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Male Circumcision and Anatomic Sites of Penile High-Risk Human Papillomavirus in Rakai, Uganda

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Abstract

Male circumcision (MC) reduces penile high-risk human papillomavirus (HR-HPV) on the coronal sulcus and urethra. HR-HPV varies by anatomic site, and it is unknown whether MC decreases HR-HPV on the penile shaft. We assessed the efficacy of MC to reduce HR-HPV on the penile shaft and compared it to known efficacy of MC to reduce HR-HPV on the coronal sulcus. HIV-negative men randomized to receive immediate circumcision (intervention) or circumcision delayed for 24 months (control) were evaluated for HR-HPV at 12 months post-enrollment using the Roche HPV Linear Array assay. Among swabs with detectable beta-globin or HPV, year 1 HR-HPV prevalence on the coronal sulcus was 21.5% in the intervention arm and 36.3% in the control arm men (adjusted prevalence risk ratios (PRR)=0.57, 95%CI 0.39–0.84, p=0.005). On the shaft, year 1 HR-HPV prevalence was 15.5% in the intervention and 23.8% in the control arm (adjusted PRR=0.66, 95%CI 0.39–1.12, p=0.12). Efficacy of MC to reduce HR-HPV on the shaft was similar to efficacy on the coronal sulcus (p=0.52). In a sensitivity analysis in which swabs without detectable beta-globin or HPV were included as HPV negative, prevalence of HR-HPV on the shaft was lower in the intervention arm (7.8%) than control arm (13.6%) (PRR 0.57, 95%CI 0.33–0.99, p<0.05). HR-HPV was more frequently detected on the coronal sulcus than penile shaft among uncircumcised men (36.3% vs 23.8%, respectively, p=0.02) and circumcised men (21.5% vs 15.5%, respectively, p=0.24). MC reduced HR-HPV prevalence on both the coronal sulcus and shaft.

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Disclosures

Dr. Gravitt received research funding from Roche Molecular Diagnostics who manufacture the HPV genotyping test used in this study. There are no other potential conflicts of interest relevant to this article.

Keywords

Male circumcision; human papillomavirus (HPV); HIV; Uganda; foreskin; penis; coronal sulcus; penile shaft; cervical cancer; sexually transmitted infections

Introduction

Human papillomavirus (HPV) is common and can cause genital warts, and high-risk HPV (HR-HPV) genotypes cause penile and anal cancer in men, as well as cervical cancer in women.[1–2]

Some observational studies suggest that male circumcision (MC) decreases penile HPV carriage on the urethra, coronal sulcus, and shaft, but not on the scrotum, anal canal, and perianal area.[3–4] Other studies, however, found no effect of MC on HPV infection.[5–6] Two randomized trials demonstrated that male circumcision decreased HR-HPV infection by 35% on the coronal sulcus [7] and by 34% on the urethra.[8] Male circumcision reduced the acquisition of new HR-HPV infections and increased clearance of pre-existing HR-HPV infection on the coronal sulcus.[9–10]

HPV detection varies by anatomic site [5, 11–12], and it has been suggested that evaluating HR-HPV only on the coronal sulcus and urethra might bias the estimated protective efficacy of male circumcision.[13] Studies of the anatomic site of penile HPV infection are rare in Africa. Understanding the differences in HPV prevalence by penile site may provide insight into the potential role of male circumcision to decrease HPV in female partners and prevent cervical cancer. Therefore, we evaluated whether male circumcision reduces HR-HPV on the penile shaft and the relation between infections detected on the penile shaft and coronal sulcus.

Materials and Methods

Study Design and Participants

Two trials of male circumcision enrolled men aged 15–49 for HIV and STI prevention in Rakai District, Uganda. The design and results of the study have been reported previously.[7, 14–15] In brief, eligible men were informed of study procedures and risks and provided written informed consent prior to screening and enrollment. Men were excluded from the trial if they had anemia, active genital infections, anatomical abnormalities (e.g., hypospadias), or medical indications (e.g., severe phimosis) or contraindications for surgery. Men were randomly assigned to receive immediate circumcision (intervention arm) or circumcision delayed for 24 months (control arm). Serologic testing for HIV, physical examinations and interviews to ascertain sociodemographic characteristics and sexual risk behaviors were conducted at baseline and repeated at 6, 12 and 24 month follow-up visits. There were 459 HIV-negative men (231 intervention arm, 228 control arm) at the 12 month visit who had separate swabs obtained from the penile shaft and coronal sulcus which were stored in separate vials at −80°C. Separately stored shaft and sulcus swabs were not available for other study visits for the 459 men and not available for any study visits for the other enrollees in the trial since HPV at the coronal sulcus was the primary HPV trial endpoint.

At each visit, participants were provided free HIV counseling and testing, health education and condoms. Those found to be HIV-positive were referred to an HIV treatment program funded by the Presidential Emergency Fund for AIDS Relief.

The trials were approved by four institutional review boards: the Science and Ethics Committee of the Uganda Virus Research Institute (Entebbe, Uganda), the HIV subcommittee of the National Council for Research and Technology (Kampala, Uganda), the Committee for Human Research at Johns Hopkins University Bloomberg School of Public Health (Baltimore, MD, USA), and the Western Institutional Review Board (Olympia, WA, USA). The trials were overseen by independent Data Safety Monitoring Boards[7, 14] and were registered with Clinical.Trials.Gov numbers NCT00425984 and NCT00124878.

HPV and HIV Detection

Separate samples were obtained from pre-moistened Dacron swabs of the coronal sulcus and shaft at the 12 month visit. All swabs from both the coronal sulcus and shaft were obtained by rotating the swab around the full circumference of the penis. Dual site swabs were not available for enrollment or the other visits. Swabs were placed in Digene specimen transport medium (Digene Corporation, Gaithersburg, MD) and stored at −80°C until the time of assay. HPV genotyping was performed using the Roche HPV Linear Array (Roche Diagnostics, Indianapolis, IN) as previously described.[16] HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were considered the primary HR-HPV carcinogenic viral genotypes. Penile samples which were HPV negative and had no detectable beta-globin (i.e., cellular DNA) were excluded from the denominator for the estimation of HPV prevalence in primary analyses since the presence of cellular material could not be demonstrated.

HIV status was determined using two separate ELISAs and discordant results were confirmed by HIV-1 Western Blot as previously described.[14]

Statistical Analysis

Enrollment and follow-up characteristics, sexual risk behaviors and STI symptoms were tabulated by study arm and differences assessed by Pearson's chi-squared tests.

The primary assessment of the efficacy of MC for reduction of HR-HPV infection used an intention-to-treat analysis. An as-treated analysis was also carried out, in which an intervention arm crossover was classified as uncircumcised if the man failed to accept surgery within six months after randomization or control arm men were circumcised outside of the trial.

Samples obtained at the 12 month visit were used to assess prevalent HR-HPV infection by study arm, estimated as the proportion of men positive for one or more HR-HPV genotypes among samples with amplifiable cellular and/or viral DNA. The prevalence data were summarized using 2×2 tables and the prevalence risk ratios (PRR) of HPV in the circumcised relative to the uncircumcised men were estimated separately for shaft and coronal sulcus sites. Multivariate log-binomial regression was used to estimate the adjusted PRRs. The interaction term between circumcision and anatomic site was also included in the model in order to assess whether the efficacy of circumcision for HR-HPV prevention was statistically different between coronal sulcus and shaft samples. An alternating logistic regression GEE technique was used to account for the correlation between sulcus and shaft samples from the same individual.[17] The alternating logistic regression model was also used to estimate the association of HR-HPV detection between the two anatomic sites. In addition, to compare HR-HPV detection risk between the two sites, we used McNemer's test for matched pairs among individuals having amplifiable sulcus and shaft samples.

All tests are 2-sided and analyses were performed using R 2.8.1 and SAS 9.2 (Cary NC).

Results

There were 231 men in the intervention arm and 228 men in the control arm who were assessed at the 12 month visit. Sociodemographic characteristics, sexual behaviors, and symptoms of STIs were similar between the two groups at year one, except a greater proportion of men in the control arm were older (p=0.02), and drank alcohol prior to sexual intercourse (p=0.01) (Table 1). There were no statistical differences between the two groups for education, religion, marital status, number of sexual partners, condom use, self-reported symptoms of genital ulcer disease, urethral discharge and dysuria, and number of crossovers (Table 1). There were significantly more men with swabs that did not amplify either beta-globin or HPV in the intervention arm on the coronal sulcus compared to the control arm on the coronal sulcus (p<0.001).

In the primary intention-to-treat analysis, the point prevalence of any HR-HPV infection at the one year visit on the coronal sulcus was lower in the intervention men (21.5%) than control men (36.3%), with an unadjusted PRR of 0.59 (95% CI 0.40–0.88, p=0.01) (Table 2). Adjustment for age, education, and alcohol consumption before sex at year 1 did not materially affect efficacy estimates (adjusted PRR = 0.57, 95% CI 0.39 – 0.84, p=0.005). The point prevalence of any HR-HPV infection on the shaft at year one was lower in the intervention arm (15.5%) than control arm (23.8%) with an unadjusted PRR of 0.65 (95% CI 0.39–1.10, p=0.11) (Table 2). Adjustment for year one characteristics and sexual behaviors did not affect this estimate (adjusted PRR =0.66, 95% CI 0.39 – 1.12, p=0.12). Efficacy of MC to reduce HR-HPV on the shaft was similar to the efficacy of MC to reduce HR-HPV on the colonal sulcus (p=0.52). In an as treated analysis, the point prevalence of any HR-HPV infection at the one year visit was lower in circumcised men on both the coronal sulcus (unadjusted PRR 0.59, 95% CI 0.40–0.88, p=0.01) and shaft (unadjusted PRR 0.71 (95% CI 0.33–1.52, p=0.19). HR-HPV detection was consistently lower in shaft samples than coronal sulcus samples among uncircumcised men (23.8% vs. 36.3%, respectively, p=0.02) and circumcised men (15.5% vs 21.5%, respectively, p=0.24), suggesting lower detection of HR-HPV on the shaft than the coronal sulcus, irrespective of circumcision status.

The number of individuals without detectable HPV or beta-globin differed both by circumcision status and sampling site. Among intervention arm men, 47.6% (110/231) had undetectable viral or cellular DNA on the coronal sulcus and 49.8% (115/231) had undetectable DNA on the shaft. Among controls, the proportion of samples with undetectable viral or cellular DNA was 25.0% (57/228) on the coronal sulcus and 43.0% (98/228) on the shaft (p<0.001). We conducted a sensitivity analysis in which samples without detectable beta-globin or HPV were included in the denominator as HPV negative. The point prevalence of any HR-HPV infection on the shaft was lower in the intervention arm (7.8%, 18/231) than control arm (13.6%, 31/228) with an unadjusted PRR of 0.57 (95%CI 0.33–0.99, p<0.05).

We also assessed the association of HR-HPV detection between the two anatomic sites. To compare HR-HPV prevalence between anatomic locations of the penis, 203 men (90 circumcised and 113 uncircumcised) with detectable cellular or viral DNA samples on both the coronal sulcus and shaft were evaluated (Table 3A). HR-HPV was more frequently detected on the coronal sulcus (29.1%, 59/203) than on the penile shaft (22.7%, 46/203), (p=0.04). The absolute differences in HR-HPV prevalence between the coronal sulcus and shaft was statistically significant among control arm men (Table 3C, p=0.04), but not among intervention arm men (Table 3B, p=0.75). Among men with positive HR-HPV detected on either sampling site, only 52.2% were dually positive on both sites (36/69), and concordance between the sampling sites was similar among both circumcised (52.4%, 11/21) and uncircumcised men (52.1%, 25/48). We also assessed the concordance of specific HR-HPV

genotypes detected on the two sampling sites. There were a total of 100 HR-HPV genotype infections detected on either site among the 69 HR-HPV positive individuals. There were 88 (88.0%) HR-HPV genotypes detected on the coronal sulcus, of which 41 (41.0%) were concurrently detected on the shaft.

Discussion

Circumcision of adolescent and adult men in a rural Ugandan population reduced HR-HPV prevalence in men on both the coronal sulcus and penile shaft. Although the sample size was small and findings did not reach statistical significance for the shaft samples, the efficacy of male circumcision for HR-HPV prevention was similar for samples from the two anatomic sites. These findings are compatible with observational studies of the association between male circumcision and HR-HPV detected on the coronal sulcus and shaft.[3–4, 18] In conjunction with prior trial results evaluating HR-HPV on the male urethra and coronal suclus,[7–8] these findings indicate that male circumcision reduces heterosexually acquired penile HR-HPV at multiple anatomic sites.

We found more frequent HR-HPV detection on the coronal sulcus than the shaft in uncircumcised men (Table 3) and this is similar to findings from a Kenyan study,[12] suggesting that the moist subpreputial space might provide a more favorable environment for HR-HPV infection.[14, 19–20] Consequently, reduced auto-infection by removal of the foreskin may be the biological mechanism whereby circumcision could reduce HR-HPV on the penile shaft, as suggested by data in the female genital tract that one site may serve as a reservoir for HR-HPV infection at other anatomical sites.[21] HR-HPV replicates in basal epithelial cells of the epidermis [22] and the inner mucosa of the foreskin is lightly keratinized which may facilitate access of HR-HPV to underlying epithelial cells in uncircumcised men. After circumcision and keratinization of the surgical scar, such epithelial infection is likely reduced. Thus, by reducing HR-HPV on the coronal sulcus, the prevalence of HR-HPV on the shaft may also be decreased as a consequence of lower autoinfection.

A limitation of this study is that the assessment of the efficacy of male circumcision for HR-HPV prevention was confined to a subgroup of men who provided separate coronal sulcus and shaft samples only at the year one follow-up. Since only cross-sectional samples were evaluated, we cannot determine whether the reduced HPV prevalence was due to lower HR-HPV acquisition and/or less persistence of HPV infection following circumcision. Our study was also constrained by the small sample size and by the high proportion of samples with no amplifiable viral or cellular DNA.

The standard method of HPV detection in women utilizes an internal beta-globin positive control to ensure the presence of cellular nuclear material. However, unlike the cervix which is not keratinized, the squamous epithelium of the coronal sulcus and shaft of the penis have layers of keratinized and anucleated cells, such that exfoliated sampling from the penile epithelium yields fewer nucleated cells compared to exfoliated sampling of the cervix. This is likely accentuated on the shaft compared to the coronal sulcus, particularly in uncircumcised men. There were significantly more men in the control arm with no beta-globin or HPV detection on the shaft compared to the coronal sulcus ($p<0.001$), whereas no significant differences in unamplifable DNA were observed in the intervention arm. The heavily keratinized scar tissue following circumcision likely contributes to higher proportion of beta-globin negative samples from the coronal sulcus in the circumcised men. Consequently, in our primary HPV analysis, a greater number of HPV-negative and beta-globin-negative men were excluded from the population at risk in the intervention arm than in the control arm, and this could bias the estimate of efficacy towards the null. This is

supported by the sensitivity analysis that included all men, and showed a significant reduction in HR-HPV on the penile shaft of circumcised men ($p<0.05$).

In summary, we found that male circumcision was associated with lower HR-HPV detection on both the coronal sulcus and the shaft. Since there is a high degree of genotype-specific concordance between sexual partners within couples,[23] the reduced HR-HPV on the coronal sulcus, uretha and shaft of circumcised men will likely lead to reduced transmission of HR-HPV to their female partners.

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Abbreviations

MC	Male circumcision
HR-HPV	high-risk human papillomavirus
PRR	prevalence risk ratios

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Table 1

Behavioral characteristics, sexual practices, and symptoms of sexually transmitted infections at year one.

	Intervention group (n=231)	Control group (n=228)	p-value
Age (years)			0.03
15–19	60 (26.0%)	40 (17.5%)	
20–24	70 (30.3%)	57 (25.0%)	
25–29	43 (18.6%)	56 (24.6%)	
30–49	58 (25.1%)	75 (32.9%)	
Education			0.09
No education	6 (2.6%)	15 (6.6%)	
Primary	146 (63.2%)	152 (66.7%)	
Secondary	64 (27.7%)	48 (21.0%)	
Post-secondary	15 (6.5%)	13 (5.7%)	
Religion			0.89
Catholic	159 (68.8%)	155 (68.0%)	
Protestant	57 (24.7%)	54 (23.7%)	
Saved/Pentecostal/other	13 (5.6%)	17 (7.5%)	
Muslim	2 (0.9%)	2 (0.9%)	
Marital Status			0.23
Not married	109 (47.1%)	90 (39.5%)	
Monogamous	107 (46.3%)	123 (53.9%)	
Polygamous	15 (6.5%)	15 (6.6%)	
Number of sexual partners past 6 months			0.12
0	49 (21.2%)	32 (14.0%)	
1	121 (52.4%)	134 (58.8%)	
2+	61 (26.4%)	62 (27.2%)	
Condom use past 6 months*			0.52
None	89 (38.5%)	103 (45.2%)	
Inconsistent use	54 (23.4%)	60 (26.3%)	
Consistent condom use	39 (16.9%)	33 (14.5%)	
Alcohol use with sex*	84 (36.4%)	109 (47.8%)	0.01
Self-reported symptoms of STDs			
Genital ulcer disease	3 (1.3%)	7 (3.1%)	0.19
Urethral discharge	1 (0.4%)	5 (2.2%)	0.10
Dysuria	4 (1.7%)	6 (2.6%)	0.51
Amplifiable sample			
Coronal sulcus	121 (52.4%)	171 (75.0%)	<0.001
Shaft	116 (50.2%)	130 (57.0%)	0.25
Crossovers**	2 (0.9%)	4 (1.8%)	0.40

Data are n (%).

* Condom use and alcohol use with sexual intercourse were only evaluated in sexually active individuals, although the percentages in these categories were calculated on the basis of the total number of subjects in each arm.

** Crossovers are defined as individuals in the intervention arm who failed to accept surgery or individuals in the control arm who were circumcised outside of the trial.

Table 2

Male circumcision and the prevalence of high-risk human papillomavirus (HR-HPV) at year one on the penile coronal sulcus and shaft.

	Intervention group		Control group		PRR (95% CI)
	HR-HPV	%	HR-HPV	%	
Coronal Sulcus	n=121		n=171		
Any Infection	26	21.5	62	36.3	0.59 (0.40–0.88)
Multiple Infections	9	7.4	18	10.5	0.71 (0.33–1.52)
Shaft	n=116		n=130		
Any Infection	18	15.5	31	23.8	0.65 (0.39–1.10)
Multiple Infections	2	1.7	5	3.8	0.45 (0.09–2.27)

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Table 3

Presence of high-risk human papillomavirus (HR-HPV) genotypes on both the penile coronal sulcus and shaft. There were 203 men with amplifiable samples on both the coronal sulcus and shaft.

A. All Individuals

		Coronal Sulcus		
		HR-HPV+	**HR-HPV −**	**Total**
Shaft	HR-HPV+	36 (17.7%)	10 (4.9%)	46 (22.7%)
	HR-HPV −	23 (11.3%)	134 (66.0%)	157 (77.3%)
	Total	59 (29.1%)	144 (70.9%)	

B. Intervention group

		Coronal Sulcus		
		HR-HPV+	**HR-HPV −**	**Total**
Shaft	HR-HPV+	11 (12.2%)	4 (4.4%)	15 (16.7%)
	HR-HPV −	6 (6.7%)	69 (76.7%)	75 (83.3%)
	Total	17 (18.9%)	73 (81.1%)	

C. Control group

		Coronal Sulcus		
		HR-HPV+	**HR-HPV −**	**Total**
Shaft	HR-HPV+	25 (22.1%)	6 (5.3%)	31 (27.4%)
	HR-HPV −	17 (15.0%)	65 (57.5%)	82 (72.6%)
	Total	42 (37.2%)	71 (62.8%)	