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ORIGINAL ARTICLE

Male Health

Relationship between circumcision and human papillomavirus infection: a systematic review and meta-analysis

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Male circumcision (MC) is reported to reduce human papillomavirus (HPV) prevalence in men. However, the efficacy remains imprecise. The aim of this study was to conduct a systematic review and meta-analysis to assess the relationship between MC and genital HPV infection and genital warts. PUBMED, EMBASE, and Web of Science were searched from inception to March 22, 2015. We identified 30 papers, including a total of 12149 circumcised and 12252 uncircumcised men who were evaluated for the association of circumcision with genital HPV or genital warts. Compared with men who were not circumcised, circumcised men may have had significantly reduced odds of genital HPV prevalence (odds ratio [OR]: 0.68; 95% confidence interval [95% CI]: 0.56–0.82). There was no significant association between MC and genital HPV acquisition of new infections (OR: 0.99; 95% CI: 0.62–1.60), genital HPV clearance (OR: 1.38; 95% CI: 0.96–1.97), and prevalence of genital warts (OR: 1.17; 95% CI: 0.63–2.17). This meta-analysis suggests that circumcision reduces the prevalence of genital HPV infections. However, no clear evidence was found that circumcision was associated with decreased HPV acquisition, increased HPV clearance, or decreased the prevalence of genital warts. More studies are required to evaluate adequately the effect of MC on the acquisition and clearance of HPV infections and prevalence of genital warts.

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INTRODUCTION

Human papillomavirus (HPV) infection is common and can cause genital warts, invasive cervical cancer in women, and penile and anal cancer in men.[1] Cervical cancer is the second most common cancer among women worldwide. Up to 99% of cervical cancers are associated with infection of oncogenic HPV genotypes.[2] Therefore, finding interventions that can reduce the risk of HPV infection may have a protective impact on HPV-related diseases, both in men and women.

Male circumcision (MC) is a simple, rapid operation; however, it remains unclear whether it has a protective effect against genital HPV infection. A systematic review of studies conducted by Van Howe *et al.*[3] found no evidence of an association between MC and genital HPV infections. However, two meta-analyses[4,5] and several studies[6–8] found that MC could help reduce HPV infections. Recently, a randomized controlled trial (RCT) with a large patient population demonstrated that MC was not associated with the acquisition and clearance of genital HPV infection.[9] Based on the discrepancy between these findings, there is an urgent need to perform an updated meta-analysis on this topic. In the present systematic review and meta-analysis, we added five recent papers[1,9–12] (including 4103 circumcised and 5916 uncircumcised men) to provide a comprehensive survey to address this controversy.

MATERIALS AND METHODS

Data sources and search strategy

PUBMED, EMBASE, and Web of Science were searched from inception until March 22, 2015. The search was performed using the following terms: "circumcision, male," "HPV," "papillomaviridae," "genital diseases, male," "genital warts," and "condylomata acuminata." We also examined the reference lists of all relevant papers. The criteria for eligibility were as follows: (1) evaluate the potential association between MC and HPV infection or MC and genital warts; (2) give a precise description about how MC status was ascertained; and (3) reporting of HPV sampling techniques, sampling sites, and details of the different polymerase chain reaction assays used for HPV DNA detection. We excluded studies if they (1) did not report any of the outcomes of interest, (2) enrolled men who were HIV-positive, (3) had interventions that did not include MC, and (4) contained data that could not be extracted in an appropriate format and any attempts to obtain the relevant data from the authors had failed.

Data extraction and quality assessment

We systematically assessed the quality of all the studies included. Data were extracted independently by two authors (YP-Z and ZW-J) and disagreements were discussed to reach consensus between the two authors or consultation with a third reviewer. We classified as separate studies

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if more than one outcome (HPV prevalence, HPV acquisition, HPV clearance, and genital warts) was evaluated in one paper. The following data were extracted from the studies: (1) publication details, including first author and year of publication; (2) study design; (3) characteristics of the studied population, including sample size, age range, study population, and country in which the study was conducted; (4) method of ascertaining MC status (self-reported or physical examination); (5) the proportion of circumcised and uncircumcised men; and (6) positive events among circumcised and uncircumcised men.

Statistical analysis

Review Manager version 5.2 software (Cochrane Collaborative, Oxford, UK) was used to integrate all of the individual outcomes. Heterogeneity among the studies was measured by a random-effects model using the χ^2 test, P values, and I^2 statistics. $P < 0.05$ was considered statistically significant. Publication bias was estimated by the funnel plot and Begg's rank regression test using STATA version 12.0 software (Stata Corporation, College Station, TX, USA).[13] $P < 0.1$ was considered statistically significant publication bias.

RESULTS

Data retrieval

A total of 5082 citations were identified after the initial database search. After reading the titles and abstracts, 78 papers were retrieved. Fifty-four of these papers were excluded after full-text review. In addition, seven papers were retrieved from the reference lists of all relevant papers.[7,8,14–17] Thus, 30 papers (39 studies) involving a total of 12 149 circumcised and 12 252 uncircumcised men were finally included in this meta-analysis (**Figure 1**).

Study characteristics

The characteristics of patients enrolled in our meta-analysis are summarized in **Tables 1–3**. Twenty-four studies evaluated the association between MC and HPV prevalence;[1,6–8,10–12,14–16,18–31] six evaluated the association between MC and HPV acquisition;[9,10,15,16,23,32] four evaluated the association between MC and HPV clearance;[9,16,23,32] and five evaluated the association between MC and genital warts.[7,17,33–35]

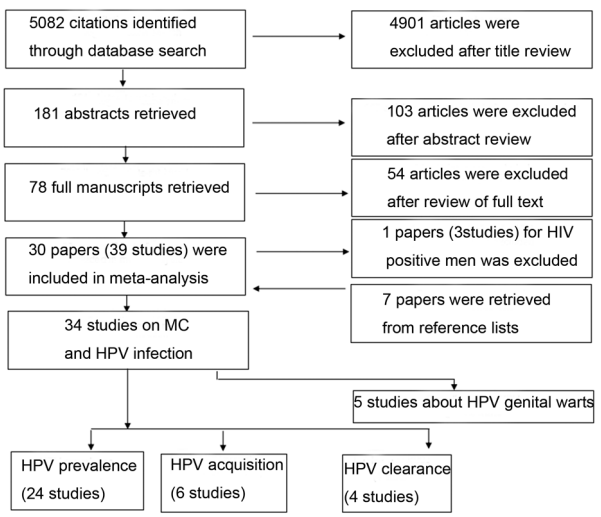

Figure 1: Flowchart of the studies identified in the meta-analysis. MC: male circumcision; HPV: human papillomavirus.

HPV specimens were collected from different regions including glans, penile shaft, coronal sulcus, scrotum, foreskin, urethra, and perianal region. All studies measured HPV DNA by polymerase chain reaction. The sampling method and specimen collection sites of studies about MC and HPV prevalence are summarized in **Table 4**.

MC and HPV prevalence

Twenty-four studies evaluated the association between MC and HPV prevalence[1,6–8,10–12,14–16,18–31] (**Table 1**). The random-effects model was applied to calculate the pooled odds ratio (OR) and its 95% CI. HPV-positive rates among circumcised and uncircumcised men ranged from 2.4% to 78.0% and 7.0% to 81.2%, respectively. HPV prevalence was lower in circumcised than in uncircumcised men in 10 of the 24 studies[8,11,18,19,22–24,27,28,31] but higher in one study.[15] In addition, 13 studies showed MC had no effect on HPV prevalence.[1,6,7,10,12,14,16,20,21,25,26,29,30] In general, MC significantly reduced the odds of genital HPV prevalence (OR: 0.68; 95% CI: 0.56–0.82), but substantial between-study heterogeneity was observed ($I^2 = 70\%$) (**Figure 2**).

MC and HPV acquisition

Five cohort studies and one RCT examined the effect of MC on genital HPV acquisition[9,10,15,16,23,32] (**Table 2**). HPV acquisition was defined as follows: a new infection identified in men who were initially negative for any HPV and who acquired one or two or more new HPV infections during the next follow-up or men who were initially positive for a specific HPV genotype but acquired one or more new HPV genotypes during the next follow-up.[32] The proportion of men who were circumcised ranged from 17.1% to 87.7%. The interval of follow-up ranged from 12 to 24 months. The proportion of HPV acquisition among circumcised and uncircumcised men ranged from 15.7% to 62.6% and 21.3% to 66.2%, respectively. In general, there was no significant association between MC and genital HPV acquisition (OR: 0.99; 95% CI: 0.62–1.60). Substantial heterogeneity was observed among the studies ($I^2 = 87\%$) (**Figure 3**).

MC and HPV clearance

Three cohort studies and one RCT examined the effect of MC on genital HPV clearance[9,17,23,32] (**Table 2**). Clearance was defined as the proportion of men with preexisting HPV, who were negative for that genotype at a subsequent sequential study visit.[32] The study population ranged from 105 to 4033. The proportion of men who were circumcised ranged from 7.6% to 87.7%. The interval of follow-up ranged from 12 to 24 months. The proportion of HPV clearance among circumcised and uncircumcised men ranged from 31.2% to 100% and 25.7% to 72.8%, respectively. In general, there was no significant association between MC and genital HPV clearance (OR: 1.38; 95% CI: 0.96–1.97). Substantial heterogeneity was observed among the studies ($I^2 = 56\%$) (**Figure 4**).

MC and genital warts

Three cross-sectional two case–control studies examined the effect of MC on genital warts[7,17,33–35] (**Table 3**). The study population was men attending sexually transmitted disease (STD) clinics, general population, or partners of women with cervical intraepithelial neoplasia. Three studies assessed current warts[7,33,34] and two assessed historic warts.[17,35] The proportion of men who were circumcised ranged from 4.0% to 83.5%. In general, there was no significant association between MC and genital warts (OR: 1.17; 95% CI: 0.63–2.17). Substantial heterogeneity was observed among the studies ($I^2 = 68\%$) (**Figure 5**).

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of studies on HPV prevalence. The funnel plots did

Table 1: Summary of studies reporting on the association between MC and HPV prevalence in men

Study	*Country*	*Design*	*Study population*	*Age*	*Study size*	*Male circumcision assessment*
Aynaud *et al*. 2002[20]	France	Cross-sectional	Partners of women with HPV-associated genital lesions	19–42	111	Physical examination
Castellsague *et al*. 2002[19]	Brazil, Colombia, Thailand, Philippines, and Spain	Pooled data case-control	Husbands/stable partners of woman with or without cervical cancer	37–57	1139	Physical examination
Svare *et al*. 2002[18]	Denmark	Cross-sectional	STD clinics patients	18–40	198	Self-reported
Shin *et al*. 2004[21]	South Korea	Cross-sectional	University students	18–28	368	Self-reported
Weaver *et al*. 2004[6]	The USA	Cross-sectional	Undergraduate students	18–25	279	Physical examination
Baldwin *et al*. 2004[22]	The USA	Cross-sectional	STI clinic attendees (high risk)	18–70	344	Physical examination
Bleeker *et al*. 2005[7]	The Netherlands	Cross-sectional	Partners of women with CIN	-	224	Clinical exam
Lajous *et al*. 2005[23]	Mexico	Cohort	Healthy military men	16–40	925	Self-reported
Vaccarella *et al*. 2006[24]	Mexico	Cross-sectional	Men who requested a vasectomy in public clinics	25–45	779	Physical examination
Rombaldi *et al*. 2006[14]	Brazil	Cross-sectional	Partners of women with CIN	-	99	Not reported
Partridge *et al*. 2007[15]	The USA	Cohort	Male university students	18–20	239	Physical examination
Hernandez *et al*. 2008[27]	The USA	Cohort	University population, primarily heterosexual adult males	18–79	254	Physical examination
Nielson *et al*. 2007[25]	The USA	Cross-sectional	General population volunteers and STD clinic attendees	18–40	463	Physical examination
Ng'Ayo *et al*. 2008[26]	Africa	Cross-sectional	Men worked in the fishing industry	18–63	250	Physical examination
Lu *et al*. 2009[16]	The USA	Cohort	General population	18–44	285	Physical examination
Giuliano *et al*. 2009[28]	Brazil, Mexico, and the USA	Cohort	General population, universities, and organized health care systems (Mexico only)	18–70	988	Physical examination
Ogilvie *et al*. 2009[29]	Canada	Cross-sectional	STD clinics patients	16–69	262	Physical examination
Muller *et al*. 2010[31]	South Africa	Cross-sectional	Sexual health clinic attendees, HIV prevalence 49.5%	-	208	Physical examination
Tobian *et al*. 2009[30]	Africa	RCT	HIV-negative, uncircumcised male subjects	15–49	520	Physical examination
Auvert *et al*. 2009[8]	Africa	RCT	General population of uncircumcised men	18–24	1264	Physical examination
Vanbuskirk *et al*. 2011[10]	Washington	Cohort	Male University of Washington students	18–20	477	Physical examination
Tobian *et al*. 2011[1]	Rakai, Uganda	RCT	General population	15–49	459	Immediate circumcision
Tarnaud *et al*. 2011[11]	South Africa	RCT	General population	18–24	1573	Physical examination
Backes *et al*. 2012[12]	Kenya	RCT	Participants were recruited from STI clinics, workplaces, and community organizations	18–24	275	Physical examination

MC: male circumcision; HPV: human papillomavirus; STD: sexually transmitted disease; STI: sexually transmitted infection; CIN: cervical intraepithelial neoplasia; RCT: randomized controlled trial

Table 2: Summary of studies reporting on the association between MC and HPV acquisition and HPV clearance in men

Study	*Country*	*Design*	*Study population*	*Age*	*Male circumcision assessment*	*Study size*	
						HPV acquisition	*HPV clearance*
Lajous *et al*. 2005[23]	Mexico	Cohort	Healthy military men	16–40	Self-reported	210	105
Partridge *et al*. 2007[15]	The USA	Cohort	Male university students	18–20	Physical examination	240	N/A
Lu *et al*. 2009[16]	The USA	Cohort	General population residents of southern Arizona	18–44	Physical examination	285	285
Gray *et al*. 2010[32]	Rakai, Uganda	RCT	HIV-uninfected men	15–49	Physical examination	840	645
Vanbuskirk *et al*. 2011[10]	Washington	Cohort	Male University of Washington students	18–20	Physical examination	477	N/A
Albero *et al*. 2014[9]	Brazil, Mexico, and the USA	Cohort	General population, universities, and organized health-care systems	18–70	Physical examination	4033	4033

N/A: not applicable; RCT: randomized controlled trail; MC: male circumcision; HPV: human papillomavirus

Table 3: Summary of studies reporting on the association between MC and genital warts in men

Study	*Country*	*Design*	*Study population*	*Age*	*Circumcised (%)*	*Study size*	*Male circumcision assessment*
Cook *et al*. 1994[33]	The USA	Cross-sectional	STI clinic attendees	N/A	2236	2776	Physical examination
Donovan *et al*. 1994[17]	Australia	Cross-sectional	STI clinic attendees	N/A	185	300	Physical examination
Van Den Eeden *et al*. 1998[34]	The USA	Case-control	General population	N/A	198	237	Self-reported
Tseng *et al*. 2001[35]	The USA	Case-control	General population	<75	43	100	Physical examination
Bleeker *et al*. 2005[7]	The Netherlands	Cross-sectional	Partners of women with CIN	N/A	9	224	Clinical exam

N/A: not applicable; MC: male circumcision; STI: sexually transmitted infection; CIN: cervical intraepithelial neoplasia

not reveal any evidence of obvious asymmetry among the 24 studies included (**Figure 6**). Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias ($P = 0.271$).

Table 4: Summary of studies reporting on the association between MC and genital HPV Prevalence 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*	*Semen*
Aynaud *et al*. 2002[20]	Unknown	Unknown	–	–	–	–	–	–	–	+
Castellsague *et al*. 2002[19]	Swabs	PCR MY09/11	+	+	+	–	–	–	–	–
Svare *et al*. 2002[18]	Swabs	PCR GP5+/6+	–	+	+	–	+	+	+	–
Shin *et al*. 2004[21]	Cytobrush	PCR SPF10	+	+	+	+	+	+	–	–
Weaver *et al*. 2004[6]	Emery paper and swabs	PCR PGMY09/11	+	+	–	+	+	+	–	–
Baldwin *et al*. 2004[22]	Swabs	PCR PGMY09/11	–	+	+	–	–	–	–	–
Bleeker *et al*. 2005[7]	Brush	PCR GP5+/6+	–	+	+	+	–	–	–	–
Lajous *et al*. 2005[23]	Swabs cytobrush	PCR PGMY09/11	+	–	+	–	+	+	–	–
Vaccarella *et al*. 2006[24]	Cytobrush	PCR PGMY09/11	+	+	+	+	+	+	–	–
Rombaldi *et al*. 2006[14]	Brush	PCR PGMY09/11	+	–	+	+	+	–	–	–
Partridge *et al*. 2007[15]	Emery paper and swabs	PCR PGMY09/11	+	+	–	+	+	+	–	–
Hernandez *et al*. 2008[27]	Textured paper and swabs	PCR PGMY09/11	–	+	+	+	+	+	–	–
Nielson *et al*. 2007[25]	Swabs	PCR PGMY09/11	+	+	+	+	+	+	+	–
Ng'Ayo *et al*. 2008[26]	Swabs	PCR PGMY09/11	–	+	+	–	+	+	+	–
Lu *et al*. 2009[16]	Swabs	PCR PGMY09/11	–	+	+	–	+	+	–	–
Giuliano *et al*. 2009[28]	Swabs	PCR GMY09/11	–	+	+	+	+	+	–	–
Ogilvie *et al*. 2009[29]	Emery paper and swabs	PCR Roche Amplicor HPV test	–	+	–	+	+	+	–	–
Muller *et al*. 2010[31]	Swabs	LA HPV genotyping test	–	+	+	–	+	–	–	–
Tobian *et al*. 2009[30]	Swabs	PCR GMY09/11	–	+	+	+	–	–	–	–
Auvert *et al*. 2009[8]	Swabs	PCR Roche Amplicor HPV test	+	+	–	–	–	–	–	–
Vanbuskirk *et al*. 2011[10]	Swabs	PCR PGMY09/11	+	+	+	–	+	–	–	–
Tobian *et al*. 2011[1]	Swabs	Roche HPV LA	–	–	+	–	+	–	–	–
Tarnaud *et al*. 2011[11]	Swabs	HPV LA	+	–	–	–	–	–	–	–
Backes *et al*. 2012[12]	Swabs	PCR GP5+/6+	–	+	+	–	+	–	–	–

PCR: polymerase chain reaction; MC: male circumcision; HPV: human papillomavirus; LA: linear array

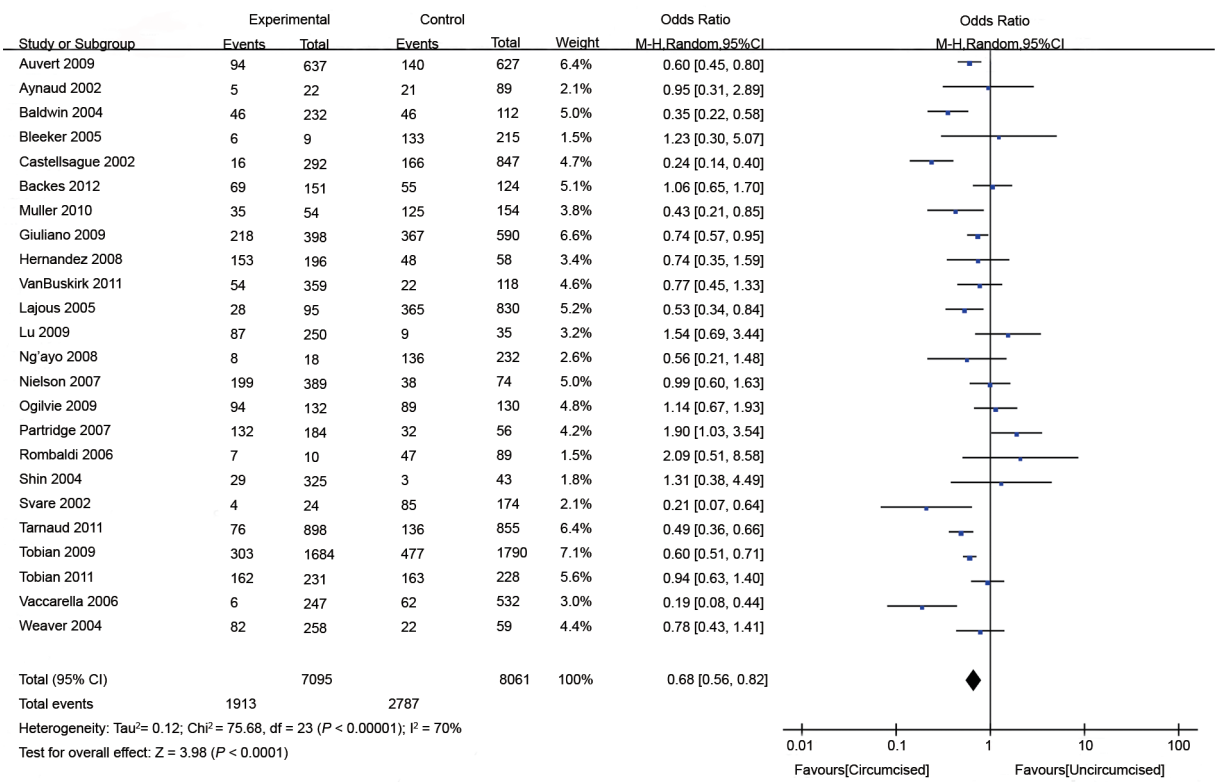

Figure 2: Forest plot of the studies assessing the association between MC and HPV prevalence. MC: male circumcision; HPV: human papillomavirus.

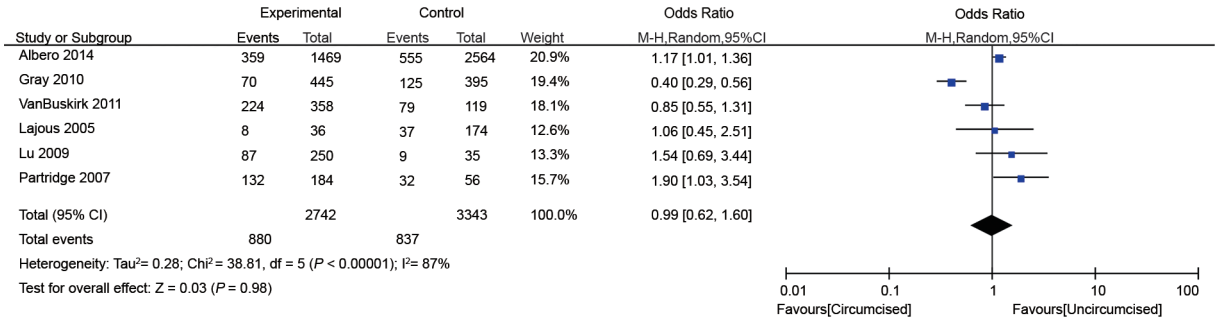

Figure 3: Forest plot of the studies assessing the association between MC and HPV acquisition. MC: male circumcision; HPV: human papillomavirus.

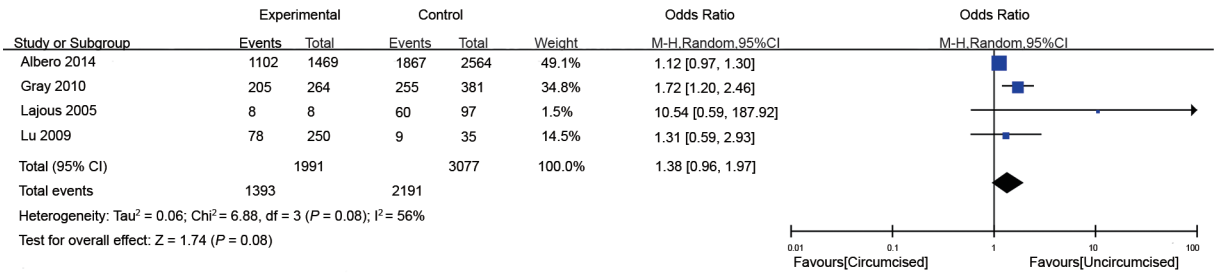

Figure 4: Forest plot of the studies assessing the association between MC and HPV clearance. MC: male circumcision; HPV: human papillomavirus.

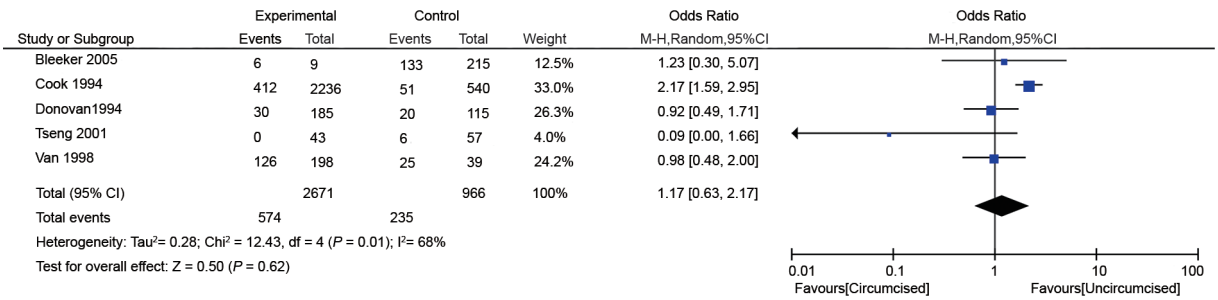

Figure 5: Forest plot of the studies assessing the association between MC and genital warts. MC: male circumcision.

DISCUSSION

The existing evidence, which includes data from case–control, cross-sectional and cohort studies, and RCTs, was analyzed in our meta-analysis to ascertain pooled estimates of the relationship between MC and genital HPV prevalence. Overall, our results revealed that MC reduced the prevalence of genital HPV infection in an average of 32% of men. This means that there is a need to perform three circumcisions to prevent one infection. While a series of studies and our meta-analysis demonstrated an inverse association between MC and HPV prevalence in men, one meta-analysis conducted in September 2006 revealed that there was no significant association between circumcision status and HPV prevalence.[3] Because HPV is a topical infection in the skin and mucosa, one possible explanation for the discrepancy may be the varied specimen collection sites in the different studies.

HPV detection varies by anatomical site and evaluating HPV only on the coronal sulcus and urethra might bias the estimated protective efficacy of MC.[1] More frequent HPV infection was detected on the coronal sulcus than the shaft in uncircumcised men, suggesting that the moist subpreputial space might provide a more favorable environment for HPV infection.[10] When interpreting the effect of different sampling methods on our results, we should note that the effectiveness of sampling methods at different anatomical sites and the sampling method itself may affect the efficacy of the sampling methods. However, it is impossible to make a comment on those effects; thus, the method used to sample HPV may be a source of heterogeneity.

Only a few studies assessed the association between MC and HPV acquisition or clearance. The present meta-analysis suggests no evidence of an effect of decreased HPV acquisition (OR: 0.99; 95% CI: 0.62–1.60)[9,10,15,16,23,32] and increased HPV clearance (OR: 1.38; 95% CI: 0.96–1.97).[8,16,23,32] However, one RCT conducted in Uganda[32] and a cohort study in the USA[9] found that MC reduced acquisition of HPV infection. On the contrary, one recently published cohort study[9] which enrolled 4033 healthy men and three observational prospective studies[15,16,23] suggested that MC was not associated with an overall reduction of genital HPV acquisition, which was consistent with our findings. Although limited data prevented us from performing a subgroup analysis according to sample sites, only a few studies used specimens collected from the scrotum, perianal area, and semen, which might have resulted in selection bias in our meta-analysis. In addition, our results suggested that there was no evidence of MC increasing HPV

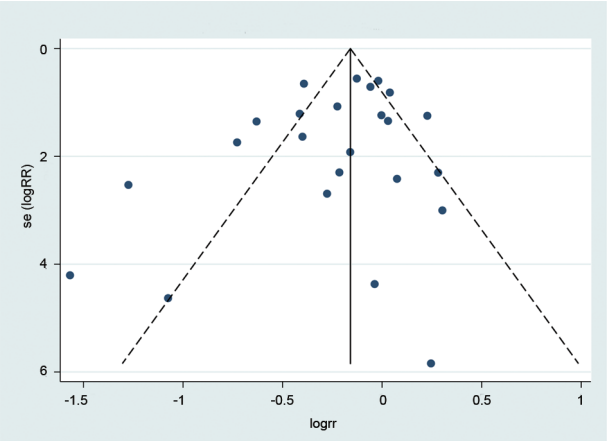

Figure 6: Publication bias in studies on HPV prevalence. HPV: human papillomavirus.

clearance (OR: 1.38; 95% CI: 0.96–1.97).[9,16,23,32] When interpreting the results of our meta-analysis, we must note that HPV has a high rate of spontaneous clearance, and we suggest that the sampling sites also played an important role in the final results. One RCT suggested that MC increased HPV clearance when sampled on the coronal sulcus.[32] However, when sampled on the scrotum and penile shaft, Hernandez *et al*.[27] found that HPV clearance was not affected by MC. In addition, when interpreting the differences in findings between reduced prevalence of HPV after MC and no reduction in acquisition or increased clearance after MC, we suggest that this might have been because the study population for HPV acquisition and clearance was smaller than for HPV prevalence. Therefore, the results need to be validated using a larger number of studies.

Our meta-analysis suggested that there was no significant association between MC and genital warts (OR: 1.17; 95% CI: 0.63–2.17).[7,17,33–35] One study suggested that genital warts were more likely at distal lesions on the penis among uncircumcised men.[33] Another study suggested that uncircumcised men were more likely to present with extensive warts.[36] In contrast, one prospective cohort study conducted in Kenya[37] suggested that the risk of genital warts was not affected by the presence of a foreskin. One plausible explanation for our results may be that genital wart lesions usually appear on the penile shaft; a site that is not often affected by MC.[38] As we only found five papers suitable for our meta-analysis,[7,17,33–35] additional studies are necessary to investigate the relationship between MC and genital warts.

It is plausible that MC might reduce genital HPV infection; however, the mechanism is unclear.[19] In uncircumcised men, the inner preputial mucosa is exposed to vaginal and cervical secretions as the foreskin is retracted during intercourse.[27] The penile shaft and surface of the foreskin are covered by a keratinized stratified squamous epithelium that could provide a protective effect against HPV infection. However, the foreskin mucosa is not keratinized and might be more susceptible to HPV infections.[27] In addition, the moist environment of the foreskin may provide a favorable condition for HPV survival.[27] It has been proposed that keratinization of the circumcision scar may also reduce the chance of HPV infection.[19] Therefore, MC may reduce the chance of HPV access to epidermal basal cells.

Our meta-analysis included five additional papers[1,9–12] that were not included in the most recent systematic review about MC and genital HPV infection. At the same time, we enrolled an additional 4103 circumcised and 5916 uncircumcised men to provide a comprehensive survey about the relationship between MC and genital HPV infection. As the results of previous meta-analyses[3–5] and several other studies[7,14] showed major differences, it is urgent that an agreement is reached. Even though our results are consistent with the recent two meta-analyses,[4,5] our meta-analysis validated the results through using a larger sample size. Compared to the recent two meta-analyses, to reduce the heterogeneity among the enrolled studies, enrollment in our meta-analysis were restricted to HIV-negative men, and one RCT conducted among HIV-positive men was excluded.[38]

Our meta-analysis had several limitations. First, there was considerable heterogeneity among the studies. This was because of different study types (case–control, cross-sectional, cohort, and RCT), patients coming from different regions, and differences in results between the normal population (lower risk) and those attending sexually transmitted disease (STD) clinics or partners of HPV-infected women (higher risk). It was not possible to run a subset analysis with the existing data; therefore, these factors might have influenced our results. Second, sampling methods and specimen collection sites varied considerably among the included studies. Third, some of the studies were observational, the MC status was ascertained by self-report, and it was hard to give an accurate assessment of the effect of the surgical procedure. At the same time, age at circumcision and different surgical methods may also have affected our results. Finally, our results for HPV acquisition and clearance could have been influenced by a single study providing two-thirds of all the patients and this may have introduced bias to the overall results.

HPV infection has been established as an important cause of invasive cervical cancer in women and penile cancer in men. Our results suggested that MC could reduce the odds of genital HPV prevalence. MC as a useful intervention could reduce the risk of HPV infection in men and may also have a preventive impact on HPV-related diseases both in men and women.

CONCLUSIONS

This meta-analysis suggested that MC was strongly associated with reduced odds of genital HPV prevalence. MC as a useful intervention to prevent HPV infection should be advocated, especially in countries where HPV vaccines are not yet available.

AUTHOR CONTRIBUTIONS

YPZ and ZWJ designed the study, collected the clinical data, and drafted the manuscript. BD and DWY supervised and revised the manuscript. YYK analyzed some of the data. KC and YW performed the literature search and selected the studies. All authors reviewed and approved the manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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REFERENCES

1 Tobian AA, Kong X, Gravitt PE, Eaton KP, Kigozi G, *et al*. Male circumcision and anatomic sites of penile high-risk human papillomavirus in Rakai, Uganda. *Int J Cancer* 2011; 129: 2970–5.
2 Bosch FX, Shan KV, Manos MM, Munoz N, Sherman M, *et al*. Prevalence of human

papillomavirus in cervical cancer: a worldwide perspective. *J Natl Cancer* 1995; 87: 796–802.
3 Van Howe RS. Human papillomavirus and circumcision: a meta-analysis. *J Infect* 2007; 54: 490–6.
4 Albero G, Castellsagué X, Giuliano AR, Bosch FX. Male circumcision and genital human papillomavirus. *Sex Transm Dis* 2012; 39: 104–13.
5 Larke N, Thomas SL, Dos Santos Silva I, Weiss HA. Male circumcision and human papillomavirus infection in men: a systematic review and meta-analysis. *J Infect Dis* 2011; 204: 1375–90.
6 Weaver BA, Feng Q, Holmes KK, Kiviat N, Lee SK, *et al*. Evaluation of genital sites and sampling techniques for detection of human papillomavirus DNA in men. *J Infect Dis* 2004; 189: 677–85.
7 Bleeker MC, Hogewoning CJ, Voorhorst FJ, van den Brule AJ, Berkhof J, *et al*. HPV-associated flat penile lesions in men of a non-STD hospital population: less frequent and smaller in size than in male sexual partners of women with CIN. *Int J Cancer* 2005; 113: 36–41.
8 Auvert B, Sobngwi Tambekou J, Cutler E, Nieuwoudt M, Lissouba P, *et al*. 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.
9 Albero G, Castellsague X, Lin HY, Fulp W, Villa LL, *et al*. Male circumcision and the incidence and clearance of genital human papillomavirus (HPV) infection in men: the HPV Infection in men (HIM) cohort study. *BMC Infect Dis* 2014; 14: 75.
10 Vanbuskirk K, Winer RL, Hughes JP, Feng Q, Arima Y, *et al*. Circumcision and acquisition of human papillomavirus infection in young men. *Sex Transm Dis* 2011; 38: 1074–81.
11 Tarnaud C, Lissouba P, Cutler E, Puren A, Taljaard D. Association of low-risk human papillomavirus infection with male circumcision in young men: results from a longitudinal study conducted in Orange Farm (South Africa). *Infect Dis Obstet Gynecol* 2011; 2011: 1–7.
12 Backes DM, Bleeker MC, Meijer CJ, Hudgens MG, Agot K, *et al*. Male circumcision is associated with a lower prevalence of human papillomavirus-associated penile lesions among Kenyan men. *Int J Cancer* 2012; 130: 1888–97.
13 Kjaer SK, van den Brule AJ, Bock JE, Poll PA, Engholm G, *et al*. Determinants for genital human papillomavirus (HPV) infection in 1000 randomly chosen young Danish women with normal Pap smear: are there different risk profiles for oncogenic and nononcogenic HPV types? *Cancer Epidem Biomarkers* 1997; 6: 799–805.
14 Rombaldi RL, Serafini EP, Villa LL, Vanni AC, Baréa F. Infection with human papillomaviruses of sexual partners of women having cervical intraepithelial neoplasia. *Braz J Med Biol Res* 2006; 39: 177–87.
15 Partridge JM, Hughes JP, Feng Q, Winer RL, Weaver BA, *et al*. Genital human papillomavirus infection in men: incidence and risk factors in a cohort of university students. *J Infect Dis* 2007; 196: 1128–36.
16 Lu B, Wu Y, Nielson CM, Flores R, Abrahamsen M, *et al*. Factors associated with acquisition and clearance of human papillomavirus infection in a cohort of US men: a prospective study. *J Infect Dis* 2009; 199: 362–71.
17 Donovan B, Bassett I, Bodsworth NJ. Male circumcision and common sexually transmissible diseases in a developed nation setting. *Genitourin Med* 1994; 70: 317–20.
18 Svare EI, Kjaer SK, Worm AM, Osterlind A, Meijer CJ. Risk factors for genital HPV DNA in men resemble those found in women: a study of male attendees at a Danish STD clinic. *Sex Transm Infect* 2002; 78: 215–8.
19 Castellsague X, Bosch FX, Munoz N, Meijer CJ, Shah KV, *et al*. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *N Engl J Med* 2002; 346: 1105–12.
20 Aynaud O, Poveda JD, Huynh B, Guillemotonia A, Barrasso R. Frequency of herpes simplex virus, cytomegalovirus and human papillomavirus DNA in semen. *Int J STD AIDS* 2002; 13: 547–50.
21 Shin HR, Franceschi S, Vaccarella S, Roh JW, Ju YH, *et al*. Prevalence and determinants of genital infection with papillomavirus, in female and male university students in Busan, South Korea. *J Infect Dis* 2004; 190: 468–76.
22 Baldwin SB, Wallace DR, Papenfuss MR, Abrahamsen M, Vaught LC. Condom use and other factors affecting penile human papillomavirus detection in men attending a sexually transmitted disease clinic. *Sex Transm Dis* 2004; 31: 601–7.
23 Lajous M, Mueller N, Cruz-Valdez A, Aguilar LV, Franceschi S, *et al*. Determinants of prevalence, acquisition, and persistence of human papillomavirus in healthy Mexican military men. *Cancer Epidem Biomarkers* 2005; 14: 1710–6.
24 Vaccarella S, Lazcano-Ponce E, Castro-Garduño JA, Cruz-Valdez A, Díaz V, *et al*. Prevalence and determinants of human papillomavirus infection in men attending vasectomy clinics in Mexico. *Int J Cancer* 2006; 119: 1934–9.
25 Nielson CM, Flores R, Harris RB, Abrahamsen M, Papenfuss MR, *et al*. Human papillomavirus prevalence and type distribution in male anogenital sites and semen. *Cancer Epidem Biomarkers* 2007; 16: 1107–14.
26 Ng'Ayo MO, Bukusi E, Rowhani-Rahbar A, Koutsky LA, Feng Q, *et al*. Epidemiology of human papillomavirus infection among fishermen along Lake Victoria Shore in the Kisumu District, Kenya. *Sex Transm Infect* 2008; 84: 62–6.
27 Hernandez BY, Wilkens LR, Zhu X, McDuffie K, Thompson P, *et al*. Circumcision and human papillomavirus infection in men: a site-specific comparison. *J Infect Dis* 2008; 197: 787–94.
28 Giuliano AR, Lazcano E, Villa LL, Flores R, Salmeron J, *et al*. Circumcision and sexual behavior: factors independently associated with human papillomavirus detection among men in the HIM study. *Int J Cancer* 2009; 124: 1251–7.
29 Ogilvie GS, Taylor DL, Achen M, Cook D, Krajden M. Self-collection of genital human papillomavirus specimens in heterosexual men. *Sex Transm Infect* 2009; 85: 221–5.
30 Tobian AA, Serwadda D, Quinn TC, Kigozi G, Gravitt PE, *et al*. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *New Engl J Med* 2009; 360: 1298–309.
31 Muller EE, Chirwa TF, Lewis DA. Human papillomavirus (HPV) infection in heterosexual South African men attending sexual health services: associations between HPV and HIV serostatus. *Sex Transm Infect* 2010; 86: 175–80.
32 Gray RH, Serwadda D, Kong X, Makumbi F, Kigozi G, *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.
33 Cook LS, Koutsky LA, Holmes KK. Circumcision and sexually transmitted diseases. *Am J Public Health* 1994; 84: 197–201.
34 Van Den Eeden SK, Habel LA, Sherman KJ, McKnight B, Stergachis A. Risk factors for incident and recurrent condylomata acuminata among men. A population-based study. *Sex Transm Dis* 1998; 25: 278–84.
35 Tseng H, Morgenstern H, Mack T, Peters RK. Risk factors for penile cancer: results of a population-based case-control study in Los Angeles County (United States). *Cancer Cause Control* 2001; 12: 267–77.
36 Oriel JD. Natural history of genital warts. *Br J Vener Dis* 1971; 47: 1–13.
37 Lavreys L, Rakwar JP, Thompson ML, Jackson DJ, Mandaliya K, *et al*. Effect of circumcision on incidence of human immunodeficiency virus type 1 and other sexually transmitted diseases: a prospective cohort study of trucking company employees in Kenya. *J Infect Dis* 1999; 180: 330–6.
38 Serwadda D, Wawer MJ, Makumbi F, Kong X, Kigozi G, *et al*. Circumcision of HIV-infected men: effects on high-risk human papillomavirus infections in a randomized trial in Rakai, Uganda. *J Infect Dis* 2010; 201: 1463–9.