Male Circumcision and Genital Human Papillomavirus: A Systematic Review and Meta-Analysis

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Background: Human papillomavirus (HPV) infection is the principal cause of invasive cervical cancer. There is some evidence that male circumcision (MC) may protect against HPV infection and related disease in both men and women. The purpose of this study was to conduct a systematic review of the literature to assess the association between MC and genital HPV infection indicators including genital warts.

Methods: A systematic search of Medline was conducted to identify all relevant studies from February 1971 to August 2010. Effect estimates were included in random effects models.

Results: A total of 21 studies with 8046 circumcised and 6336 uncircumcised men were included in the meta-analysis. MC was associated with a statistically significant reduced odds of genital HPV prevalence (odds ratio = 0.57, 95% confidence interval: 0.42–0.77). This association was also observed for genital high-risk HPV prevalence in 2 randomized controlled trials (odds ratio = 0.67, 95% confidence interval: 0.54–0.82). No associations were found between MC and genital HPV acquisition of new infections, genital HPV clearance, or genital warts.

Conclusions: This meta-analysis shows a robust inverse association between MC and genital HPV prevalence in men. However, more studies are needed to adequately assess the effect of MC on the acquisition and clearance of HPV infections. MC could be considered as an additional one-time preventative intervention likely to reduce the burden of HPV-related diseases both in men and women, particularly among those countries in which HPV vaccination programs and cervical screening are not available.

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Human papillomavirus (HPV) infection has been established as the necessary cause of invasive cervical cancer in women. It is also an important cause of a fraction of vaginal, vulvar, oropharyngeal, and anal cancer in women as well as of anal, oropharyngeal, and penile cancer in men.[1] HPV-infected men play a key role in the transmission of HPV infection to their female partners. HPV infection in men also causes genital warts[2] and is associated with HPV infection[3] and cervical cancer in their female partners.[4] Interventions that reduce the risk of HPV infection in men may have a preventative impact on HPV-related diseases both in men and women.

The evidence for a beneficial effect of male circumcision (MC) on HIV infection has repeatedly been demonstrated in randomized controlled trials (RCTs).[5–7] There is growing evidence that MC may also protect against HPV infection and related disease.[8–12] Little is know about the natural history of HPV infection in men with only a few small prospective studies undertaken in Europe,[13–15] Latin America,[16] and the United States (US).[17–19] Most published studies to date have been cross-sectional. A prior meta-analysis of 8 observational studies found no evidence of an association between MC and prevalent genital HPV.[20] However, a reanalysis of the same studies found a strong protective effect (odds ratio [OR] = 0.56, 95% confidence interval [CI]: 0.39–0.82).[21] Here, we present the first meta-analysis that includes for the first time data from 2 recently completed RCTs on MC, and adds 9 observational studies to assess the association between MC and genital HPV infection.

MATERIALS AND METHODS

Identification and Eligibility of Relevant Studies

A systematic MEDLINE search was conducted to identify case-control studies, cross-sectional studies, RCTs of MC or cohort studies that reported data on genital HPV and/or genital warts in men by MC status. Reports published from February 1971 up to August 31st, 2010 were included. The search was performed using the following terms: "Papillomaviridae," "Circumcision, Male," "condylomata acuminata," "genital diseases, male." In addition, reference lists of all relevant publications were examined.

Included studies had to meet the following criteria: (1) reporting of separate genital HPV and/or genital warts by MC status, (2) inclusion of a precise description of how MC status was ascertained (e.g., clinical examination or self-reported), (3) for studies on genital warts, lesions had to be identified by clinical examination, and for studies on genital HPV, detailed methodological description of genital sampling techniques, specimen collection, anatomical sites sampled, and details of the different polymerase chain reaction assays used for HPV DNA detection, and (4) inclusion of at least 15 circumcised or uncircumcised men.

We examined genital HPV and genital warts by MC status as the primary endpoint. In studies in which the outcome was genital HPV, we further examined genital HPV prevalence, acquisition, clearance, high-risk HPV prevalence, high-risk HPV acquisition, and high-risk HPV clearance as endpoints.

Data Extraction

Data were extracted by an independent reviewer (G.A.) using a standardized format. Studies included were verified by a second reviewer (X.C.). The following data were extracted: first author, journal name, year of publication, country of study population, source of the study population, age range, study design, method of ascertaining MC status, proportion circumcised, sample size, outcome of interest, measure of association, crude and adjusted effects, and confounders adjusted for when available. In studies in which the outcome was genital HPV, data on the outcome, as well as the sampling method used, subsites sampled, and HPV DNA detection assay used were extracted. When key information was not available, missing data were requested from the authors.

Statistical Methods

Effect estimates were computed using hazard ratios (HR) for cohort studies, risk ratio (RR) for RCTs, and OR for cross-sectional studies, case series, and case-control studies. If the OR was not reported but the raw data were available, the OR and 95% CI were calculated manually. Effect estimates (adjusted when available) were included in random effects models. Heterogeneity between studies was tested using the Q statistic. Pooled effect estimates were derived from random effects models. Sensitivity analyses were conducted restricting meta-analysis by study design and HPV outcome.[22] We assessed associations with 3 different genital HPV outcomes: HPV prevalence, HPV acquisition, and HPV clearance. Genital HPV acquisition was defined as the first positive HPV result after at least one negative result had been observed in a previous visit. Genital HPV clearance was defined as the absence of one or multiple HPV types that had been observed during the previous visit. Publication bias was evaluated visually using the funnel plot and statistically using both the Begg and the Egger tests of funnel plot for correlation between the effect estimates and their variances.[23,24] The systematic review was performed according to the standards recommended by the Cochrane Collaboration. Statistical and graphical analyses were carried out using Stata 11.0 and R 2.11.1[25,26] following the PRISMA guidelines.[27]

RESULTS

Selection of Studies

In total, the MEDLINE database identified 995 individual publications, of which 37 articles included original data and were eligible for review. The remaining 958 publications were review articles and opinion pieces. Fourteen studies were finally excluded because they did not meet the pre-established inclusion criteria: 2 reported on other penile lesions,[28,29] 1 lacked description on how penile lesions were diagnosed,[30] 1 lacked description on how genital warts were diagnosed,[31] 6 were studies in which genital warts were not diagnosed by clinical examination,[10,32–36] and 4 included fewer than 15 circumcised or uncircumcised men.[37–40] A total of 21 studies (23 publications) were thus included in this meta-analysis, involving a total of 8046 circumcised and 6336 uncircumcised men.

Two RCTs investigating MC were identified. One was conducted in Orange Farm, South Africa.[41] Although the primary endpoint was the acquisition of HIV the trial also investigated the association between MC and the prevalence of high-risk HPV. A total of 3274 uncircumcised men were randomized to a control or a MC intervention group with follow-up visits at months 3, 12, and 21. The meta-analysis included data from 1264 participants from whom a urethral swab sample was collected at the 21-month visit. The second RCT identified included 2 parallel but independent trials of MC in the prevention of HIV infection and other sexually transmitted infections and were conducted in Rakai, Uganda.[42] The 2 trials had identical protocols. As a secondary objective the trial assessed the efficacy of MC in the prevention of HPV infections in HIV-negative men. A total of 3393 HIV-negative uncircumcised men were randomized to a control or a MC intervention group with follow-visits at months 6, 12, and 24. HPV was assessed in a subgroup of trial participants with 24 months follow-up. For our analysis, we included data on 520 participants from whom preputial and coronal sulcus swabs were collected and tested for HPV DNA detection.

Association Between MC and Genital HPV

Sixteen studies (18 publications), examined the association between MC and some measure of genital HPV infection. The studies were conducted in the US, Mexico, Africa, South Korea, Denmark, Canada, a multinational study conducted in Brazil, Colombia, Spain, Thailand, and the Philippines, and a multinational study conducted in Brazil, Mexico, and the US. The study populations included students, patients attending sexually transmitted disease or vasectomy clinics, military men, men from the general population, workers in the fishing industry, and husbands or stable partners of women with or without cervical cancer (Table 1).

Variability in methodologies such as sampling methods, HPV DNA detection assays, and specimen collection sites was observed. The most common sampling method to obtain exfoliated cells from the genital epithelium was swabs alone followed by the use of emery or textured paper and swabs, swabs and cytobrush, and cytobrush only. All studies used polymerase chain reaction to amplify HPV DNA. The majority of studies used the PGMY09/11 primer for HPV DNA detection. One multinational study used the MY09/11 primer for the samples collected from Colombia and Spain and the GP5+/6+ primer for the samples collected from Brazil, Thailand, and the Philippines. One study used the GP5+/6+ primer, 2 the Roche Amplicor HPV Test, and 1 the SPF10 primer. Samples were collected from various genital sites or a combination of sites. Fourteen studies collected samples from the glans, 13 from the penile shaft, and 12 from the corona sulcus, or scrotum. Nine studies collected samples from the foreskin, 8 from the urethra, and 3 from the perianal region. Samples from urine, semen, perianal region, anal canal, and fingernails were excluded from this meta-analysis (Table 2).

Association Between MC and Genital HPV Prevalence

Fourteen studies examined genital HPV prevalence by MC status.[8,9,11,16–19,43–49] The proportion of men who were circumcised ranged from 7.2% to 88.3%. Study size ranged from 198 to 1139 men. Significant heterogeneity among studies that examined genital HPV prevalence was observed (Q statistic, $P < 0.001$). Overall, MC was associated with a

TABLE 1. Summary of Studies Reporting on the Association Between Male Circumcision and Genital HPV in Men

Study	Country	Design	Study Population	Study Size	Age	Male Circumcision Assessment	HPV Outcome	Effect Estimate OR (95% CI)*	Adjustment for Potential Confounders
Svare et al[11]	Denmark	Cross-sectional	STD clinics patients	198	18–40+	Self-reported	Prevalence	0.2 (0.06–0.6)	Yes[†]
Castellsagué et al[9]	Brazil[‡]	Pooled data case-control	Husbands/stable partners of woman with or without cervical cancer	1139	~37–57	Physical examination[§]	Prevalence	0.37 (0.16–0.85)	Yes[¶]
Shin et al[43]	South Korea	Cross-sectional	University students	368	18–28	Self-reported	Prevalence	1.8 (0.4–8.2)	Yes[‖]
Baldwin et al[8]	The US	Cross-sectional	STD Clinics patients	344	18–70	Physical examination	Prevalence	0.34 (0.20–0.57)	Yes**
Weaver et al[44]	The US	Cross-sectional	Undergraduate students	279	18–25	Physical examination	Prevalence	1.00 (0.53–1.91)	No
Lajous et al[16]	Mexico	Cohort	Healthy military men	925	16–40	Self-reported	Prevalence Acquisition	0.48 (0.30–0.77) 1.12 (0.45–2.80)	Yes[††] Yes[‡‡]
Vaccarella et al[45]	Mexico	Cross-sectional	Men who requested a vasectomy in public clinics	779	~25–45	Physical examination	Prevalence	0.2 (0.1–0.4)	Yes[§§]
Nielson et al[46]	The US	Cross-sectional	General population volunteers and STD clinic attendees	461	18–40	Physical examination	Prevalence	1.24 (0.75–2.05)	No[¶¶]
Partridge et al[17]	The US	Cohort	Male university students	239	18–20	Physical examination	Prevalence Acquisition	0.67 (0.35–1.28) HR 1.1 (0.6–2.0)	No No
Ng'ayo et al[47]	Africa	Cross-sectional	Men worked in the fishing industry	250	18–63	Physical examination	Prevalence	0.56 (0.21–1.48)	No
Hernandez et al[18,51]	The US	Cohort	University population, primarily heterosexual adult males	300	18–79	Physical examination	Prevalence Clearance	0.59 (0.30–1.18) HR 0.96 (0.71–1.31)	Yes[‖‖] Yes***
Lu et al[19]	The US	Cohort	General population residents of southern Arizona	285	18–44	Physical examination	Prevalence Acquisition Clearance	0.31 (0.15–0.65) HR 0.8 (0.4–1.9) HR 3.1 (1.2–8.2)	No Yes[†††] Yes[†††]
Giuliano et al[48]	Brazil, Mexico, and the US	Cohort	General population, universities, and organized health care systems (Mexico only)	988	18–70	Physical examination	Prevalence	0.70 (0.52–0.94)	Yes[‡‡‡]
Ogilvie et al[49]	Canada	Cross-sectional	STD Clinics patients[§§§]	262	16–69	Physical examination	Prevalence	1.14 (0.67–1.93)	No
Auvert et al[41]	Africa	RCT	General population of uncircumcised men	1264	18–24	Physical examination[¶¶¶]	High risk prevalence	RR 0.68 (0.52–0.89)	Yes[‖‖‖]

(*Continued*)

TABLE 1. Summary of Studies Reporting on the Association Between Male Circumcision and Genital HPV in Men

Study	Country	Design	Study Population	Study Size	Age	Male Circumcision Assessment	HPV Outcome	Effect Estimate OR (95% CI)*	Adjustment for Potential Confounders
Tobian et al[42]; Gray et al[50]	Africa	RCT	HIV-negative, uncircumcised male subjects	520	15–49	Physical examination****	High risk prevalence	RR 0.65 (0.46–0.90)	Yes††††
				840			High risk acquisition	RR 0.67 (0.50–0.91)	Yes‡‡‡‡
							High risk clearance	RR 1.39 (1.17–1.64)	Yes§§§§

*Effect estimates are adjusted when available, otherwise unadjusted.
†Odds ratio adjusted for age, lifetime number of sex partners, sex partners in the past year, and genital warts.
‡Brazil, Colombia, Spain, Thailand and The Philippines.
§Physical examination and self-reported but self-reported was used for all analyses.
¶Odds ratio adjusted for age, study location, level of education, age at first sexual intercourse, lifetime number of sexual partners, and frequency of genital washing after sex.
‖Odds ratio adjusted for age, and number of lifetime sex partners.
**Odds ratio adjusted for sexual frequency per month (mo), genital warts, condom use in past 3 mo, and steady partner.
††Odds ratio adjusted for age, SES (socioeconomic status), and lifetime number of partners.
‡‡Odds ratio adjusted for age, SES (socioeconomic status), lifetime number of partners and anal intercourse with males.
§§Odds ratio adjusted for age group (<25, 25–29, 30–34, 35–39, 40–44, ≥45) and lifetime number of sexual partners.
¶¶They adjusted for potential confounders but we used a not adjusted estimate effect because we excluded samples from perianal region, anal canal and semen.
‖‖Odds ratio adjusted for age, birthplace, race/ethnicity, education level, lifetime no. of female sex partners, history of sex with men, age at initial sex, condom use, history of genital warts, and history of cigarette smoking.
***Hazard ratio adjusted for age, birthplace, race/ethnicity, education, lifetime number of female sex partners, history of sex with men, condom use during prior 4 mo, and history of genital warts.
†††Hazard ratio adjusted for cigarette smoking and lifetime no. of sex partners.
‡‡‡OR adjusted for lifetime number of female partners, sex in the past 3 mo and number of female partners in the past 3 mo.
§§§Men who reported never having sex with another man and who presented for STD screening.
¶¶¶Circumcision status was assessed by a nurse through genital examination.
‖‖‖Risk ratio adjusted for ethnic group, age, education, lifetime number of sex partners, marital status, number of non spousal partners in the past 12 mo, condom use in the past 12 mo, number of sex acts in the past 12 mo, and HIV status.
****Circumcision status was assessed assigned to undergo immediate circumcision along with performing physical examinations.
††††Risk ratio adjustment for enrollment characteristics and rates of sexual practices and symptoms of sexually transmitted infections.
‡‡‡‡Risk ratio adjustment for covariates associated with high-risk HPV at enrollment (age, education, condom use, alcohol consumption with sex, and number of sex partners).
§§§§Risk ratio adjustment for age, education, number of sex partners, and condom use.
RCT indicates randomized controlled trial; STD, sexually transmitted diseases; OR, odds ratio; CI, confidence interval; HR, hazard ratio; RR: risk ratio.

TABLE 2. Summary of Studies Reporting on the Association Between Male Circumcision and Genital HPV in Men by Sampling Method and Specimen Collection Sites

Study	Sampling Methods	HPV DNA Detection Assay	Specimen Collection Sites Included							
			Urethra Meatus	Glans	Coronal Sulcus	Foreskin	Penile Shaft	Scrotum	Perianal Region	Samples Excluded*
Svare et al[11]	Swabs	PCR GP5+/6+	No	Yes	Yes	No	Yes	Yes	Yes	No
Castellsagué et al[9]	Swabs	PCR MY09/11[†]	Yes	Yes	Yes	No	No	No	No	No
Shin et al[43]	Cytobrush	PCR SPF10	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Baldwin et al[8]	Swabs	PCR PGMY09/11	No	Yes	Yes	No	No	No	No	No
Weaver et al[44]	Emery paper and Swabs	PCR PGMY09/11	Yes	Yes	No	Yes	Yes	Yes	No	Urine samples
Lajous et al[16]	Swabs-cytobrush	PCR PGMY09/11	Yes	No	Yes	No	Yes	Yes	No	No
Vaccarella et al[45]	Cytobrush	PCR PGMY09/11	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Nielson et al[46]	Swabs	PCR PGMY09/11	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Perianal[‡]
Partridge et al[17]	Emery paper and swabs	PCR PGMY09/11	Yes	Yes	No	Yes	Yes	Yes	No	Urine and fingernails
Ng'ayo et al[47]	Swabs	PCR PGMY09/11	No	Yes	Yes	No	Yes	Yes	Yes	No
Hernandez et al[18]	Textured paper and swabs	PCR PGMY09/11	No	Yes	Yes	Yes	Yes	Yes	No	Urine[§]
Hernandez et al[51]	Textured paper and swabs	PCR PGMY09/11	No	Yes	Yes	No	Yes	Yes	No	No
Lu et al[19]	Swabs	PCR PGMY09/11	No	Yes	Yes	No	Yes	Yes	No	No
Giuliano et al[48]	Swabs	PCR PGMY09/11	No	Yes	Yes	Yes	Yes	Yes	No	No
Ogilvie et al[49]	Emery paper and swabs	PCR Roche Amplicor HPV Test	No	Yes	No	Yes	Yes	Yes	No	No
Auvert et al[41]	Swabs	PCR Roche Amplicor HPV Test	Yes	No	No	No	No	No	No	Urine
Tobian et al[42]	Swabs	PCR PGMY09/11	No	No	Yes	Yes	No	No	No	No
Gray et al[50]	Swabs	PCR PGMY09/11	No	Yes	Yes	No	Yes[¶]	No	No	No

*Sites sampled in the study but we excluded in this meta-analysis.
[†]This multinational study used the MY09/11 primer for the samples collected from Colombia and Spain and the GP5+/6+ primer for the samples collected from Brazil, Thailand, and the Philippines.
[‡]Perianal region, anal canal and semen.
[§]Urine and semen.
[¶]They only had resources to assay the corona sulcus–glans samples.
PCR indicates polymerase chain reaction.

significant reduced odds of genital HPV prevalence (OR = 0.57, 95% CI: 0.42–0.77) (Fig. 1, panel A). A similar inverse association was also statistically significantly observed for high-risk HPV genital prevalence as assessed in the 2 RCTs of MC, (RR = 0.67, 95% CI: 0.54–0.82).[41,42] No heterogeneity between the 2 RCTs was observed (Q statistic, $P = 0.84$) (Fig. 1, panel A).

Association Between MC and Genital HPV Acquisition

Three cohort studies and 1 RCT examined the effect of MC on genital HPV acquisition of new HPV infections (Table 1).[16,17,19,50] Time between the first HPV positive result after a negative result ranged from 4 to 24 months. No heterogeneity between the cohort studies was observed (Q statistic, $P = 0.79$). MC was not associated with risk of genital HPV acquisition (summary effect 1.01, 95% CI: 0.66–1.53) (Fig. 1, panel A).

Association Between MC and Genital HPV Clearance

Two cohort studies and 1 RCT examined the effect of MC on the rate of genital HPV clearance in men (Table 1).[19,50,51] Time until the first HPV negative result after a positive result for 1 or multiple HPV types ranged from 1.3 to 42.1 months. Only 1 study limited analyses to incident HPV infections.[51] Signif-

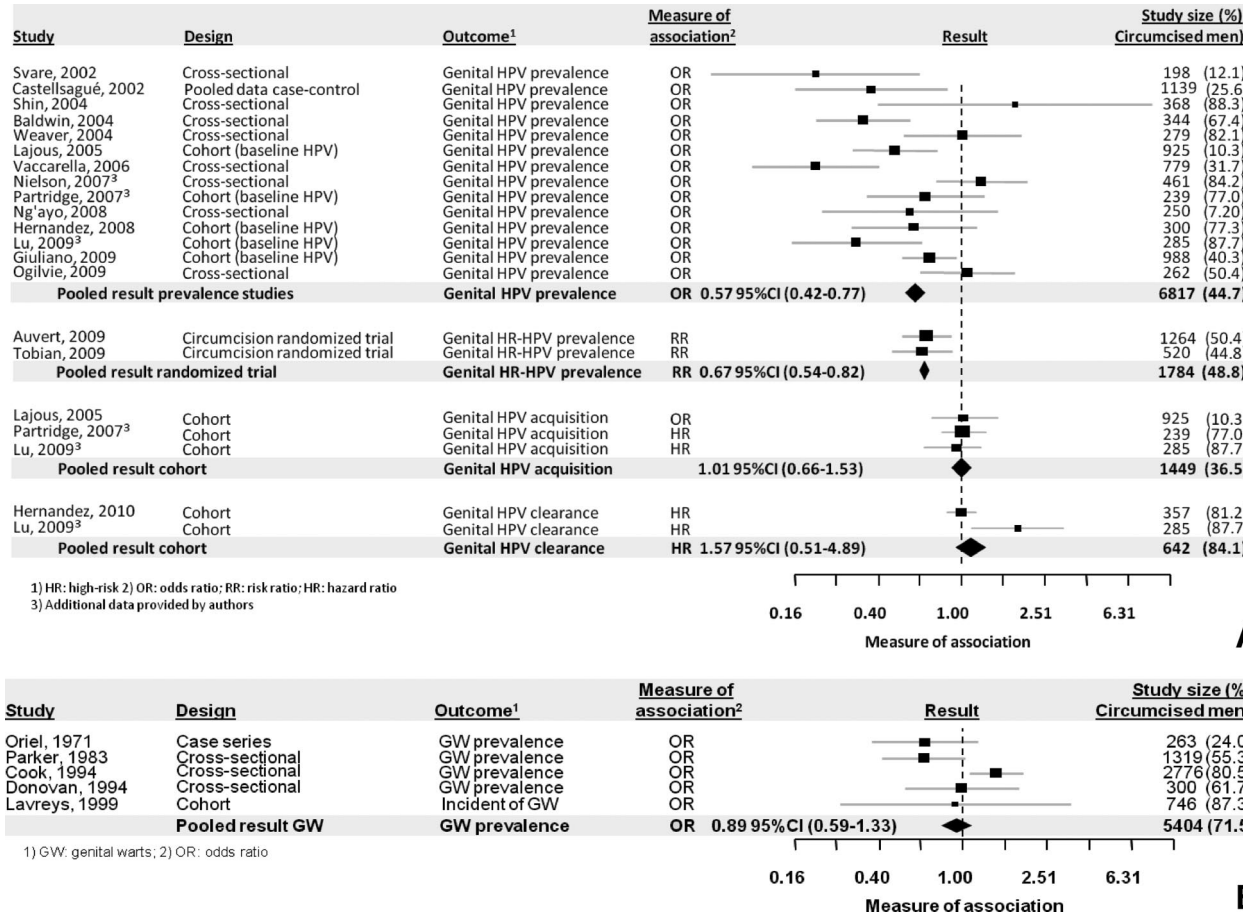

Figure 1. Meta-analysis of studies reporting on the association between MC and genital HPV (panel A) and genital warts (panel B) in men.

icant heterogeneity among cohort studies that examined genital HPV clearance was observed (Q statistic, $P = 0.02$). MC was not associated with genital HPV clearance (HR = 1.57, 95% CI: 0.51–4.89) (Fig. 1, panel A).

Sensitivity Analyses on the Association Between MC and Genital HPV

Sensitivity analyses by key methodological variables were performed. As shown in Table 3, regardless of inclusion of the penile shaft or the scrotum specimens, a consistent protective effect was found for the association between MC and genital HPV prevalence. MC was associated with a significant reduced odds of genital HPV prevalence among studies that sampled the penile shaft or the scrotum (OR = 0.61, 95% CI: 0.44–0.85). A protective effect between MC and genital HPV prevalence was observed among studies using physical examination for ascertainment of circumcision status (OR = 0.58, 95% CI: 0.42–0.81). However, MC was not associated with genital HPV prevalence among studies using self-reported circumcision status (OR = 0.50, 95% CI: 0.20–1.26). MC was associated with a significant reduced odds of genital HPV prevalence among studies that reported adjusted estimate effects (OR = 0.44, 95% CI: 0.30–0.64). In contrast, the inverse association was not significant among studies that did not adjust for potential confounders (OR = 0.79, 95% CI: 0.52–1.19).

MC was associated with a significant reduced risk of genital high-risk HPV acquisition among the RCT that used physical examination to ascertain circumcision status or did not sample that penile shaft or the scrotum (RR = 0.67, 95% CI: 0.50–0.91). MC was not associated with a reduced risk of genital HPV acquisition among cohort studies that sampled the penile shaft or the scrotum (summary effect 1.01, 95% CI: 0.66–1.53). Finally, MC was associated with a nonsignificant increased probability of genital HPV clearance among cohort studies that sampled the penile shaft or scrotum (HR = 1.57, 95% CI: 0.51–4.89) and a significant increased probability of genital high-risk HPV clearance among the RCT that did not sample the penile shaft or scrotum (RR = 1.39, 95% CI: 1.17–1.64).

Association Between MC and Genital Warts

Five studies of genital warts were identified, including 2 from Australia, 1 from England, 1 from Africa, and 1 from the US.[52–56] Four studies recruited men attending sexually transmitted disease clinics and 1 recruited HIV-seronegative truck drivers. The proportion of circumcised men ranged from 24.0% to 87.3%. Study size ranged from 263 to 2776 men. Only 2 studies adjusted for key covariates that were potential confounders (Table 4). Significant heterogeneity among studies of genital warts was observed (Q statistic, $P = 0.02$). MC was not associated with genital warts (OR = 0.89, 95% CI: 0.59–1.33) (Fig. 1, panel B).

TABLE 3. Sensitivity Analyses on the Association Between Male Circumcision and Genital HPV in Men

Sensitivity Analyses	Study Design	HPV Outcome	Effect Estimate (95% CI)*	Q Statistic
By HPV sampling sites				
Penile shaft or scrotum (n = 12)[11,16–19,43–49]	Cross-sectional	Prevalence	**OR: 0.61 (0.44–0.85)**	<0.001
Other site than penile shaft or scrotum (n = 2)[8,9]	Cross-sectional†	Prevalence	**OR: 0.35 (0.22–0.55)**	0.86
Penile shaft or scrotum (n = 3)[16,17,19]	Cohort	Acquisition	1.01 (0.66–1.53)	0.79
Other site than penile shaft or scrotum (n = 1)[50]	RCT	High risk acquisition	**RR: 0.67 (0.50–0.91)**	—
Penile shaft or scrotum (n = 2)[18,19]	Cohort	Clearance	HR: 1.57 (0.51–4.89)	0.02
Other site than penile shaft or scrotum (n = 1)[50]	RCT	High risk clearance	**RR: 1.39 (1.17–1.64)**	—
By method of ascertaining circumcision status				
Self-reporting (n = 3)[11,16,43]	Cross-sectional	Prevalence	OR: 0.50 (0.20–1.26)	0.08
Physical examination (n = 11)[8,9,17–19,44–49]	Cross-sectional	Prevalence	**OR: 0.58 (0.42–0.81)**	<0.001
Physical examination (n = 2)[19,17]	Cohort	Acquisition	HR: 0.98 (0.61–1.57)	0.53
Self-reporting (n = 1)[16]	Cohort	Acquisition	OR: 1.12 (0.45–2.80)	—
Physical examination (n = 1)[50]	RCT	High risk acquisition	**RR: 0.67 (0.50–0.91)**	—
By adjustment for confounders				
Not adjusted (n = 6)[17,19,44,46,47,49]	Cross-sectional	Prevalence	OR: 0.79 (0.52–1.19)	0.03
Adjusted (n = 8)[8,9,11,16,18,43,45,48]	Cross-sectional	Prevalence	**OR: 0.44 (0.30–0.64)**	0.006

*Since adjusted effects were not reported, crude effects were used for the estimation of the combined estimate effect.
†Cross-sectional and pooled data case-control.
The values in bold indicate statistical significance.
CI indicates confidence interval; OR, odds ratio; HR, hazard ratio; RR, risk ratio.

Assessment of Publication Bias

We found no evidence of publication bias among the 21 studies included (Egger test $P = 0.15$). Consistent with this, the funnel plot was not asymmetric (Fig. 2). We also found no evidence of publication bias for each genital outcome studied: warts studies ($P = 0.26$), HPV prevalence studies ($P = 0.32$), HPV acquisition studies ($P = 0.18$), and HPV clearance studies ($P = 0.84$). Furthermore, we found no evidence of publication bias among studies that did not meet the inclusion criteria in this meta-analysis for reporting on other penile lesions[28,29] and those that included fewer circumcised or uncircumcised men, if data were available ($P = 0.69$).[37–40] Similar results were found using Begg test. Consistent with these results the funnel plot for each outcome was not asymmetric (data not shown).

DISCUSSION

Results of this meta-analysis, which includes data from case-control, cross-sectional, cohort, and RCTs studies, show that MC is associated with an overall reduction in the prevalence of genital HPV infection in men.[8,9,11,16,19,41,42,45,48]

Few studies have evaluated the association between MC and acquisition of new genital HPV infections or HPV clearance which require a prospective design. However, one RCT conducted in Uganda showed that MC was associated with a significant reduction in the acquisition of new genital high-risk HPV infections.[50] These findings are consistent with the observed reduction in the prevalence of high-risk HPV in 2 RCTs[41,42] and in several observational studies.[8,9,11,16,19,45,48] In contrast, 3 observational prospective studies[16,17,19] found inconsistent results with an overall nonsignificant pooled estimate effect for the association between MC and genital HPV acquisition risk.

Consistent with the association observed between MC and HPV acquisition, one RCT conducted in Uganda, also showed a statistically significant increase in the clearance of high-risk HPV infections with MC.[50] This finding was also consistent with the results from a small US cohort study.[19] However, the overall pooled estimate of the association between MC and HPV clearance did not reach statistical signif-

TABLE 4. Summary of Studies Reporting on the Association Between Male Circumcision and Genital Warts in Men

Study	Country	Study Population	Study Size	Age (yr)	Effect Estimate OR (95% CI)	Adjustment for Potential Confounders
Oriel[52]	England	STD clinics patients	263	16–40	0.66 (0.37–1.17)	No
Parker et al[53]	Australia	STD clinics patients	1319	~19–40	0.65 (0.41–1.02)	Yes*
Cook et al[54]	United States	STD clinics patients	2776	11–35+	1.43 (1.06–1.92)	Yes†
Donovan et al[55]	Australia	STD clinics patients	300	18–69	0.92 (0.49–1.71)	No
Lavreys et al[56]	Kenya	HIV-seronegative truck drivers	746	16–62	0.77 (0.22–2.70)	No

In each study, male circumcision assessment was conducted via physical examination.
*Adjusted for age.
†Adjusted for age group, in years (13–19, 20–24, 25–29, 30–34, 35+), race/ethnicity (white, African American, other), number of sexual partners in the last month (0, 1, 2+), place of residence (6 Seattle areas and 1 non-Seattle area defined by zip codes), and the other sexually transmitted diseases.
STD indicates sexually transmitted diseases; OR, odds ratio; CI, confidence interval.

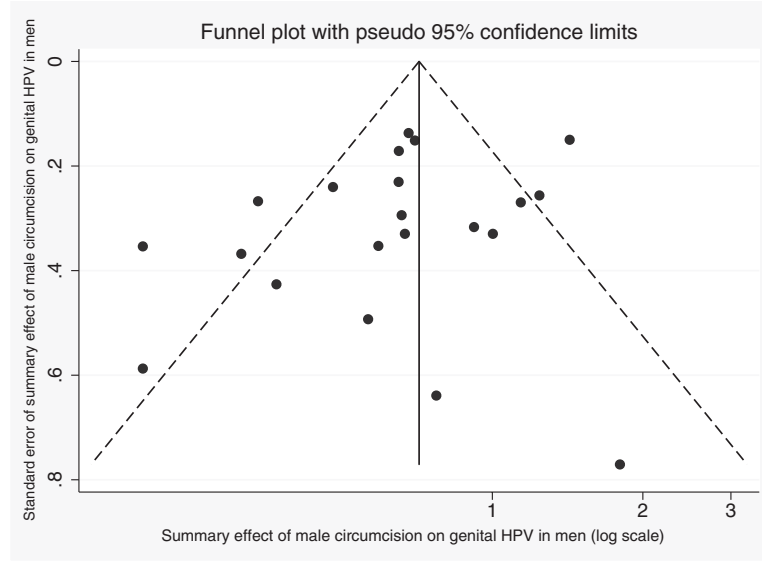

Figure 2. Funnel plot to assess publication bias. Studies are indicated by circle.

icance. The influence that MC may have on HPV clearance may be dependent on the genital site examined as one study found a significant increased rate of HPV clearance of high-risk HPV infection when only the glans or coronal sulcus were examined.[51] Further, the RCT conducted in Uganda sampled the glans and coronal sulcus only and demonstrated also an increased genital high-risk HPV clearance with MC. Another study observed greater clearance of high-risk HPV infections as well as any HPV infections.[19] However, site-specific estimations are rarely reported in the literature.

When interpreting the results of this meta-analysis, importance should be given to the consistent results derived from RCTs of MC, in which significant associations were found for all 3 HPV outcomes.[41,42,50] The consistency of results when restricting the data to RCTs is relevant as it is well accepted that this study design provides the strongest evidence with which to draw conclusions regarding causality. However, all RCTs were conducted among African adult men and caution should be taken in generalizing these results to other populations, including infants.

In this meta-analysis, the inverse association between MC and genital warts prevalence was not statistically significant. Only 5 studies were included, of which 2 did report that MC status influenced the distribution of warts on the penis. One study found that uncircumcised men were more likely to present with distal lesions and circumcised men with proximal lesions on the penis.[57] Another study found that extensive wart formations were more common in uncircumcised men.[52] The lack of a strong effect of MC on genital warts may be because these lesions often appear on the penile shaft, a site for which circumcision is unlikely to strongly influence.[58] Additional studies are necessary to investigate if circumcision status affects the risk and distribution of warts on the penis.

The mechanism by which circumcision might protect against HPV infection is unclear. The penile shaft and the outer surface of the foreskin are covered by a keratinized stratified squamous epithelium that provides a protective barrier against HPV infection. In contrast, the mucosal lining of the prepuce is not keratinized and might be more susceptible to the virus.[9,59] In uncircumcised men, the foreskin is pulled back during intercourse, and the inner mucosa surface of the prepuce is exposed to vaginal and cervical secretions. It has been proposed that retraction of the foreskin during intercourse exposes the inner mucosal surface to HPV providing access to the basal cells through small abrasions.[9,18,60,61] Removal of the foreskin thus could minimize the chance of viral entrance as a result of both the reduced size of the mucosal surface area vulnerable to HPV and the increased chance of mucosal trauma during intercourse.[9] Thus, it is plausible that circumcision might reduce high-risk HPV acquisition.[50] It is not understood how circumcision facilitates greater clearance of HPV. It has been proposed that HPV enters and persists more efficiently in the inner mucosal surface of the prepuce of uncircumcised men than in the keratinized penile surface of circumcised men.[51]

There are a number of limitations that must be considered in interpreting these results. One is the variability in study designs and sampling methodologies across studies. Sensitivity analyses were carried out restricting the meta-analysis by study design and genital HPV outcome studied: warts, HPV prevalence, HPV acquisition studies, and HPV clearance to examine the robustness of the pooled results. In all analyses, a consistent inverse association of MC with genital HPV prevalence was observed. Another limitation is that a substantial proportion of the included published studies were cross-sectional, which limits the causality inference of MC on HPV infection. However, similar to what has been observed in cross-sectional studies, 2 RCTs have consistently shown an association between MC and lower risk of genital HPV infection. Another limitation is a possible selection bias in the studies we included in this meta-analysis. However, publication bias was not observed. Although this meta-analysis included studies from several countries, it is possible that our results may not be generalizable to all men. Finally, there may be other factors that could influence the association between MC and HPV infection that were not considered in our analysis, such as the effect of age at circumcision or the surgical procedure used to remove the prepuce.

There is literature to suggest that MC for the prevention of HIV infection is cost-effective across a broad range of age groups in Africa.[62] Ideally, MC should be a procedure conducted before potential exposure to HPV through sexual contact. However, this recommendation should be consistent with

other factors such as the culture and the specific needs of different populations.

In conclusion, this meta-analysis shows a robust inverse association between MC and genital HPV prevalence in men. Additional studies that include diverse populations and data on HPV acquisition, clearance, or both in men are necessary to more clearly define how MC reduces genital HPV prevalence in men and to address the limitations of the current study. Given the consistent protective effects also found for HIV, MC should be considered as an additional one-time preventative intervention likely to reduce the burden of associated diseases in both men and women, particularly among those countries in which HPV vaccination programs and cervical cancer screening are not available.

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