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INVESTIGATIVE REPORT

The Spectrum of Genital Human Papillomavirus Infection Among Men Attending a Swedish Sexually-transmitted Infections Clinic: Human Papillomavirus Typing and Clinical Presentation of Histopathologically Benign Lesions

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There have been a number of Swedish studies on human papillomavirus (HPV) typing in men, most of which have used less sensitive HPV-typing techniques. The present study included male patients with genital HPV-induced lesions planned for surgery. Samples were prepared for histopathology and PCR. HPV was detected in 233/253 (92%) and HPV 6 or 11 in 89% of the HPV-positive lesions. There were statistically significant differences regarding morphology ($p=0.002$), location ($p=0.000001$) and colour ($p=0.005$) of the lesions for low- vs. mixed or high-risk HPV types. For example, acuminate lesions were mostly found among men with low-risk HPV types, whereas macular lesions were over-represented among them with mixed or high-risk types. The HPV type distribution is similar to that in earlier studies, but we also found correlations with some clinical parameters. ***Key words: genital wart; condyloma; human papillomavirus; men; PCR.***

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Common locations for genital warts in non-circumcised men are the inner aspect of the foreskin, the frenulum and the sulcus coronarius, whereas circumcised men often have lesions on the penile shaft (1). The meatus is affected in up to 25% of male patients with genital warts (2). Warts in the anus are common in gay men, but perianal warts can also occur in heterosexual men (3).

In many countries human papillomavirus (HPV) vaccination has become part of the national school vaccination programme, and has been given to young girls (4, 5). For the vaccination programmes to result in health benefits in the population in terms of cancer and genital dysplasia attributable to HPV 16 and 18, will probably take many years or decades (6, 7). In contrast, a reduction in the prevalence of genital warts should be the first marker of vaccine efficacy if the quadrivalent vaccine is used, a phenomena already seen in Australia (8, 9).

Since it is not possible to culture HPV *in vitro*, other laboratory methods have to be used. Early studies were performed using immunohistochemistry. Subsequently, microbiological techniques, such as Southern blot hybridization, dot blot and *in situ* hybridization, were developed, which could be used to differentiate between various HPV types. These techniques have been replaced by PCR technique, by which the HPV detection rate is usually > 90% (10). There are principally 2 groups of HPV, low- and high-risk HPV types. The high-risk HPV types can cause genital dysplasia and cancer, whereas the low-risk types lead to genital warts (2). However, the occurrence of high-risk HPV types has also been reported in clinically benign lesions (11, 12).

A study of genital warts in men in Stockholm was performed in the 1980s. In that study (13) only HPV 6, 11, 16 and 18 were tested using *in situ* hybridization, and HPV 6 or 11 was found in 89% (81/91) of the HPV-positive samples and most commonly in acuminate lesions. Mild or moderate dysplasia was found in as many as 41% of the lesions.

The objective of this study was to elucidate the spectrum of HPV in Stockholm and whether it has changed since the 1980s. The study also included both HPV typing and histopathology to characterize the lesions with regard to morphology, colour and location and their HPV-type distribution.

MATERIALS AND METHODS

Patients

Male patients attending the STI clinic at Karolinska Hospital between 2004 and 2007 with clinical genital HPV infection planned for surgical treatment were invited to participate in the study. Diathermy was the surgical method used for all patients. The men were mainly seen by one doctor (AW). Patient files were retrospectively evaluated until May 2009. All men exhibited multiple lesions; those with solitary lesions were excluded. Two clinically identical lesions from the same genital site were collected with punch biopsy or scissor excision. One sample was

placed in formalin for routine histopathological preparation and evaluation, and the other was frozen at –70°C for PCR analysis. The macroscopic morphology of the lesions was classified into acuminate, papular, macular and seborrhoeic keratosis-like. Colour and location were also recorded. Anamnestic data on previous therapy, how long the lesions had been present, and whether the patients had had genital symptoms, such as itching, redness and dyspareunia, was recorded. HIV tests were offered and subjects were asked about sexual orientation. Circumcision status was noted.

Histopathological evaluation

Biopsies were prepared according to the routine at the histopathological laboratory and stained with haematoxylin-eosin. The lesions were categorized as benign or as dysplastic (penile intraepithelial neoplasia; PIN). HPV-induced lesions have hyperkeratotic and parakeratotic surface and coarse keratohyalin granules. The epidermis is acanthotic and shows some papillomatosis. Superficial vacuolated keratinocytes (koilocytes) are characteristic, showing perinuclear vacuolization and hyperchromatic round nuclei (14–16). The histopathological report is based on the overall picture where all criteria are rarely present. Several sections were made for each biopsy, since some criteria might otherwise be missed.

DNA extraction and HPV genotyping

Frozen biopsy samples were cut into small pieces and DNA extracted with the high-salt method (17). The samples were lysed with proteinase K at 37°C overnight. The proteins were then precipitated with saturated 6M NaCl, followed by centrifugation. After centrifugation, the supernatant was removed and DNA was precipitated with absolute ethanol. The DNA pellet was dissolved in sterile water and kept frozen at –20°C.

HPV DNA was detected with nested PCR using MY09/MY11 as external primers and GP05+bio-GP06+ as internal primers, targeting the L1 open-reading frame of the HPV genome. PCR was carried out in a 50 µl reaction containing PCR buffer, 20 pmol of each primer, 200 µM each of deoxynucleotide triphosphate and 1.25 U AmpliTaq Gold® DNA polymerase (Perkin Elmer, New Jersey, USA) and 300 ng DNA. Amplification was started with initial denaturation at 95ºC for 10 min, followed by 30 cycles of denaturation at 95ºC for 30 s, annealing at 55ºC for 55 s and elongation at 72ºC for 60 s. A 1 µl volume of the PCR product was taken for the second PCR and biotinylation with the internal primer pair of GP05+bio-GP06+. The cycle consisted of denaturation at 95ºC for 60 s, annealing at 40ºC for 60 s and extension at 72ºC for 90 s. A total of 40 cycles were performed. DNA extraction, master mix for PCR and the adding of target DNA to the reaction mixture were all carried out in separate rooms.

After HPV amplification, the PCR products were HPV-genotyped with hybridization to fluorescence-labelled polystyrene bead microarrays (Luminex suspension array technology) using the Multimetrix kit (Progen Biotechnik GmbH, Heidelberg, Germany). The assay can detect the following 24 HPV types: low-risk HPV: 6, 11, 42, 43, 44, 70; high-risk HPV: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82. In the final step, the beads were washed 3 times with 100 µl blocking buffer, and finally re-suspended in 100 µl blocking buffer for 5 min on a shaker. They were then analysed for internal bead colour and R-phycoerythrin reporter fluorescence on a Luminex 100 analyser (18). The median reporter fluorescence intensity (MFI) of at least 100 beads was computed for each bead set in the sample. The cut-off value was defined for each HPV probe individually, as follows: 1.5 times the background MFI+5MFI.

Ethics approval was obtained by the ethics committee of the Karolinska Institutet. Patient consent was also approved.

Statistical analysis

Fisher's exact test was used to evaluate whether the proportional distribution of the clinical parameters (morphology, colour and location) differed for groups of low-risk vs. mixed and high-risk HPV types.

RESULTS

A total of 303 men were included in the study. Of these, 47 (16%) exhibited lesions of PIN and have been described previously (19). The remaining 256 men had benign lesions and are described here. In 250/256 subjects a histopathological picture consistent with genital HPV infection was shown. In 6 cases diagnoses other than HPV-genital infection were revealed (3 melanocytic naevi, and one each of angiofibroma, lichen sclerosus and circinate balanitis).

HPV was detected in 233/253 (92%) analysed lesions (Table I). Low-risk HPV types only, were found in 192/233 (82%) of the lesions and 18/233 (8%) of the lesions contained only high-risk HPV types. Multiple

Table I. *Human papillomavirus (HPV) type distribution (n = 256)*

HPV type (s)	Total, *n*
HPV 6	179
HPV 11	9
HPV 16	6
HPV 18	1
HPV 42	2
HPV 45	1
HPV 58	1
HPV 66	1
6,11	1
6, 16	6
6, 18	1
6, 53	1
6, 58	2
6, 66	1
6,70	1
11, 56	1
16, 18	1
16, 33	1
16,42	1
16, 44	2
16, 56	1
16, 59	1
16, 82	1
42, 45	1
42, 53	1
43, 73	1
6, 16, 66	2
6, 42, 53	1
11, 16, 70	1
16, 33, 52	1
16, 53, 66	1
45, 56, 58	1
6, 16, 52, 56, 73	1
HPV-negative	20
No HPV test performed	3

HPV types were found in 33/233 (14%): in 23/233 (10%) cases there was a mix of low- and high-risk types, in 8/233 (3%) cases there was a mix of high-risk types only and in 2/233 (1%) of the biopsies a mix of low-risk types only was found. A single HPV type was found in 200/233 (86%) HPV-positive lesions: of these 190/200 were low-risk types and 10/200 were high-risk types. Of the low-risk types, HPV 6 was most common occurring in 179 cases, followed by HPV 11 (9 cases) and HPV 42 found in 2 cases. HPV 6 and/or 11 were also found in 19/33 of the cases with multiple HPV types. In total, these 2 low-risk types were found in 207/233 (89%) of HPV-positive lesions, but in 188/233 (81%) as single infections and in one case both HPV 6 and 11 in the same sample. Of the high-risk types, HPV 16 was found in 6/10 cases, and HPV 18, 45, 58 and 66 in one case each. All of the 6 cases with histopathological diagnoses other than HPV infection were HPV-positive. The 3 melanocytic naevi and the lichen sclerosus case harboured HPV 6. In the angiofibroma (HPV 6, 42, 53) and the circinate balanitis case (HPV 16, 18) mixed infections were found.

In Table II clinical parameters (morphology, location and colour) are shown with respect to HPV type involvement. There were statistically significant differences regarding morphology of the lesions for low- vs. mixed or high-risk HPV types ($p=0.002$): the acuminate lesions were mostly found among men with low-risk HPV types, whereas macular lesions were over-represented among them with mixed or high-risk types. Also, location of the lesions differed statistically significantly between the groups of low- and mixed or high-risk HPV types ($p=0.000001$): lesions induced by mixed or high-risk HPV types were located on the foreskin in 66% cases, compared with 18% of the lesions induced by low-risk types. The penile shaft and pubis were affected in 38% and 33%, respectively, among lesions induced by low-risk HPV types compared with 22% and 10% among those induced by mixed or high-risk types. Most lesions on the foreskin were HPV-positive (61/62). On the other hand, almost half of the HPV-negative lesions were located on the penile shaft. Regarding colour, there was a statistically significant difference between the groups ($p=0.005$): brown lesions were more common in the group of low-risk HPV types, whereas pink lesions were more equally distributed between the groups.

Circumcision status was noted in 255/256 men; of these, 22/255 (9%) were circumcised and 233/255 (91%) were not (Table III). As expected, the majority of the circumcised men (68%) had their warts located on the penile shaft, while among the non-circumcised men the warts were more equally located on the foreskin (27%), the penile shaft (33%) and the pubic area (29%). The colour of the lesions also varied: the most common colour among the non-circumcised men was pink (51%), and the lesions of the circumcised men were generally brown (73%). Since the size of the circumcised group is small, no statistics have been calculated for this table.

The mean duration of genital symptoms and/or warts before inclusion in the study was 24 (range 1–180) months and the median time was 18 months. In total,

Table II. *Clinical parameters (morphology, location and colour) with regard to human papillomavirus (HPV) type distribution (low-risk, high-risk or mixed and HPV-negative)*

Patients, $n=253$	Low-risk HPV$^+$ $n=192$ n (%)	High-risk or mixed HPV$^+$ $n=41$ n (%)	HPV$^-$ $n=20$
Morphology			
Acuminate	90 (47)	9 (22)	7 (35)
Papular	66 (34)	13 (32)	7 (35)
Macular	24 (12)	17 (41)	3 (15)
Seborrhoeic keratosis-like	12 (6)	2 (5)	3 (15)
Location			
Foreskin	34 (18)	27 (66)	1 (5)
Glans	2 (1)	1 (2)	2 (10)
Penile shaft	73 (38)	9 (22)	9 (45)
Pubis	63 (33)	4 (10)	7 (35)
Anal	12 (6)		
Scrotum	4 (2)		1 (5)
Perineum	1		
Groin	2 (1)		
Unknown	1		
Colour			
Pink	90 (47)	21 (51)	6 (30)
Red	9 (5)	4 (10)	1 (5)
Brown	81 (42)	9 (22)	13 (65)
White	9 (5)	7 (17)	
Unknown	3 (2)		

In 3/256 patients no HPV tests were performed.

Table III. *Circumcision status with respect to clinical parameters (morphology, location and colour)*

Patients	Circumcised, no $n=233$ n (%)	Circumcised, yes $n=22$ n (%)
Morphology		
Acuminate	96 (41)	10 (45)
Papular	82 (35)	6 (27)
Macular	42 (18)	3 (14)
Seborrhoeic keratosis-like	13 (6)	3 (14)
Location		
Foreskin	63 (27)	0
Glans	5 (2)	0
Penile shaft	78 (33)	15 (68)
Pubis	68 (29)	5 (23)
Anal	10 (4)	2 (9)
Scrotum	5 (2)	0
Perineum	1	0
Groin	2 (1)	0
Unknown	1	0
Colour		
Pink	118 (51)	2 (9)
Red	11 (5)	3 (14)
Brown	86 (37)	16 (73)
White	16 (7)	0
Unknown	2 (1)	1

In 1/256 patient circumcision status was unknown.

211/256 (82%) men had been treated previously for genital warts.

DISCUSSION

In our study of benign HPV-induced lesions in men, HPV 6 and 11 were detected in as many as 89% of HPV positive lesions. When the potential reduction in prevalence of warts due to HPV vaccination has been discussed, it has been concluded that 90% of genital warts are induced by HPV 6 and 11 (20, 21). This is in accordance with our present results, and corresponds with the results of the previous Stockholm study performed in the 1980s (13). In this earlier study, only HPV 6, 11, 16 and 18 could be tested for, so it would be interesting to study these samples retrospectively. Dysplastic lesions were seen in as many as 41% of the cases, compared with 16% in our study. The inclusion criteria for the 2 studies were the same, but the size of the previous study was only one-third of the current study; thus the difference may be an effect of that. In a study from the south of Sweden, PCR was used on brush samples (22). HPV 6 and 11 were found in only 60% of cases of genital warts, with 53% positive for HPV 6. No histopathological analysis was done, and the low rate of HPV 6 can be explained because dysplastic lesions were probably also included. In a Chinese study on genital warts HPV 6/11 was found in 89% (23). A French national study was conducted in which the low-risk genotypes predominated, with a prevalence of 89% (24). In none of these studies was histopathology performed and lesions were not described in detail.

It is extremely important to take the histopathological analysis into account when comparing studies on HPV typing of genital warts. Obviously also, for an experienced physician, it might be difficult to be certain about the clinical diagnosis of genital HPV infection, since 6/256 samples showed a histopathological diagnosis of other dermatological conditions; an aspect of importance when evaluating studies in which histopathology has not been performed. We included these patients in the analyses since all were HPV-positive, and it is not excluded that the lesion taken for PCR from each of these patients was indeed a condyloma.

In the present study, the clinical presentation differed between low- and mixed or high-risk HPV-positive lesions. Acuminate warts were significantly more common among the low-risk HPV positive lesions, whereas papular and macular lesions were more common among those induced by mixed or high-risk HPV. We chose to calculate the statistics such that we compared low-risk HPV types vs. high-risk or mixed infections together. This was done because, although all lesions were benign, without knowing the "leading" HPV, the presence of a high-risk HPV in addition to a low-risk HPV may be enough to imply a higher risk of progression. It is possible that a histopathologically benign lesion can progress into a pre-malignant or malignant lesion if induced by a high-risk HPV type. Regarding location, a higher proportion of lesions induced by mixed or high-risk HPV types were located on the foreskin, whereas the penile shaft and pubis were common locations for lesions induced by low-risk HPV types. It is likely that lesions on the foreskin are more contagious to vulnerable partners than warts in the pubic area, and this difference regarding HPV-type distribution is therefore of clinical interest. Warts on the glans penis were uncommon. This might be due to the usually good response to treatment with podophyllotoxin in this location (at least in non-circumcised men) (2), and therefore patients did not need surgical treatment. Interestingly, brown lesions were often induced by low-risk HPV types; an important finding since a common definition of the premalignant lesions, called bowenoid papulosis, is papular lesions with a red-brown colour (25). All of these described differences may be of clinical significance to keep in mind, since it would not be possible to examine all patients with genital warts by histopathology. On the other hand, as this is a selected group of patients with long-lasting problems, they are not representative of genital warts patients in general, and one should exercise caution when drawing general conclusions.

HPV genotyping used a sensitive PCR method, and only 8% of the analysed lesions were HPV negative. The high HPV detection rate may have several explanations, such as careful clinical examination, taking of representative biopsy samples, the use of frozen samples for HPV testing and the HPV testing method as such. Two different samples from 2 clinically identical lesions were taken from each patient, one for routine histopathology and one for HPV typing. This was done instead of splitting one lesion into 2 parts, because the lesions are sometimes quite small and might be difficult to prepare; sectioning for histopathology is difficult for small lesions. By this procedure, we hope to have minimized the risk of taking lesions induced by different HPV types, a possibility that unfortunately cannot be fully ruled out.

From a clinical point of view, knowledge about visible and symptomatic lesions is more relevant than showing the prevalence of asymptomatic viral DNA. Also, to preclude the benefit of HPV vaccines in men, data on HPV-type distribution in clinical visible lesions is important. Penile, anal and oropharyngeal cancer might be protected to some extent, but the greatest health benefit of HPV vaccination in men should be prevention of anogenital warts, which is the main indication for vaccination in men (26). The clinical problem with genital warts, not least the psychosexual consequences (27), is substantial, and the costs of HPV-associated benign lesions have also been debated (28, 29). This

fact is often neglected and most focus is on dysplastic lesions, not least in discussion about HPV vaccines. We hope that these aspects will be taken into account when setting up national strategies.

The authors declare no conflicts of interest.

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