Published in final edited form as:
Int J Cancer. 2013 September 1; 133(5): 1247–1252. doi:10.1002/ijc.28100.

Male circumcision decreases high-risk human papillomavirus viral load in female partners: a randomized trial in Rakai, Uganda

Mitzie-Ann Davis, MD[1,2], **Ronald H Gray, MD**[2,3], **Mary K. Grabowski, ScM**[2], **David Serwadda, MMed**[3,4], **Godfrey Kigozi, MBChB**[3], **Patti E. Gravitt, PhD**[2,5], **Fred Nalugoda, MHS**[3], **Stephen Watya, MMed**[6], **Maria J. Wawer, MD**[2,3], **Thomas C. Quinn, MD**[3,7,8,9], and **Aaron A. R. Tobian, MD, PhD**[2,3,7,8]

[1] Department of Gynecology Oncology, Moores Cancer Center, UCSD, La Jolla, CA [2] Department of Epidemiology, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, Maryland. [3] Rakai Health Sciences Program, Entebbe, Uganda. [4] School of Public Health, Makerere University, Kampala, Uganda. [5] Perdana University Graduate School of Medicine, Serdang, Malaysia [6] Department of Urology, Makerere University, Kampala, Uganda [7] Department of Pathology, School of Medicine, Johns Hopkins University, Baltimore, Maryland. [8] Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, Maryland. [9] Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA.

Abstract

Male circumcision (MC) reduces high-risk human papillomavirus (HR-HPV) infection in female partners. We evaluated the intensity of HR-HPV viral DNA load in HIV-negative, HR-HPV-positive female partners of circumcised and uncircumcised men. HIV-negative men and their female partners were enrolled in randomized trials of MC in Rakai, Uganda. Vaginal swabs were tested for HR-HPV genotypes by Roche HPV Linear Array which provides a semi-quantitative measure of HPV DNA by the intensity of genotype-specific bands (graded:1-4). We assessed the effects of MC on female HR-HPV DNA load by comparing high intensity linear array bands (3-4) to low intensity bands (1-2) using an intention-to-treat analysis. Prevalence risk ratios (PPR) of high intensity bands in partners of intervention versus control arm men were estimated using log-binomial regression with robust variance. The trial included 335 women with male partners in the intervention arm and 340 in the control arm. At enrollment, the frequency of HR-HPV high intensity linear array bands was similar in both study arms. At 24 months follow-up, the prevalence of high intensity bands among women with detectable HRHPV was significantly lower in partners of intervention arm (42.7%) than control arm men (55.1%, PRR= 0.78, 95%CI 0.65-0.94, p=0.02), primarily among incident HR-HPV infections (PRR=0.66, 95% CI 0.50-0.87, p=0.003), but not persistent infections (PRR=1.02, 95% CI 0.83-1.24). Genotypes with high HR-HPV band intensity were more likely to persist (adjHR=1.27 95% CI 1.07-1.50), irrespective of male partner circumcision status. MC reduces HR-HPV DNA load in newly infected female partners.

Keywords

Human papillomavirus (HPV); male circumcision; Uganda; cervical cancer; sexually transmitted infections; viral shedding; viral load; linear array band intensity; HIV

Corresponding Author: Aaron Tobian, MD, PhD, Department of Pathology, Johns Hopkins University, Carnegie 437, 600 N. Wolfe St., Baltimore, MD 21287, 443-287-0527, atobian1@jhmi.edu.

Introduction

High-risk human papillomavirus (HR-HPV) is a common sexually transmitted infection, especially in developing nations.[1] While the majority of women clear or immunologically control HR-HPV infection within 1-2 years without clinical sequelae,[2] persistent HR-HPV detection is linked to squamous cell cervical cancer.[1, 3] High HR-HPV viral load is associated with persistent infection and cervical lesions.[4-5] Cervical cancer is the third most common cancer in women worldwide;[6] greater than 85% of the disease burden is in developing countries, and cervical cancer is the leading cause of cancer mortality in women in Eastern Africa.[6] Therefore, interventions to potentially reduce persistent HR-HPV infection and cervical dysplasia/neoplasia are needed.

Male circumcision (MC) holds promise as an intervention to reduce HR-HPV in both men and women.[7-8] Two trials demonstrated that MC reduced the prevalence of penile HR-HPV infection by approximately 35%,[9-11] reduced the acquisition of new HR-HPV infection, and increased clearance of pre-existing HR-HPV infection in HIV-negative men.[12] Circumcised men in a randomized trial also have reduced HPV-associated penile lesions.[13] Female partners of circumcised men had a lower prevalence and incidence of HR-HPV infection,[14] and women married to circumcised men have lower cervical cancer risk.[15] MC reduces penile HR-HPV viral load,[16] which may underlie the pathophysiology of reduced HR-HPV transmission from circumcised men to female partners.

There are no data on the effect of MC on the HR-HPV viral load in female partners of circumcised males. We utilized data from a randomized controlled trial of MC conducted in Rakai, Uganda to assess whether MC reduced HR-HPV DNA load in female partners.

Materials and Methods

Study design and participants

Two parallel but independent trials of MC for HIV/STI prevention were conducted in Rakai, Uganda, as previously described.[9, 14, 17] HIV-negative, uncircumcised men aged 15-49 with no medical indications or contraindications for MC, provided written informed consent and were randomly assigned to receive immediate MC (intervention arm) or MC delayed for 24 months (control arm). Consenting females who were married or in committed relationships with male trial participants were invited to participate in a separate parallel study with follow up at 12 and 24 months.[14] The effects of MC on female STIs were secondary trial outcomes.

At each study visit, women were interviewed to obtain sociodemographic characteristics, sexual risk behaviors, and symptoms of genital-tract infections (genital ulcer disease, vaginal discharge, and dysuria). Women who reported symptoms were referred for treatment. At each study visit, women were asked to provide a vaginal swab for HPV detection and instructed to insert a saline moistened 20 cm Dacron or cotton-tipped swab high in the vaginal vault. A fieldworker collected the swab samples, and stored them in specimen transport medium (Digene Corporation, Gaithersburg, MD, USA). This approach to specimen collection was well accepted, with compliance rates over 90%, and studies have shown that self-collected vaginal swabs are comparable to physician collected cervical swabs for HPV detection.[18] The specimens were maintained at 4–10°C for less than 6 h then frozen at –80°C.

This analysis is restricted to HIV-negative, HPV-positive female partners who provided swab samples at enrollment and at 12 and/or 24 months follow-up. Women who were HIV

positive were excluded from this analysis because HIV infection increases the risk of persistent HPV.[2, 19] HPV negative women were also excluded from this analysis because the primary outcome was evaluation of HPV DNA load.[9]

There were 2706 HIV-negative, married men enrolled in the trial (1357 intervention arm and 1349 control arm). There were 1463 female partners of intervention arm men and 1429 female partners of control arm men, and of these women, 648 women in the intervention arm and 597 women in the control arm enrolled concurrently with their male partner, were persistently HIV-negative and were evaluated for HPV, as previously described.[14] Of these women, a total of 675 (335 intervention arm and 340 control arm) with at least a baseline and one follow-up visit who were positive for HR-HPV at least one point in the trial (enrollment, year one, or year two) were included in this study.

The trials were approved by the Uganda National Council for Science and Technology, and by three institutional review boards: the Science and Ethics Committee of the Uganda Virus Research Institute (Entebbe, 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), as previously described.[14] The trials were overseen by independent Data Safety Monitoring Boards, and were registered with Clinical.Trials.Gov numbers NCT00425984 and NCT00124878.

HR-HPV Detection and Viral load testing

At each study visit vaginal swabs were tested for HPV and genotyped using HPV Linear Array (Roche Diagnostics, Indianapolis, IN, USA). The laboratory testing was performed at Johns Hopkins University. The HPV genotypes that are considered high-risk and primary carcinogenic types are HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.[3, 20] For each positive HR-HPV genotype, the band intensity was visually scored as 1-4, with intensity 4 representing the strongest Linear Array hybridization band strength.

It has been previously demonstrated in both men and women that the linear array hybridization signal is correlated with HPV viral load.[16, 21] A linear array band signal strength of 4 was approximately equivalent to a viral load of ≥2000 copies/5μl. Band signal strength of 3 was approximately 200-2000 copies/5μL. Thus, band signals of 3 and 4 represent >200 copies/5μL.[16, 21] Therefore, we estimated the proportion of linear array results with band intensities 3 and 4, relative to lower intensity bands 1-2, among women with detectable HPV infections. All laboratory technologists and evaluators of band intensity were blinded to trial arm.

Statistical Analysis

Female enrolment and follow-up characteristics were tabulated among women with detectable HR-HPV at baseline (n=440) and 12 (n=409) and 24 (n=305) month visits. Women were stratified by their male partner's study arm, and differences were assessed using chi-squared tests with two-sided p-values.

The unit of observation was the HR-HPV genotype at baseline and 12 and 24 months follow-up. An incident HR-HPV infection was defined as a newly detected genotype in a woman negative for that genotype at the previous study visit. Persistent HR-HPV was defined as continued infection with same genotype detected at the previous study visit.

Prevalence of either high viral DNA load (band intensities 3-4) or low viral DNA load (band intensities 1-2) were assessed for each HR-HPV genotype, irrespective of the number of HR-HPV infections per individual. Prevalence risk ratios (PRRs) and 95% confidence intervals (CI) were estimated for high relative to low intensity bands in female partners of

intervention versus control arm men for all HR-HPV genotypes detected at each study visit using log binomial regression with generalized estimating equation (GEE) robust variance estimates to account for correlation between HPV genotypes within the same woman and repeat observations over time. Covariates in adjusted analyses included age and number of sexual partners during the last 12 months reported by the women.

We examined the association between HR-HPV DNA load and HR-HPV persistence using discrete time proportional hazards regression models where the outcome was HR-HPV clearance (i.e., loss of detection) of baseline HR-HPV genotypes at 12 or 24 months follow-up. The hazards of persistence were estimated from the inverse of the coefficients for persistence from these models. Age of the woman and MC status of the male partners were included in multivariate analyses.

Statistical analyses were conducted in STATA Version 11.0 (STATA Corp LP, College Station, Texas) and R version 2.14.

Results

There were 226 women with male partner in the intervention arm and 214 women with partners in the control arm who were positive for HR-HPV at enrollment. Baseline sociodemograhic characteristics, sexual behaviors, and symptoms of sexually transmitted infections were similar between study arms (Table 1). The female partners of men in the control arm had a higher number of HR-HPV genotypes compared to female partners of men in the intervention arm (p=0.05) at enrolment. Among women who were infected with HR-HPV at year one and two, there were no differences between randomization arms in sociodemographic characteristics, sexual behaviors, and number of HR-HPV genotypes (Table 1). Women married to men in the intervention arm had lower rates of self-reported genital ulcer disease at year two (p=0.03).

At enrolment, the frequency of high intensity linear array bands (signals 3-4) for HRHPV genotypes was similar in the intervention arm (58.8%) and the control arm (62.1%, PRR=0.94, 95 %CI 0.83-1.07) (Table 2). By year two, however, the prevalence of high band intensities was significantly lower in the intervention arm (42.7%) than the control arm (55.1%) with a multivariate PRR=0.78, 95% CI 0.65-0.94, p=0.02).

The HR-HPV genotypes were classified as either persistent or incident (i.e., newly acquired). MC had no impact on the prevalence of linear array high band intensity among persistent infections at either year one (PRR=0.97, 95% CI 0.97-1.13) or year two (PRR=1.02, 95% CI 0.83-1.24) (Table 2). However, the prevalence of band intensities 3-4 was lower in incident female HR-HPV infections among women married to intervention arm men at year two (PRR=0.66, 95% 0.50-0.87, p=0.003).

Women with high HR-HPV band intensity3-4 at enrollment were significantly more likely to remain persistent during follow up (Table 3) for both women married to circumcised men (adjHR=1.24, 95% CI 0.99-1.55) and uncircumcised men (adjHR=1.25, 95% CI 0.98-1.60) with an overall adjHR of 1.27 (95% CI 1.07-1.50).

Discussion

This study showed that the prevalence of high intensity linear array band signals for HRHPV, which can be used as a surrogate for viral load, was significantly lower in HR-HPV positive female partners of circumcised men at 24 months follow-up (Table 2). The reduction in HR-HPV viral DNA load in female partners of circumcised men was observed in incident female infections, but not in persistent female infections (Table 2), possibly

reflecting a lower infectious dose from circumcised male partners. This is biologically plausible since MC reduces viral DNA load of newly acquired HR-HPV genotypes in men.[16] In conjunction with prior trial findings that MC reduced female partner HR-HPV incidence, prevalence and increased clearance,[14] and observational studies showing reduced cervical cancer,[15] these findings suggest that MC reduces female partner HR-HPV viral DNA load which may ultimately decrease cervical cancer.

We also found that women with higher viral DNA load have increased HR-HPV persistence, which is consistent with previous studies.[4, 22] HR-HPV persistence by viral load intensity was not affected by the male partner's circumcision status in this study. However, MC decreases overall rates of HR-HPV persistence in female partners[14] likely by reducing the infectious dose (or HR-HPV viral load) transmitted.

Although the mechanism of reduced penile HR-HPV infection by MC is unclear, it is believed that the keratinized skin surface and scar formation after MC reduces viral access to the basal epidermal cells which are target cells for HPV infection.[23] Furthermore, the moist subpreputial space between the unretracted foreskin and the glans penis in uncircumcised men may increase HPV viral persistence. Higher detectable viral load has been associated with increased HPV genotype concordance between male and female sex partners.[24] Thus, the reduced HR-HPV prevalence and DNA load in female partners of circumcised men[14] is likely due to decreased male HPV acquisition and lower viral load in the men who do acquire HRHPV.[9-10, 16]

This study has several limitations. Follow-up data was collected only once a year therefore an initial HR-HPV infection might have cleared or the subject may have been re-infected with another genotype during a follow up interval, potentially resulting in over or underestimation of the frequency of high intensity HPV infections. The 22% reduced prevalence of HR-HPV viral load among female partners of circumcised men is likely an underestimate of the protective efficacy of male circumcision since it takes approximately 12-24 months to clear HR-HPV[2] and the trial only evaluated the first 24 months after male circumcision. Thus, the reduced HR-HPV viral load of 34% among incident infections is more likely accurate among men and women in a community. The impact of male circumcision on HR-HPV for both men and their female partners is also not known beyond two years. However, both during the trial and during extended trial follow-up, the protective effect of male circumcision for HIV acquisition increased over time.[7] Thus, male circumcision may also be more efficacious for HRHPV prevention over extended time. The interpretation of HPV epidemiology is problematic since newly detected HPV infections could be a combination of new infections, reactivation of previously undetected dormant infections or sampling unpredictability.[25]

The study population consisted of individuals who were HIV negative and all women were either married or in long term relationships. Therefore the findings may not be generalizable to unmarried or HIV-infected populations. There were a higher number of women married to men in the intervention arm at enrollment possibly because women with male partners in the MC arm were more motivated to participate than women with control arm partners. This slight imbalance between study arms should not have biased comparisons of HR-HPV viral DNA load by MC status. There were more HR-HPV infected women married to control arm men compared to women married to intervention arm men during follow-up because MC reduced overall HR-HPV infection in the intervention arm men and women.

There is now substantial evidence that MC reduces HIV, herpes simplex virus-2, genital ulcer disease, and HR-HPV in men and HR-HPV infection and genital ulcer disease in their female partners.[7, 9-10, 17] This study showed that MC moderately reduces HR-HPV viral

load in infected female partners, providing further evidence for the potential public health benefit of MC. Reducing viral load is likely to reduce transmission of HR-HPV and possibly may avert cervical neoplasia in women and penile cancer in men.

Acknowledgments

We are most grateful to the study participants and the Rakai Community Advisory Board whose commitment and cooperation made this study possible.

The trials were funded by the National Institutes of Health (#UO1AI51171) and the Bill and Melinda Gates Foundation (#22006.02). The Fogarty International Center (#5D43TW001508 and #2D43TW000010-19-AITRP) contributed to training. National Institute of Allergy and Infectious Diseases (NIAID), NIH grants U01-AI-068613 and 3U01-AI075115-03S1 and the NIAID Intramural Program provided laboratory support. A.A.R.T. was supported by the NIH 1K23AI093152-01A1 and Doris Duke Charitable Foundation Clinician Scientist Development Award (#22006.02).

References

1. de Sanjose S, Diaz M, Castellsague X, Clifford G, Bruni L, Munoz N, Bosch FX. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect Dis. 2007; 7:453–9. [PubMed: 17597569]
2. Moscicki AB, Ellenberg JH, Farhat S, Xu J. Persistence of human papillomavirus infection in HIV-infected and -uninfected adolescent girls: risk factors and differences, by phylogenetic type. J Infect Dis. 2004; 190:37–45. [PubMed: 15195241]
3. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, Snijders PJ, Meijer CJ. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003; 348:518–27. [PubMed: 12571259]
4. Dalstein V, Riethmuller D, Pretet JL, Le Bail Carval K, Sautiere JL, Carbillet JP, Kantelip B, Schaal JP, Mougin C. Persistence and load of high-risk HPV are predictors for development of high-grade cervical lesions: a longitudinal French cohort study. Int J Cancer. 2003; 106:396–403. [PubMed: 12845680]
5. Ylitalo N, Sorensen P, Josefsson AM, Magnusson PK, Andersen PK, Ponten J, Adami HO, Gyllensten UB, Melbye M. Consistent high viral load of human papillomavirus 16 and risk of cervical carcinoma in situ: a nested case-control study. Lancet. 2000; 355:2194–8. [PubMed: 10881892]
6. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010; 127:2893–917. [PubMed: 21351269]
7. Tobian AA, Gray RH. The medical benefits of male circumcision. JAMA. 2011; 306:1479–80. [PubMed: 21972310]
8. Giuliano AR, Lazcano E, Villa LL, Flores R, Salmeron J, Lee JH, Papenfuss M, Abrahamsen M, Baggio ML, Silva R, Quiterio M. Circumcision and sexual behavior: factors independently associated with human papillomavirus detection among men in the HIM study. Int J Cancer. 2009; 124:1251–7. [PubMed: 19089913]
9. Tobian AA, Serwadda D, Quinn TC, Kigozi G, Gravitt PE, Laeyendecker O, Charvat B, Ssempijja V, Riedesel M, Oliver AE, Nowak RG, Moulton LH, et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. N Engl J Med. 2009; 360:1298–309. [PubMed: 19321868]
10. Auvert B, Sobngwi-Tambekou J, Cutler E, Nieuwoudt M, Lissouba P, Puren A, Taljaard D. Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: results of a randomized controlled trial conducted in orange farm, South Africa. J Infect Dis. 2009; 199:14–9. [PubMed: 19086814]
11. Tobian AA, Kong X, Gravitt PE, Eaton KP, Kigozi G, Serwadda D, Oliver AE, Nalugoda F, Makumbi F, Chen MZ, Wawer MJ, Quinn TC, et al. Male circumcision and anatomic sites of penile high-risk human papillomavirus in Rakai, Uganda. Int J Cancer. 2011; 129:2970–5. [PubMed: 21462185]
12. Gray RH, Serwadda D, Kong X, Makumbi F, Kigozi G, Gravitt PE, Watya S, Nalugoda F, Ssempijja V, Tobian AA, Kiwanuka N, Moulton LH, et al. Male Circumcision Decreases

Acquisition and Increases Clearance of High-Risk Human Papillomavirus in HIV-Negative Men: A Randomized Trial in Rakai, Uganda. J Infect Dis. 2010; 201:1455–62. [PubMed: 20370483]

13. Backes DM, Bleeker MC, Meijer CJ, Hudgens MG, Agot K, Bailey RC, Ndinya-Achola JO, Hayombe J, Hogewoning CJ, Moses S, Snijders PJ, Smith JS. Male circumcision is associated with a lower prevalence of human papillomavirus-associated penile lesions among Kenyan men. Int J Cancer. 2012; 130:1888–97. [PubMed: 21618520]
14. Wawer MJ, Tobian AA, Kigozi G, Kong X, Gravitt PE, Serwadda D, Nalugoda F, Makumbi F, Ssempiija V, Sewankambo N, Watya S, Eaton KP, et al. Effect of circumcision of HIV-negative men on transmission of human papillomavirus to HIV-negative women: a randomised trial in Rakai, Uganda. Lancet. 2011; 277:209–18. [PubMed: 21216000]
15. Castellsague X, Bosch FX, Munoz N, Meijer CJ, Shah KV, de Sanjose S, Eluf-Neto J, Ngelangel CA, Chichareon S, Smith JS, Herrero R, Moreno V, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med. 2002; 346:1105–12. [PubMed: 11948269]
16. Wilson L, Gravitt P, Tobian A, Kigozi G, Serwadda D, Nalugoda F, Watya S, Wawer M, Gray R. Male circumcision reduces penile high risk human papillomavirus (HPV) viral load in a randomized clinical trial in Rakai, Uganda. Sex Transm Infect. 2012 In press.
17. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, Kiwanuka N, Moulton LH, Chaudhary MA, Chen MZ, Sewankambo NK, Wabwire-Mangen F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007; 369:657–66. [PubMed: 17321311]
18. Serwadda D, Wawer MJ, Shah KV, Sewankambo NK, Daniel R, Li C, Lorincz A, Meehan MP, Wabwire-Mangen F, Gray RH. Use of a hybrid capture assay of self-collected vaginal swabs in rural Uganda for detection of human papillomavirus. J Infect Dis. 1999; 180:1316–9. [PubMed: 10479163]
19. Tobian AA, Kigozi G, Gravitt PE, Xiao C, Serwadda D, Eaton KP, Kong X, Wawer MJ, Nalugoda F, Quinn TC, Gray RH. Human papillomavirus incidence and clearance among HIV-positive and HIV-negative men in Rakai, Uganda. AIDS. 2012; 26:1555–65. [PubMed: 22441255]
20. Cogliano V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F. Carcinogenicity of human papillomaviruses. Lancet Oncol. 2005; 6:204. [PubMed: 15830458]
21. Wentzensen N, Gravitt PE, Long R, Schiffman M, Dunn ST, Carreon JD, Allen RA, Gunja M, Zuna RE, Sherman ME, Gold MA, Walker JL, et al. Human papillomavirus load measured by linear array correlates with quantitative PCR in cervical cytology specimens. J Clin Microbiol. 2012; 50:1564–70. [PubMed: 22337992]
22. Xi LF, Hughes JP, Edelstein ZR, Kiviat NB, Koutsky LA, Mao C, Ho J, Schiffman M. Human Papillomavirus (HPV) type 16 and type 18 DNA Loads at Baseline and Persistence of Type-Specific Infection during a 2-year follow-up. J Infect Dis. 2009; 200:1789–97. [PubMed: 19848609]
23. Tobian AA, Gray RH. Male foreskin and oncogenic human papillomavirus infection in men and their female partners. Future Microbiol. 2011; 6:739–45. [PubMed: 21797689]
24. Bleeker MC, Hogewoning CJ, Berkhof J, Voorhorst FJ, Hesselink AT, van Diemen PM, van den Brule AJ, Snijders PJ, Meijer CJ. Concordance of specific human papillomavirus types in sex partners is more prevalent than would be expected by chance and is associated with increased viral loads. Clin Infect Dis. 2005; 41:612–20. [PubMed: 16080082]
25. Gravitt PE. The known unknowns of HPV natural history. J Clin Invest. 2011; 121:4593–9. [PubMed: 22133884]

Novelty and Impact

Male circumcision has been shown to decrease both HR-HPV prevalence and incidence in men and reduce HR-HPV infection and cervical cancer in their female partners. However, the mechanisms are not known. We evaluated women married to men in a male circumcision trial, and demonstrate that male circumcision reduces HR-HPV viral load among incident infection in female partners which may play a role in the pathophysiology of reduced cervical cancer.

Table 1

Sociodemographic characteristics, risk behaviors, symptoms of sexually transmitted diseases, and number of HR-HPV genotypes detected among female partners at enrollment and follow up, by study arm.

	Enrollment			Year One			Year Two		
	Intervention (n=226)*	Control (n=214)	p-value	Intervention (n=195)	Control (n=214)**	p-value	Intervention (n=139)***	Control (n=166)****	p-value
Age (years)			0.96			0.54			0.70
15-19	36 (15.9%)	36 (16.8%)		26 (13.3%)	30 (14.0%)		16 (11.5%)	21 (12.7%)	
20-24	77 (34.1%)	69 (32.2%)		62 (31.8%)	65 (30.4%)		47 (33.8%)	46 (27.7%)	
25-29	63 (27.9%)	58 (27.1%)		51 (26.2%)	68 (31.8%)		47 (33.8%)	59 (35.5%)	
30-49	50 (22.1%)	51 (23.8%)		56 (28.7%)	51 (23.8%)		29 (20.9%)	40 (24.1%)	
Education						0.70			0.39
No education	25 (11.1%)	33 (15.4%)	0.18	29 (14.9%)	29 (13.6%)		17 (12.2%)	26 (15.7%)	
Primary or Secondary	201 (88.9%)	181 (84.6%)		166 (85.1%)	185 (86.4%)		122 (87.8%)	140 (84.3%)	
Number of sexual partners past year						0.52			0.85
1	213 (94.2%)	203 (94.9%)	0.78	182 (93.3%)	202 (94.8%)		126 (92.6%)	151 (92.1%)	
2+	13 (5.8%)	11 (5.1%)		13 (6.7%)	11 (5.2%)		10 (7.4%)	13 (7.9%)	
Condom use in past year						0.09			0.13
None	186 (82.7%)	169 (79.0%)	0.26	151 (77.4%)	168 (78.5%)		107 (78.7%)	119 (72.6%)	
Inconsistent use	39 (17.3%)	43 (20.1%)		43 (22.1%)	39 (18.2%)		29 (21.3%)	41 (25.0%)	
Consistent condom use	0 (0.0%)	2 (0.9%)		1 (0.5%)	7 (3.3%)		0 (0.0%)	4 (2.4%)	
Self-reported symptoms of STDs in past year									
Genital ulcer disease	36 (15.9%)	32 (15.0%)	0.78	23 (11.8%)	34 (16.0%)	0.23	16 (11.7%)	35 (21.2%)	0.03
Vaginal discharge	107 (47.3%)	114 (53.3%)	0.21	81 (41.5%)	93 (43.7%)	0.67	47 (34.3%)	69 (41.8%)	0.24
Dysuria	45 (19.9%)	50 (23.4%)	0.38	26 (13.3%)	28 (13.1%)	0.96	25 (18.2%)	37 (22.4%)	0.37
HR-HPV Genotypes									
1	154 (68.1%)	129 (60.3%)	0.05	126 (64.6%)	131 (61.2%)	0.50	81 (58.3%)	90 (54.2%)	0.61
2	40 (17.7%)	59 (27.6%)		38 (19.5%)	52 (24.3%)		40 (28.8%)	48 (28.9%)	
3+	32 (14.2%)	26 (12.2%)		31 (15.9%)	31 (14.5%)		18 (12.9%)	28 (16.9%)	

*One woman did not report any information on condom use.

**One woman did not report any information on number of sexual partners or symptoms of STDs.

*** Three women did not report any information on condom use and number of sexual partners and two women did not report any information on symptoms of STDs.

**** Two women did not report any information on condom use and and number of sexual partners and one woman did not report any information on symptoms of STDs.

Table 2

Male circumcision and HR-HPV viral DNA load in female partners.

	Intervention group		Control group		PRR (95% CI) *	adjPRR (95% CI) &
	High HR-HPV Viral Load * / N ^	Percent (%)	High HR-HPV Viral Load * / N ^	Percent (%)		
Overall						
Baseline	207/352	58.8%	210/338	62.1%	0.94 (0.83 - 1.07)	0.94 (0.83 - 1.06)
Year One	159/315	50.5%	188/353	53.3%	0.95 (0.82 - 1.11)	0.96 (0.82 - 1.12)
Year Two	99/232	42.7%	167/303	55.1%	0.78 (0.65 - 0.94)	0.80 (0.66 - 0.96)
Persistent HR-HPV						
Year One	83/124	66.9%	85/119	71.4%	0.97 (0.83-1.13)	0.98 (0.84 - 1.14)
Year Two	50/73	68.5%	80/118	67.8%	1.02 (0.83 - 1.24)	1.04 (0.86 - 1.27)
Incident HR-HPV						
Year One	76/191	39.8%	103/234	44.0%	0.91 (0.71 - 1.16)	0.94 (0.74 - 1.19)
Year Two	49/159	30.8%	87/185	47.0%	0.66 (0.50 - 0.87)	0.67 (0.50 - 0.89)

#PRR is a prevalence risk ratio.

*High HR-HPV viral load includes a linear array band signal strength of 3 or 4 which represents >200 copies/5μl.

^N is the total number of genotypes detected.

&adjPRR is an adjusted prevalence risk ratio. The multivariate analysis adjusted for age and number of sexual partners.

Table 3

HR-HPV viral load at enrollment and association with persistent infection over two years stratified by trial arm.

	Intervention		Control		Overall	
	High Viral Load^	Low Viral Load^	High Viral Load^	Low Viral Load^	High Viral Load^	Low Viral Load^
	Persistent HR-HPV / N* (%)	Persistent HR-HPV / N* (%)	Persistent HR-HPV / N* (%)	Persistent HR-HPV / N* (%)	Persistent HR-HPV / N* (%)	Persistent HR-HPV / N* (%)
Year One	89/207 (43.0%)	35/145 (24.1%)	83/210 (39.5%)	36/128 (28.1%)	172/417 (41.2%)	71/273 (26.0%)
Year Two	27/89 (30.3%)	16/35 (45.7%)	48/83 (57.8%)	17/36 (47.2%)	75/172 (43.6%)	33/71 (46.5%)
Hazard Ratio	1.07 (0.92 - 1.24)		1.24 (1.06 - 1.46)		1.15 (1.03 - 1.28)	
adjHR#	1.24 (0.99 - 1.55)		1.25 (0.98 - 1.60)		1.27 (1.07 - 1.50)	

^High HR-HPV viral load includes a linear array band signal strength of 3 or 4 which represents >200 copies/5μl. Low HR-HPV viral load comprises a linear array band signal strength of 1 or 2.

*N is the number of total genotypes detected at enrollment classified as either high VL or low VL.

#adjHR is an adjusted Hazard Ratio. The Hazard multivariate analysis adjusted for age in all models and circumcision status of male partner for the overall model.