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CLINICAL REPORT

Prevalence of Human Papillomavirus in Anal and Oral Sites Among Patients with Genital Warts

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Genital warts are caused by human papillomavirus (HPV). HPV is a leading cause of anogenital malignancies and a role of HPV in the aetiology of oro-pharyngeal cancers has been demonstrated. The frequency of oral HPV infection in patients with genital warts and the association between concomitant genital, anal and oral infection is unclear. A total of 201 men and women with genital wart-like lesions were recruited. Swab samples were obtained from the genital warts and the anal canal and an oral rinse was collected. Anal HPV was found in 46.2% and oral HPV in 10.4% of the participants. Concordance between anal and genital wart HPV types was 78.1%, while concordance between oral and genital wart types was 60.9%. A lower concordance of 21.7% was observed between anal and oral HPV types. Significantly more women than men had multiple HPV types and anal HPV. In conclusion, extra genital HPV is common in patients with genital warts. A gender inequality seems to exist. *Key words: human papillomavirus; genital warts; condyloma acuminata; oral HPV; anal HPV.*

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Genital warts are caused by human papillomavirus (HPV) which is the most common sexually transmitted infection (STI) (1–3). At least 40 HPV types can infect the genital mucosa (4) and they are classified as oncogenic (high-risk) or non-oncogenic (low-risk) HPV types, on the basis of their association with malignant genital lesions, in particular with cervical squamous cell carcinoma (5). HPV is a leading cause of anogenital malignancies, the incidence of anal cancer is particularly high among women with a history of cervical dysplasia and cervical cancer, HIV-positive individuals, men who have sex with men (MSM) and transplant recipients (6–8). Molecular and epidemiological studies have demonstrated a role for high-risk HPV, predominantly type 16, in the aetiology of oro-pharyngeal cancers (e. g. tonsillar carcinoma) (9, 10)

and that oral HPV infection, analogous to cervical infection, appears to be associated with sexual behaviour and immunosuppression (11–13). However, it is unclear to what extent our current knowledge on cervical HPV infection can be extrapolated to oral HPV infection. Likewise, it is unclear whether spread of HPV infection to the anal canal and oral cavity can develop from a genital HPV infection through self-inoculation, or whether it should be considered an independent event (14). Self-inoculation has been suggested in HPV-positive Bowen's disease of the digital nail bed (15). Interestingly, it has been reported in epidemiological studies from Sweden and Denmark, that the incidence of anal and oral cavity cancers is approximately 10- and 4-fold higher, respectively, in patients with a hospital record of genital warts (16, 17). Additionally, an American study showed that MSM who have had anal warts had a 50-fold higher risk of developing anal cancer (18). Thus, although genital warts are typically conceived as benign lesions with a low risk of progression to invasive cancer, they represent a clinical marker of risk of developing a malignant lesion, particularly vulvar cancer (16, 19). Part of the risk could be due to the presence of extra genital co-infection with high-risk HPV types.

The existence of a potential prevention of oral and anal HPV infections and associated carcinomas with HPV prophylactic vaccines makes this information even more important. Data concerning the HPV type distribution among patients with genital warts and the presence of extra genital co-infection are scarce. Therefore we studied the frequency of anal and oral HPV in patients with genital wart-like lesions and the genotypic concordance between the test sites.

MATERIAL AND METHODS

Patients

In the period from the 29th of September to the 22nd of December 2009 consecutive patients reporting at the STI clinic at Copenhagen University Hospital Bispebjerg were asked to participate. For patients to be included, they had to be at least 18 years of age and have external genital warts clinically diagnosed by the main investigator (KK). Patients who reported having at least one prior episode of genital warts were considered as having recurrent genital warts. All patients had to provide written informed consent and enrolment continued until a minimum of

200 patients was included. Upon completion of the examination, a study questionnaire was interviewer-administered. The Scientific Ethical Committee of the Capital Region approved sample collection (H-D-2009-077). All patients were offered access to their personal study results and subsequent counselling if needed.

Sample collection

Genital samples were obtained atraumatically from the most typical genital wart-like lesions using a cytobrush (Qiagen, Hilden, Germany). The brush was then placed in a sterile cryo tube containing 1 ml of isotonic NaCl solution. Anal samples were obtained by using a collection swab with a nylon fibre flocced tip (Micro rheologics s.r.l., Brescia, Italy) moistened with sterile isotonic NaCl solution. The swab was inserted \approx 2.0 cm into the anal canal and rotated 360° clockwise and counterclockwise three times. The swab was placed in a cryo tube containing 1.0 ml isotonic NaCl solution. An oral rinse was obtained by means of a 30-s oral rinse and gargle with 7 ml isotonic NaCl solution collected in a sterile 10 ml tube. All samples were stored and transported in batches at -20°C to the Department of Laboratory Medicine, Division of Medical Microbiology, Lund University, Skånes Universitetssjukhus, Malmö, Sweden.

Analysis

Preparation of samples. After centrifugation (5 min, $3,000 \times G$) the sample cell pellet was resuspended in 500 μl of the remaining saline and of this 200 μl was used for DNA extraction with MagNA Pure LC using the Total Nucleic Acid kit (Roche Diagnostics, Indianapolis, Indiana, USA). Purified nucleic acid was eluted in 100 μl of elution buffer. Five μl was used for HPV DNA amplification by PCR with modified GP5+/6+ (MGP) primers as previously described (20).

After amplification Luminex-based HPV genotyping was used to identify HPV types (21). The technique allows the detection of 39 HPV types of which 15 are high-risk HPV types, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82; and 5 probable high-risk types types 26, 53, 66, 67 and 69, and 19 low-risk HPV types, 6, 11, 30, 40, 42, 43, 54, 61, 62, 70, 74, 81, 83, 86, 87, 89, 90, 91, and 114. The Luminex assay also included 2 broadly reactive "universal" HPV probes and samples positive only for the "universal" probe were typed by DNA-sequencing. β -globin real-time PCR was included as a separate test of sample adequacy for PCR (22). All patients that were found positive for HPV DNA in the genital wart brush samples were included in the study, regardless of whether oral rinse or anal swab was β -globin or HPV DNA positive.

Statistics

Qualitative variables are given as number percentage and are compared using the 2-sided χ^2 test or Fisher's exact test, as appropriate. Quantitative data are expressed as mean \pm standard deviation (SD) or median (range), as appropriate. Data analysis was conducted using SAS statistical software (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA). p -values <0.05 were considered to be statistically significant.

RESULTS

In total 201 recruited patients, 11 had samples from the genital wart like lesions that were β -globin and HPV DNA PCR negative and 8 had samples that were

Table I. Characteristics of patients with external genital wart-like lesions

Characteristics	n (%)
Sex	
Male	124 (68.1)
Female	58 (31.9)
Age, years, median (range)	27 (18–85)
Sexual orientation	
Hetero	156 (85.7)
Men who have sex with men	24 (19.3) ^b
Women who have sex with women	2 (3.4) ^c
Lifetime sexual partners, mean \pm SD	29 \pm 43.0
Sexual practice, fellatio or cunnilingus	
Yes	177 (97.3)
No	5 (2.7)
Sexual practice, receptive anal sex	
Yes	50 (27.5)
No	129 (70.9)
Missing	3 (1.9)
Immunocompromised ^a	
Yes	11 (6.0)
No	171 (94.0)
Recurrent genital warts	
Yes	66 (36.3)
No	114 (62.6)
Missing	2 (1.1)
Location of lesions, men	
Penis	83 (66.9)
Urethral	13 (10.5)
Perianal	43 (34.7)
Anal	24 (19.4)
Other	2 (1.6)
Location of lesions, women	
Vulva	51 (87.9)
Urethral	0 (0.0)
Vaginal	4 (6.9)
Perianal	18 (31.0)
Anal	2 (3.4)

^aHuman immunodeficiency virus infection and pharmacological immunosuppression in e.g. transplant patients or autoimmune diseases. ^bPercentage of males. ^cPercentage of females.

β -globin PCR positive but negative for the tested genital HPV types. Thus 182 patients were included in the analysis. Patient characteristics are given in Table I. All of the included patients had β -globin positive oral rinse samples, but from 24 patients (13.2%) the anal sample was not β -globin positive. Almost all the patients (97.5%) had given oral sex to a partner from the opposite or the same sex (cunnilingus or fellatio), while 27.5% practiced receptive anal sex. In males the majority of lesions were penile and in women the majority was vulvar. Perianal lesions were observed in 34.1% of men and 31.0% of women. In MSM perianal warts were very common (75.0%). More men than women had anal warts. More than half of the men with anal warts were MSM (58.3%) however, 10 men reporting only having sex with women had anal warts (Table I).

HPV 6 was the most frequently detected HPV type in the genital wart like lesion (Table S1¹). The second most

¹<http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1718>

frequent type present in the genital wart was HPV 16. Single infection with HPV 16 in the genital wart was rare (2.7%). HPV 11 was found as single or co-infection in 7.1% of the genital warts making it the 9th most frequently encountered type. HPV 6 or 11 were found in 74.2% of the genital warts. HPV 18 was detected exclusively as a co-infection in the genital warts. Almost the same order of distribution was found in the anal canal. In the oral cavity there were almost identical occurrence of HPV 16 and of HPV 6, which were detected in 2.7% and 2.2% of the patients, respectively.

Co-infection was common in the genital wart and in the anal canal, where multiple HPV types were detected in 45.6% and 39.3% of the HPV positive patients, respectively. In the oral rinse multiple HPV types were found in 15.8% of the positive cases. The mean number of HPV types detected in patients with more than one HPV type was 3.4 in the genital lesion, 4.0 in the anal canal and 2.3 in the oral cavity.

Presence of HPV according to the low-risk and high-risk classification and site of infection are presented in Table II. In the genital wart-like lesion a high-risk type either as a single infection or in conjunction with other high and low-risk types was found in 47.2% of the patients, while single or multiple low-risk HPV type infections was found in the remaining 52.8%. These proportions varied significantly with sex; the presence of a single low-risk type was more common among men than among women (54.0% vs. 24.1%; $p < 0.001$). In men HPV was found in 33.1% of the anal samples, however there were large differences between MSM and men who have sex with women (MSW) (66.7% versus

25.0%). Almost all MSM (95.8%) reported practicing receptive anal intercourse while 2.0% of MSW reported practicing receptive anal intercourse. As observed in the genital warts significantly more women had high risk HPV in the anal canal.

Concordance between HPV types found in the anal canal and in the genital wart was 78.1%. Concordance between HPV types in the anal canal and oral cavity was 21.7%, which is significantly lower than the concordance of 60.9% between the HPV types found in the oral cavity and the genital wart ($p = 0.016$).

Patients with perianal warts had anal HPV more often than patients without perianal warts (74.6 vs. 31.1 %, $p < 0.001$). This was due to a higher incidence of anal HPV in men with perianal warts whereas the prevalence of anal HPV was unaffected by the presence of perianal warts in women (Table II). The prevalence of at least one high-risk HPV type in the anal sample in patients with perianal warts was 23.9% whereas it was 24.0% in patients without perianal warts. On the other hand 43.7% of patients with perianal warts had a single or multiple low-risk HPV types but no high-risk HPV types, while this was the case in 6.6% of patients without perianal warts. A concordance of 83.3% was observed between the genital and anal HPV types in the group with perianal warts while the concordance was 73.8%, in patients without perianal warts, this difference was not significant ($p = 0.15$).

DISCUSSION

Our study showed a higher prevalence of HPV DNA in anal (46.2%) than in oral (10.4%) sites among patients with genital wart-like lesions and that there is gender inequality in the prevalence of genital and anal high-risk HPV. To our knowledge no other studies on the incidence of extra genital HPV in both men and women with genital wart-like lesions have been published. There are, however, studies on the presence of HPV in the anal site in men and women without genital warts. These studies find a prevalence of 27–43% HPV positivity in women in the anal site, with the highest prevalence found in a high-risk population (23, 24). In general it seems that anal HPV is not as common in men as in women. The period prevalence defined as having an HPV infection either at enrollment or at the 6-month visit was 18.2% in MSW in "The HPV in Men Study" (25). However, in the same study the period prevalence in MSM was several folds higher (62.2%). The point prevalence of anal HPV in our study was 66.7% in MSM and 25.0% in MSW.

We found that in women the prevalence of anal HPV was unaffected by the presence of perianal warts and that high-risk HPV was much more common. Thus our results indicate a gender inequality in anal HPV. Other explanations are that high-risk HPV DNA is frequently

Table II. Human papillomavirus (HPV) infection according to the low-risk and high-risk classification and site of infection

Variable	Male n (%)	Female n (%)	Total n (%)	p^e
<i>Genital HPV types</i>				
Single low-risk	67 (54.0)	14 (24.1)	81 (44.5)	<0.001
Single high-risk	5 (4.0)	6 (10.3)	11 (6.0)	0.11
Multiple low-risk	11 (8.9)	4 (6.9)	15 (8.2)	0.78
Multiple incl. ≥ 1 high-risk type	41 (33.1)	34 (58.6)	75 (41.2)	0.001
<i>Extra genital HPV</i>				
Anal	41 (33.1)	43 (74.1)	84 (46.2)	<0.001
Low-risk only	26 (21.0)	11 (19.0)	37 (20.3)	0.84
≥ 1 high-risk type	15 (12.1)	32 (55.2)	47 (25.8)	<0.001
With perianal warts ^a	31 (72.1)	14 (77.8)	45 (73.8)	0.75
Without perianal warts ^b	10 (12.3)	29 (72.5)	39 (32.3)	<0.001
MSM and WSW ^c	16 (66.7)	0 (0.0)	16 (61.5)	0.14
Hetero ^d	25 (25.0)	43 (76.8)	68 (43.6)	<0.001
Oral	15 (12.1)	4 (6.9)	19 (10.4)	0.44
Low-risk only	5 (4.0)	2 (3.4)	7 (3.8)	1.0
≥ 1 high-risk type	10 (8.1)	2 (3.4)	12 (6.6)	0.34
No extra genital infection	76 (61.3)	14 (24.1)	90 (49.5)	<0.001

^aM=43 F=18. ^bM=81 F=40. ^cM=24 F=2. ^dM=100 F=56. ^eFisher's exact test. High-risk HPV types: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 73 and 82.

Low-risk HPV types: 6, 11, 30, 32, 40, 42, 43, 54, 61, 62, 70, 74, 81, 83, 86, 87, 89, 90, 91 and 114.

MSM: Men who have sex with men; WSW: Women who have sex with women.

encountered in women with cervical HPV infection (1, 26) and a lower sampling quality of genital lesions for men than for women (27).

The proportion of patients with anal HPV was significantly higher in patients with perianal lesions than in patients without perianal warts. Interestingly the prevalence of anal high-risk HPV was unaffected by the presence of anal or perianal warts. This indicates that the high-risk HPV found in the anal canal was not contamination from the surrounding area. On the other hand among patients with perianal warts there were significantly more that had only low-risk HPV. This must be due to the fact that the vast majority of visible lesions are caused by low-risk HPV.

The prevalence of HPV 6/11 in genital warts in our study was 74%. In previous studies the prevalence of HPV 6/11 was 71% in Swedish men and women with external genital warts (22), 84% in a French National Study of men and women with external genital warts (28), 86% among young women in the placebo arm of an HPV vaccine trail (29), 94% in men with anal and genital warts (30), and 54% in "The HPV in Men Study" (31). In general it seems that in studies using swab samples the prevalence of HPV 6/11 is lower and the proportion of oncogenic HPV is higher (28, 31) than in studies performed on biopsy samples (29, 30). Another speculative reason of our lower detection rate of HPV 6/11 is that the study was performed after the release of the quadrivalent HPV vaccine in Denmark. Based on numbers from the Danish prescription database the coverage of the HPV-vaccine for girls born in 1987–1991 was between 11 and 22% in 2009. By selection this may have resulted in the lower HPV 6/11 and higher HPV 42 detection rates observed in our study.

In the oral rinse samples HPV 16 was the most frequently detected HPV type. The prevalence of oral HPV was 12.1% in men and 6.9% in women. The pooled prevalence of oral HPV in women with cervical HPV infection estimated from a metanalysis was 18.1%, which is more than the 0–7.9% reported in women without known cervical HPV infection (32, 33). In another study on 100 women with cervical dysplasia an impressive 91.4% and 92.4% were found to have HPV in the anal canal and the oral cavity, respectively (34). Compared to these numbers the prevalence observed in our study is low and could indicate that the risk of oral HPV is not influenced by having genital warts in women. Investigation of the prevalence of oral HPV in the United States showed that among men and women aged 14 to 69 years the overall prevalence of oral HPV was 6.9% (33). The prevalence was higher among men than among women. Oral HPV was uncommon among sexually inexperienced individuals and increased significantly with number of sexual partners (33). Results from a Finnish study suggest that oral to oral HPV transmission exists (35). One spouse had a 10-fold risk of acquiring persistent oral HPV infection if the other spouse had persistent oral HPV infection (35). In

the same study oral sex was not associated with oral or genital HPV infection (35). Taken together, data indicate that oral to oral and sexual transmission are important routes of oral HPV transmission (36).

Potential limitations of the study include the possibility that exfoliated cells from the perianal region may have contaminated our anal specimens. We included possible immune-compromised patients which might have a different susceptibility and prevalence of HPV. No histology of the lesions was performed which may have resulted in that some of the lesions have been misdiagnosed, thus the isolated HPV may not have been the cause of the lesion. Additionally, some dysplastic lesions (penile, vulval and anal intraepithelial neoplasia) probably have been included, which may affect the finding of low-risk and high-risk HPV (37). The morphology of the lesions were not described in detail as it was not the purpose of the study, however acuminate lesions have been shown mainly to contain low-risk HPV types (HPV6/11), whereas macular lesions are overrepresented in persons with mixed or high-risk types (37). Two men may have misclassified themselves as MSW because they reported receptive anal intercourse. A high proportion of the anal samples were negative for β -globin, this may represent the presence of unknown inhibitors in the anal specimens. In other major studies more than 15% of samples were β -globin negative (38, 39). Only patients that indicated that they had oral symptoms were examined by inspection of the oral cavity, thus asymptomatic HPV-related lesions may have been missed and finally the detection of HPV is dependent on sampling procedure and assay sensitivity and specificity (40). In conclusion, in both men and women with genital wart-like lesions multiple HPV infections are often present and extra genital HPV is common. Both genital and anal high-risk HPV are more prevalent in women than in men, while in oral high-risk HPV could be more prevalent in men.

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