 and p = 0.4, respectively). A detectable HPV VL was found in 10/54 (19%) MSM with FPL and in 10/62 (16%) MSM without FPL (p = 0.6). Among MSM with FPL, 27/54 (50%) were HPV-positive and 5/54 (9%) were circumcised, and among MSM without FPL, 32/62 (54%) were HPV-positive and 13/62 (21%) were circumcised (p = 0.9 and p = 0.09, respectively; Table 3).

When repeating the analysis among HPV-positive and HPV-negative MSM separately, and among circumcised and uncircumcised MSM separately, the results on the association between FPL and HPV status and VL remained similar (Supplementary Tables 1a and 1b). Our results remained also similar in additional analyses, in which we separately explored the association between FPL on the shaft and HPV status and VL of the shaft, and FPL on the glans/foreskin and HPV status and VL of the glans/foreskin (Supplementary Tables 2a and 2b).

4. Discussion

This is the first study investigating flat penile lesions and their association with penile HPV in MSM. Among 116 MSM in Amsterdam, the Netherlands, the prevalence of FPL was 47%. We found no association between FPL and penile HPV infections in these participants, either when studying any HPV, hrHPV, lrHPV or HPV types separately. An association remained absent when stratifying for location (shaft versus glans/foreskin), HIV status and circumcision status. HPV viral load was measured in MSM positive for HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and/or 59, and was not correlated with presence of FPL.

Earlier studies on FPL included only heterosexual men, with the exception of a study performed by Bleeker et al., in which 4/156 (3%) of the male participants reported having had sex with other men [10]. Genital lesions related to HPV in MSM were studied in detail in the HIM study, but they did not report on FPL [18,19]. The FPL prevalence among MSM in our study (47%) was comparable to the prevalence found in male sexual partners of women with an abnormal cervical smear or cervical intraepithelial neoplasia (ranging between 25% and 60%), and higher than the observed prevalence in men without a female partner with a known HPV infection or cervical abnormality (ranging between 4% and 37%) [7,9,11,20]. Circumcision was shown to be negatively associated with FPL in a cohort of young Kenyan heterosexual males and in Dutch men attending the outpatient
We also found that the prevalence of FPL in circumcised MSM was lower (28%) than that in uncircumcised men (49%); this was near statistical significance (p = 0.09), but power to assess this association was low due to the low number of circumcised MSM in our cohort (n = 18).

Several studies among heterosexual men reported an association between FPL and penile HPV, which contrasts with our findings in MSM. The lack of an association between FPL and penile HPV in MSM might be explained by a higher prevalence of erosive penile lesions in MSM. MSM in our study reported a median of 250 (IQR 100–850) male sexual partners during their lifetime, which is higher than the median lifetime sexual partners of most heterosexual males. Sexual techniques more often practiced by MSM, such as insertive anal sex, can result in erosive skin lesions, which can also appear as acetowhite lesions after application of acetic acid [7]. Such lesions are likely classified as FPL, and apparently are not always caused by HPV infection. Due to differences in sexual behavior and techniques for MSM and heterosexual men this may have occurred more often in our study among MSM.

The current study is subject to some limitations. First, diagnosing FPL is challenging and not always straightforward, as they may be confused with non-specific erosive skin lesions, as mentioned before. Second, the study size might be too limited for some analyses. For instance, only 18 of the MSM were circumcised, so the power to detect an association between FPL and circumcision was limited. Third, HPV was detected using the highly-sensitive SPF10-PCR DEIA/LiPA25 system, which might have led to detection of clinically irrelevant HPV infections or HPV deposition. To exclude this last possibility we measured the HPV viral load to distinguish between possible HPV deposition (no viral load detectable) and actual HPV infection (viral load quantifiable), and we could not show an association between FPL and presence of quantifiable VL. Data on recent sexual behavior (e.g. last sexual encounter) was not collected in our study, which also could have been used to distinguish between true HPV infection and deposition.

Notwithstanding the limitations, our results suggest that there is no association between FPL and penile HPV in MSM in Amsterdam, the Netherlands. This is in contrast with previous studies among dermatology clinic [9,10]. We also found that the prevalence of FPL in circumcised MSM was lower (28%) than that in uncircumcised men (49%); this was near statistical significance (p = 0.09), but power to assess this association was low due to the low number of circumcised MSM in our cohort (n = 18).

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Table 2
Penile HPV status and penile HPV viral load of 116 MSM at time of peniscopy, Amsterdam, 2015–2016.

|                         | Shaft (N = 116) | Glans/Foreskin (N = 116) |
|-------------------------|----------------|--------------------------|
|                         | n (%)          | median HPV VL (IQR)      | n (%)          | median HPV VL (IQR)      |
| HPV status and VL       |                |                          |                |                          |
| Any HPV                 | 56 (48%)       | 43 (37%)                 | 28 (24%)       | 11 (9%)                  |
| Any hrHPV               | 28 (24%)       | 2 (2%)                   | 31 (25%)       | 0 (0%)                   |
| Any lrHPV               | 44 (38%)       | 0 (0–3)                  | 2 (2%)         | 0 (0–4)                  |
| HPV 6                   | 9 (8%)         | 0 (0–0)                  | 2 (2%)         | 0 (0–2)                  |
| HPV 11                  | 2 (2%)         | 0 (0–2)                  | 2 (2%)         | 2 (0–4)                  |
| HPV 16                  | 6 (5%)         | 1 (0–13)                 | 2 (2%)         | 12.032 (20–24,043)       |
| HPV 18                  | 4 (3%)         | 4 (0–9)                  | 1 (1%)         | 0 (0–0)                  |
| HPV 31                  | 2 (2%)         | 0 (0–20)                 | 0 (0%)         | –                       |
| HPV 33                  | 3 (3%)         | 2783 (17-5549)           | 0 (0%)         | –                       |
| HPV 35                  | 2 (2%)         | 2 (0–15)                 | 2 (2%)         | 141 (47-234)            |
| HPV 51                  | 5 (5%)         | 2 (0–1)                  | 1 (1%)         | 0 (0–0)                  |
| HPV 52                  | 3 (3%)         | 0 (0–0)                  | 2 (2%)         | 1 (0–1)                  |
| HPV 56                  | 4 (3%)         | 0 (0–1)                  | 2 (2%)         | 141 (47-234)            |
| HPV 58                  | 1 (1%)         | 120 (120-120)            | 1 (1%)         | 0 (0–0)                  |
| HPV 59                  | 0 (0%)         | –                        | 0 (0%)         | –                       |

HPV, human papillomavirus; hrHPV, high-risk HPV; lrHPV, low-risk HPV; MSM, men who have sex with men; VL, viral load; IQR, interquartile range.

a  HPV VL is shown as median genomes per human cell.

b hrHPV include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59.

c lrHPV include types 6, 11, 34, 40, 42, 43, 44, 53, 54, 56, 68/73, 70 and 74.

Table 3
Associations between various HPV states of the penis and other variables, and flat penile lesions of the penis among 116 MSM, Amsterdam, 2015–2016.

|                                | No FPL | FPL | Total |
|--------------------------------|--------|-----|-------|
|                                | n = 62 | n = 54 | n = 116 | P   |
| Any HPV infection at peniscopy  |        |      |       |      |
| No                             | 28 (45%) | 23 (43%) | 51 (44%) | 0.781 |
| Yes                            | 34 (55%) | 31 (57%) | 65 (56%) |      |
| Any hrHPV infection at peniscopy|        |      |       |      |
| No                             | 47 (76%) | 38 (70%) | 85 (73%) |      |
| Yes                            | 15 (24%) | 16 (30%) | 31 (27%) | 0.509 |
| Any lrHPV infection at peniscopy|        |      |       |      |
| No                             | 31 (50%) | 31 (57%) | 62 (53%) | 0.425 |
| Yes                            | 31 (50%) | 25 (43%) | 56 (47%) |      |
| HPV viral load at peniscopy    |        |      |       |      |
| HPV\(^a\) negative            | 47 (76%) | 37 (69%) | 84 (72%) |      |
| HPV\(^a\) positive with undetectable HPV VL | 5 (8%) | 7 (13%) | 12 (10%) |      |
| HPV\(^a\) positive with detectable HPV VL | 10 (16%) | 10 (19%) | 20 (17%) | 0.614 |
| HIV status                     |        |      |       |      |
| Negative                       | 30 (53%) | 27 (50%) | 57 (49%) |      |
| Positive                       | 32 (54%) | 27 (50%) | 59 (51%) | 0.862 |
| Circumcision status\(^a\)      |        |      |       |      |
| Not circumcised                | 49 (79%) | 48 (91%) | 97 (84%) |      |
| Circumcised                    | 13 (21%) | 5 (9%) | 18 (16%) | 0.090 |

\(^a\) 1 missing value.

HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and/or 59.HPV, human papillomavirus; hrHPV, high-risk HPV; lrHPV, low-risk HPV; FPL, flat penile lesion; MSM, men who have sex with men; VL, viral load.
Author contributions

MS, CM and HV were responsible for the study design. AKo performed the peniscopy under supervision of MB and HV. AKi and SB were responsible for laboratory testing. WvB performed the statistical analysis under supervision of MS and wrote the first draft of the manuscript. All authors contributed to the interpretation of the results, writing the manuscript, and providing intellectual feedback. All authors have seen and approved the final submitted version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pvr.2019.100173.

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