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Original Article

Penile intraepithelial neoplasia, penile cancer precursors and human papillomavirus prevalence in symptomatic preputium: a cross-sectional study of 351 circumcised men in Sweden

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[Correction added on 01 February 2021 after first online publication: In the original publication, all the authors' first and last names were previously reversed and have been corrected in this version.]

Objectives

To investigate the prevalence of pathological disease and spectrum of human papillomavirus (HPV) types among symptomatic foreskin tissue.

Patients and Methods

Consecutively excised symptomatic foreskins from 351 men were sent for histopathological evaluation. During the surgical procedure, a fresh biopsy was taken for HPV analysis by modified general primer polymerase chain reaction. A medical questionnaire regarding medication, smoking habits, number of lifetime sexual partners, former diseases and surgery performed on penis was completed by all participants.

Results

The most common clinical diagnosis and cause for circumcision was phimosis, seen in 85.2%. Histopathologically inflammatory dermatological conditions were present in 87% of the men. The most common histopathological diagnosis was lichen sclerosus (LS) observed among 58.7%. Notably, penile intraepithelial neoplasia (PeIN) was present in 2% without former clinical suspicion. Overall, HPV was detected in 17.1% of the men and 28 different HPV types were found. High-risk (HR) HPV types were identified in 9.1% and HPV16 was present in 2.3%. Current smoking increased the risk of HPV (crude odds ratio [OR] 2.8, confidence interval [CI] 1.4–5.6; $P = 0.005$). Having >15 lifetime sexual partners increased the risk of HPV (crude OR 2.6, 95% CI 1.4–5.1; $P = 0.003$) and when adjusted for current smoking the OR was substantially increased (OR 6.0, 95% CI CI 2.2–16.8; $P < 0001$).

Conclusions

Histopathological evaluation of circumcised symptomatic foreskin revealed PeIN in 2% of the men without any clinical suspicion of malignancy and that treatable dermatological conditions were present in 87%, LS being the most common. HR-HPV types were present in 9%. Due to risk of malignant development both in PeIN and in inflammatory skin diseases we recommend sending all excised foreskins from patients with symptoms for histopathological evaluation as guidance for further clinical management.

Keywords

penile intraepithelial neoplasia, lichen sclerosus, circumcision, preputium, histopathology, human papillomavirus, #PenileCancer, #uroonc

Introduction

Phimosis is defined by a prepuce that cannot be retracted over the glans due to narrowing of the preputial orifice and/or adhesion between glans and the prepuce [1]. Physiologically most boys are born with phimosis, called primary phimosis, which spontaneously resolves over the years. Persistent primary phimosis and secondary phimosis, acquired in adult age, is often a consequence of an underlying disease. Overall the prevalence of phimosis varies in studies between 0.5% and 13% by the age of ≥18 years [1].

Circumcision in males, defined by excision of the prepuce, can be performed due to medical, cultural or religious reasons [2]. It is one of the most frequent surgical procedures in urological practice [3,4]. Morris et al. [2] estimated that ~37.7% of all men globally are circumcised.

The WHO recommends circumcision to prevent HIV transmission in high-endemic countries, if performed by well-trained health personnel [5]. Phimosis is the most common medical reason for circumcision, often based on inflammatory skin diseases such as balanitis, lichen sclerosus (LS) or lichen planus (LP) [4,6]. Other reasons for acquired phimosis are sexually transmitted infections, diabetes, obesity, penile intraepithelial neoplasia (PeIN), and invasive penile cancer [1]. Human papillomavirus (HPV) is found in 16–42% among asymptomatic men and varies partly due to age [7–9]. Notably, HPV has been detected in up to 43% of phimotic foreskin samples collected at circumcision [8,10]. High-risk (HR) HPV can develop into PeIN and penile cancer [11].

Excised foreskin is not routinely sent for histopathological examination in clinical practice [3]. This is in alignment with Pearce and Payne [12] who analysed 93 circumcised cases and found that preoperative diagnosis was in agreement with the final histology in 83%. Contradictory other studies have reported that LS was overlooked in 49–62% if the foreskin was not sent for histopathological examination [3,13]. A recently published review of LS establishes that the incidence of LS is thought to be underestimated by as much as 50% and that the diagnosis of LS in acquired phimosis must be based on biopsy [14]. LS can develop into penile cancer in up to 13% of cases [15,16]. In a previous study from our group, we found that LS was a strong risk factor for PeIN, odds ratio (OR) 13.6 (95% CI 5.2–35.5) [17].

The aims of the present study were to investigate prevalence of pathological diseases and spectrum of HPV types among excised foreskin tissue. Our intention was to analyse the diagnoses that histopathology revealed in circumcised skin in order to elucidate the spectra of pathological diagnoses that needed further clinical management.

Patients and Methods

Men with symptomatic foreskin scheduled for consecutive elective circumcision at the departments of urology of five different hospitals in the county of Skane, Sweden, were invited. Inclusion started in April 2016 and closed in May 2020. Inclusion criteria were men aged ≥18 years able to give informed consent. A medical questionnaire regarding medication, smoking habits, number of lifetime sexual partners, former diseases, and surgery performed on the penis was completed by all participants (Table S1).

During the surgical procedure, an ~5 mm biopsy was cut from the foreskin and immersed in RNA laterTM (Invitrogen, Thermo Fisher, Vilnius, Lithuania) and sent for HPV analysis. The circumcised foreskin was sent for histopathological examination at the Department of Pathology at Skåne University Hospital.

HPV Analysis

The biopsies were transported to the Department of Microbiology in Lund where they were transferred to 1 mL GITS-solution (4 m guanidinium thiocyanate, 22 mm NaCitrate and 5% Sarcosyl [N-Lauroylsarcosine sodium salt] and 1% mercaptoethanol) and incubated at room temperature overnight. Then DNA was extracted with the Total NA-kit (Roche, Stockholm, Sweden) using MagNA Pure LC (200 μL input and 100 μL output). Sample adequacy was assessed by testing 5 μL of the sample for the human β-globin gene with a real-time PCR [18]. Simultaneous identification of 40 genital HPV types was carried out by modified general primer PCR (MGP-PCR) in a 25 μL reaction, containing 5 μL of extracted material and subsequent Luminex analysis [19,20]. The Luminex assay included probes for HPV types: 6, 11, 16, 18, 26, 30, 31, 33, 35, 39, 40, 42, 43, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68 (a and b), 69, 70, 73, 74, 81, 82, 83, 85, 86, 87, 89, 90, 91, and 114.

Histopathological Classification

Circumcised skin was subjected to routine histopathological examination at the Department of Pathology at Skåne University Hospital in Malmö. All specimens were stained with haematoxylin and eosin. All diagnoses were performed by a small team of uro-pathologists belonging to one of two existing Swedish national Penile Cancer Centres.

Ethics

The study was approved by the ethics board in Lund with Diary number (2015/907).

Statistics

Statistical analysis was performed using the IBM SPSS Statistics for Windows, Version 26.0. (IBM Corp., Armonk, NY). The chi-squared test was used to calculate differences between groups, such as cases with and without HPV. Fisher's exact test was used for small numbers. When differences were found logistic regression was used to calculate CIs and *P* values. Multivariable logistic regression was used to adjust for smoking and age; the latter was kept as a continuous variable.

Results

In all 351 men were included. The median (IQR) age was 45 (29,64) years (Table 1). According to data from the questionnaire medication was used by 39.9% (140/351) and immunosuppressants were taken by 2% (seven of 351). In all, 12 % were current smokers (44/351) and 41% (144/351) were former smokers. In the cohort, 92% (324/351) had sex with women and only 1.7% (six of 351) had sex with men. None were bisexual or had sex with transgender persons. Lifetime sexual partners between 0 and 5 were reported in 46.7% (164/351) of the men. While, 19% (67/351), 11.7% (41/351) and 18.1% (60/351) of the men reported having had 6–10, 11–15 and >15 sex partners over their lifetime, respectively. Former phimosis of the penis was reported by 54.7% (192/351) of the men. Former skin diseases of the penis, including genital warts, were reported by 14% (49/351) and genital itch was previously experienced by 26.2% (92/351). Only 2.3% (8/351) had had a biopsy of the penis, but 15.7% (55/351) had had penile surgery. None had ever had penile cancer (Table 1).

The most common clinical diagnosis was phimosis, seen in 85.2% (299/351) diagnosed by the urologist before circumcision. The second most common clinical diagnosis was visible skin changes without phimosis seen in 8.8% (31/351). Diagnoses classified as other skin disorders were observed in 5.7% (20/351), which comprised two men with clinically diagnosed plasma cells balanitis, two with recurrent balanitis, and 16 with mechanical symptoms with shortening or strictures of the frenulum (Table 2).

Histopathological diagnoses were LS in 58.7% (206/351), followed by lichenoid dermatitis in 9.1% (32/351). PeIN was seen in 2% (seven of 351) of the men. Normal skin was found only in 13.1% (46/351; Table 3). Among the men with or without phimosis, the most frequent histopathological diagnosis was LS seen in 61.2% (183/299) and 74.2% (23/31), respectively.

Overall, HPV was detected in 17.1% (60/351) of the men (Table 4). HR-HPV types were identified in 9.1% (32/351) and HPV16 was present in 2.3% (eight of 351). The presence of only low-risk (LR)-HPV types was seen in 8% (28/351).

Table 1 Characteristics of the 351 circumcised men

Characteristic	Value
Number of men	351
Age, years, median (IQR)	45 (29,64)
Taking medication, *n* (%)	
Any medication*	140 (39.9)
No medication	187 (53.3)
Missing	24 (6.8)
Smoking, *n* (%)	
Present smoker	44 (12.5)
Former smoker	144 (41.0)
Non-smoker	290 (82.6)
Missing	17 (4.8)
Number of lifetime sexual partners, *n* (%)	
0–5	164 (46.7)
6–10	67 (19.1)
11–15	41 (11.7)
>15	60 (18.1)
Missing	19 (5.4)
Sexual orientation, *n* (%)	
Heterosexual	324 (92.3)
Homosexual	6 (1.7)
Bisexual	0 (0)
Sex with transgender persons	0 (0)
Missing	21 (6.0)
Previous symptoms and procedures, *n* (%)	
Previous phimosis	192 (54.7)
Previous itch	92 (26.2)
Previous skin disease	30 (8.5)
Previous genital warts	19 (5.4)
Previous penile cancer	0 (0)
Previously biopsied	8 (2.3)
Former surgery	55 (15.7)
Missing	14 (4.0)

*IQR, interquartile range. *Medication with immunosuppressing medicine was taken by 2% (seven of 351), consisting of two with tumour necrosis factor inhibitors, two with methotrexate, and three with systemic cortisone.*

Table 2 Clinical diagnosis before circumcision in the 351 men with symptomatic foreskins

Clinical diagnosis before circumcision	*N* (%)
Phimosis	299 (85.2)
Visible skin changes	31 (8.8)
Other skin disorders	20 (5.7)
Missing	1 (0.3)
Total	351 (100)

Overall, 28 different HPV types were found, which comprised 15 HR-HPV types and 13 LR-HPV types (Table 4). Histopathological koilocytosis was seen in only 8.3% (five of 60) of the HPV-positive samples (data not shown). Being a current smoker increased the risk of HPV (OR 2.8, 95% CI 1.4–5.6, $P = 0.005$), but when adjusted for age the increased risk was not significant (OR 1.0, 95% CI 0.9–1.0; $P = 0.2$; Table 5). Having >15 sexual partners over the lifetime increased the risk of HPV (OR 2.6, 95% CI 1.4–5.1; $P = 0.003$). Current smoking in the men with >15 lifetime sexual partners enhanced the risk of HPV (adjusted OR 6.0,

Table 3 Histopathological diagnoses of the 351 circumcised men

Histopathological diagnosis	*N* (%)
PeIN	7 (2.0)*
LS	206 (58.7)
LP	20 (5.7)
Lichenoid dermatitis	32 (9.1)
Psoriasiform dermatitis	5 (1.4)
Plasma cells balanitis	5 (1.4)
Unspecific chronic inflammation	30 (8.5)†
Normal skin	46 (13.1)
Total	351 (100.0)

**Five had concomitant LS in the excised foreskin. †Including one with syringoma and one with spongiotic dermatitis.*

95% CI 2.2–16.8; $P < 0001$), but when adjusted for age the increased risk was not significant (OR 1.0, 95% CI 0.9–1.0; $P = 0.4$). Men histopathologically diagnosed with PeIN showed an increased risk of HPV (OR 6.9, 95% CI 1.5–31.5; $P = 0.01$), but the increased risk was not significant when adjusted for smoking (OR 2.0, 95% CI 0.2–20.7; $P = 0.55$) and age (OR 0.9, 95% CI 0.7–1.0; $P = 0.09$; Table 5). Men diagnosed with lichenoid dermatitis had an increased risk of HPV (OR 3.4, 95% CI 1.6–7.4; $P = 0.002$), but the increased risk was not significant when adjusted for smoking (OR 1.4, 95% CI 0.3–6.9; $P = 0.7$) and age (OR 1.0, 95% CI 1.0–1.1; $P = 0.6$; Table 5).

Discussion

This is to our knowledge the largest study analysing fresh biopsies of consecutive circumcised men for both histopathological diagnosis and HPV. Inflammatory dermatological conditions were present in 87% of the men. The most common diagnose was LS (58.7%). Seven men (2%) were diagnosed with PeIN without former clinical suspicion.

Both LS, phimosis, balanitis and genital warts are known risk factors for PeIN and invasive cancer [17,21]. PeIN is a penile cancer *in situ* that is thought to develop into invasive penile cancer in up to 30% of cases, although data are scarce [22,23]. The classification of PeIN has recently changed and is now based on clinicopathological distinctiveness and relation to HPV infection [24]. Before PeIN was called Bowens disease on keratinised skin and erythroplasia of Queyrat on mucosal skin. The current classification is in alignment with squamous cell carcinoma *in situ* of the vulva called vulvar intraepithelial neoplasia and squamous cell carcinoma *in situ* of the anus called anal intraepithelial neoplasia. PeIN is treated with topical chemotherapy with imiquimod or 5-fluorouracil as an effective first-line treatment. Other organ-sparing options are surgical excision and/or circumcision, laser ablation or total glans re-surfacing. Due to high persistence/recurrence rates, long-term surveillance is warranted up to 5 years [25].

Table 4 HPV prevalence amongst the 351 men

Histological subtype	*N*	HPV+, *n* (%)	Single HPV type, *n*	>1 HPV type, *n*	HPV types, *n*																																	
					6 LR	11 LR	16 HR	18 HR	30 HR*	31 HR	33 HR	35 HR	39 HR	40 LR	42 LR	43 LR	51 HR	52 HR	56 HR	58 HR	61 LR	62 LR	66 HR*	67 HR	68 HR*	70 HR	74 LR	83 LR	87 LR	89 LR	90 LR	91 LR
LS	206	29 (14)	22	7	4	1	4[a]	1[a]	1[b]	1[c]			1	2[b]		2[d,e]	1[f]	1	1	1[c]	2	1[g]	3[e]		2[g]		5[a,d]		1[c]		3[g]	1	
Lichenoid dermatitis	32	12 (34)	12	0						1					1[h]		1	2[h]							2		3		1	1	1[h]	1[h]	1	1
Chronic inflammation	30	3 (7)	2	1												1																					
LP	20	1 (5)	0	1			1[i]																				1[i]									
PeIN	7	4 (57)	1	3			1[j]				1	1[k]			1[j]							1[j]						1[k,l]								
Psoriasiform dermatitis	5	1 (20)	1	0																						1										
Plasma cells balanitis	5	1 (20)	1	0														1																		
Normal skin	46	9 (20)	8	1	1[m]		2	1								1					1[m]			1				1[m]	1	2						

*[a]Case positive for HPV type 16, 18 and 74 simultaneously. [b]Case positive for HPV type 30 and 40 simultaneously. [c]Case positive for HPV type 31 and 58 simultaneously. [d]Case positive for HPV type 43 and 74 simultaneously. [e]Case positive for HPV type 43, 66 and 87 simultaneously. [f]Case positive for HPV type 51 and 68 simultaneously. [g]Case positive for HPV type 62, 68 and 90 simultaneously. [h]Case positive for HPV type 42, 52, 89 and 90 simultaneously. [i]Case positive for HPV type 16 and 74 simultaneously. [j]Case positive for HPV type 16 and 62 simultaneously. [k]Case positive for HPV type 35 and 83 simultaneously. [l]Case positive for HPV type 40 and 83 simultaneously. [m]Case positive for HPV type 6, 61 and 83 simultaneously. HR, high risk; LR, low risk. *HPV30, 66 and 68 were here classified as high risk, according to WHO they are potential high-risk types [11].*

Table 5 Multivariable regression analyses adjusting for age and smoking

Variable	OR (95% CI)	*P*
HPV and smoking		
Crude	2.8 (1.4–5.6)	0.005
Adjusted for age	1.0 (0.9–1.0)	0.2
HPV and >15 sexual partners		
Crude	2.6 (1.4–5.1)	0.003
Adjusted for smoking	6.0 (2.2–16.8)	<0.001
Adjusted for age	1.0 (0.9–1.0)	0.4
HPV and PeIN		
Crude	6.9 (1.5–31.5)	0.01
Adjusted for smoking	2.0 (0.2–20.7)	0.55
Adjusted for age	0.9 (0.7–1.0)	0.09
HPV and lichenoid dermatitis		
Crude	3.4 (1.6–7.4)	0.002
Adjusted for smoking	1.4 (0.3–6.9)	0.7
Adjusted for age	1.0 (1.0–1.1)	0.6

Studies of males have shown risks between 2% and 13.6% for malignant development of LS [15,16]. One longitudinal prospective cohort study of 507 women with LS using preventive long-term treatment showed improved function, relived symptoms, reduced development or progression of scarring and an elimination of the risk of cancer development [26].

Circumcised specimens are not sent routinely for histopathological examination [3,13]. Pearce and Payne [12] argued that routine submission of a histological specimen is not required and is an unnecessary cost for society, based on circumcision of 460 adults (12–89 years). Circumcised skin was sent for histopathological evaluation in only 20% (93/460), where LS was found in 43% (40/93). They found 83% accuracy between preoperative diagnosis and diagnosis after histopathological examination. Contradictory to this, several studies have shown missed diagnosis of LS in up to 62% [3,13,27]. Kato *et al.* [27] circumcised 30 boys with phimotic foreskin and found LS in 43% (13/30) and the clinical correctness was 59%, partially due to clinical over diagnosing of LS.

In the present study of the 351 men with a symptomatic prepuce, 57.8% were diagnosed with LS, a treatable dermatological disease with malignant potential. If these tissue samples were not sent to histopathological evaluation LS cases would have been missed. Long-term follow-up studies have not been done on circumcision as a treatment of LS [28]. Edmonds *et al.* [29] showed clearance of 76% (124/163) of LS after circumcision and Kantere *et al.* [30] showed that up to 64% of patients still have active LS after circumcision. Guidelines from the British Association of Dermatology regarding management of LS recommend that circumcised foreskin should always be sent for histology to exclude PeIN and confirm the diagnosis. Although the foreskin is not always the seat or a site of disease, men who require circumcision because of persistent disease unresponsive to topical steroids, should be reviewed after surgery. Circumcision following a tight phimosis may reveal active disease on the glans and in the coronal sulcus, which will require further treatment with a topical steroid [31].

To our knowledge, only two other studies have published prevalence of HPV in biopsied material from men with phimosis without penile cancer. Afonso *et al.* [8] found HPV in 43% (13/30). The second study analysed HPV in circumcised paraffin-embedded tissue and found HPV in only 9.3% (21/226), both LR- and HR-HPV were more prevalent among boys aged 0–10 years compared to men aged 21–89 years. Heidegger *et al.* [10] argued that their low prevalence of HPV could be explained by using formalin-embedded tissue. We found a large spectrum of 28 different HPV types, represented by 15 HR- and 13 LR-HPV types. Speculatively, the relatively high proportion of LR-HPV types in the present study may indicate that foreskin tissue is a natural reservoir for such HPV types. However, we found that HR-HPV types were present in about a tenth of the men (9.1%) and that HPV16 was the most common type (2.3%). Persistent oncogenic HPV types possess a risk of developing into PeIN [11], highlighting the importance of HPV vaccination for boys. Penile shaft and glans penis/coronal sulcus are the most predominate locations for HPV in men [32,33], which suggests that circumcised tissue is representative for detection of HPV.

In our present study, we found a significant association between HPV prevalence and a high number of lifetime female sexual partners as previously shown [9,34]. The crude OR showed that HPV infection was significantly associated with current smoking, in agreement with former studies showing a higher incidence and prevalence of HPV amongst smokers [35]. Adjusted for age the OR decreased to 1.0, suggesting age to be a confounder, albeit with no statistical significance, due to only a few cases. Smoking is also a known risk factor for penile cancer [21]. HPV prevalence in PeIN has been shown to be between 87% and 100% in studies mostly of paraffin-embedded tissue [36,37]. Our present results with HPV in only 57% of PeIN and an increased crude OR for HPV of 6.9 with a wide CI interval (95% CI 1.5–32.1, $P = 0.01$) could be due to only seven included PeIN cases.

Our present study has several strengths. It is amongst the largest studies performing histopathology evaluation of consecutively circumcised foreskins and the only study simultaneously presenting a large spectrum of HPV from fresh biopsies in men with no suspected malignant penile cancer. The histopathology was performed by a small dedicated team of uro-pathologists experienced in diagnosing penile cancer and PeIN. One limitation of the study was that no specific classification was used for the diagnosis of

phimosis; instead, different degrees of phimosis were derived from the medical chart and the referral note to the Department of Pathology. A limitation was also that the median age of included patients was relatively low, due to elderly patients with phimosis often going through a dorsal slit and not a total circumcision, and therefore was underrepresented in this material. Another limitation was that the prevalence of smoking among the included men was derived from the questionnaire and comprised only full data on current smoking, not lifetime tobacco exposure.

In conclusion, histopathological evaluation of circumcised foreskin discovered PeIN in 2% of all men without any clinical suspicion of malignancy and 87% of treatable dermatological conditions, LS being the most common. Although 28 different HPV types were found, the overall prevalence of HPV in fresh tissue of symptomatic foreskin was moderate (17.1%) and the presence of HR-HPV types was even lower (9.1%). When PeIN and penile cancer precursors are found it is important to offer the patients treatment and follow-up, either by experienced urologists or by dermatologists. We recommend sending all excised foreskins from patients with symptoms for histopathological examination, to enhance treatment and management of skin diseases and malignancies of the penis.

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Conflict of Interest

Neither Dr Kristiansen nor any of the other researchers/ authors have anything to disclose.

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Abbreviations: HPV, human papillomavirus; HR, high risk; LP, lichen planus; LR, low risk; LS, lichen sclerosus; OR, odds ratio; PeIN, penile intraepithelial neoplasia.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Questionnaire distributed to all men.