

The Role of Male Circumcision in the Prevention of Human Papillomavirus and HIV Infection

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(See the articles by Nielson et al., Auvert et al., and Warner et al., on pages 7–13, 14–9, and 59–65, respectively.)

Two articles in this issue of the *Journal* [1, 2] add to the growing body of evidence that male circumcision may reduce carriage of penile human papillomavirus (HPV). The first article [1] is a secondary analysis from a randomized trial of male circumcision for HIV prevention among South African men aged 18–24 years. The investigators reported that, after 21 months of follow-up, the point prevalence of high-risk HPV (HR-HPV) in urethral swab samples was 14.8% among men in the intervention arm compared with 22.3% in uncircumcised control subjects. The adjusted prevalence rate ratio (PRR) was 0.66 (95% confidence interval [CI], 0.51–0.86), suggesting a 34% efficacy. There are limitations to these trial data, however, because HPV infection was assessed only in a subsample of men seen at their 21-month visits during a limited period of time and not at enrollment or at any intermediate follow-up visits. This raises 2 concerns. First, a possible lack of baseline comparability cannot be excluded; however, because the intervention and control arm participants had similar characteristics at enrollment, serious bias is unlikely. Second, because there was only 1 assessment of HPV infection at 21 months, it cannot be determined whether the protective effect of circumcision on the point prevalence of HPV infection was mediated by

reduced acquisition of new infections or by increased clearance of preexisting infection due to the absence of foreskin-reducing autoreinfection at the urethral site. An additional limitation to the trial is that HPV was detected in urethral swab samples, and it has been shown that the urethral site yields lower HPV recovery than do the glans, coronal sulcus, or shaft [3]; thus, less than optimal HPV detection may have led to misclassification and possible underestimation of efficacy.

The second article [2] is a cross-sectional analysis of HPV detected at multiple anogenital sites in 463 US men, 16% of whom were uncircumcised. There were substantial differences in risk profiles between the circumcised and uncircumcised men. In particular, the uncircumcised men were younger, less likely to be white, and more likely to be Hispanic, and they reported having had significantly more sex partners during the prior 3 months. These characteristics are likely to be associated with increased HPV infection and could confound associations. The investigators found a prevalence of any HPV genotype at any sampling site of 51.2% in circumcised men and 51.4% in uncircumcised men, suggesting that there was no protective effect. However, after adjustment for sociodemographic and behavioral characteristics, the authors found a significant adjusted odds ratio (AOR) of 0.53 (95% CI, 0.28–0.99), suggesting substantial confounding due to differences in characteristics between the circumcised and uncircumcised participants. The source of this confounding was not adequately explained in the article. Another limitation to this study is the use of ORs as a measure of association. Because the prevalence of HPV infection was high, the OR is biased as a proxy measure for potential efficacy (i.e., the OR is likely to overestimate the apparent protective effect). The PRR is more

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informative as an indicator of possible efficacy, and the authors reported an adjusted PRR of 0.77 (95% CI, 0.53–1.12) for any HPV type at any sampling site, which was not statistically significant ($P = .17$). Clearly, the PRR suggests lower protection than the OR, owing to the bias of the latter metric.

Given these complexities, it is difficult to directly compare the findings of the randomized trial [1] with those of the observational study [2]. Urethral samples were used in the former, and the urethra was but one of the sampling sites in the latter. In the trial, the prevalence of urethral HR-HPV was 14.8% and 22.3%, respectively, in circumcised and uncircumcised trial participants aged 18–24 (PRR, 0.66), compared with 3.9% and 2.1% for the equivalent sampling site in the observational study of men aged 18–40 years. These differences in viral recovery and estimates of circumcision effects are clearly incompatible.

Prior observational studies do not provide consistent evidence for a protective effect of circumcision for penile HPV infection. A large multinational case-control study found a lower prevalence of HPV infection in circumcised men (AOR, 0.37 [95% CI, 0.16–0.85]) [4], and similar findings have been reported in sexually transmitted disease (STD) clinic attendees in the United States (AOR, 0.36 [95% CI, 0.18–0.71]) [5] and in Denmark (OR, 0.2 [95% CI, 0.06–0.6]) [6, 7]. Similar estimates were reported for Mexican men attending a vasectomy clinic (OR, 0.2 [95% CI, 0.1–0.4]) [8] and for incident infections in Mexican soldiers (OR, 0.28 [95% CI, 0.45–2.80]) [9]. However, no effect of circumcision on HPV infection was observed in STD clinic patients in Seattle [10] or in Korean students (OR, 1.8 [95% CI, 0.4–8.2]) [11]. In a French study of HPV-associated genital lesions among men with HPV-infected female sex partners, circumcision was associated with an increased risk of lesions (OR, 1.8 [95% CI, 0.98–3.62]) [12].

What are we to make of these divergent findings? The variability in estimates may arise because of population differences with respect to age and risk behaviors, the genital site used for HPV sampling, and the sensitivity and specificity of the assays used for HPV detection. There clearly is a need for standardized methods. A review by Giuliano et al. concluded that sampling from the penile shaft or the glans/coronal sulcus provides the best viral recovery [13]. It is also probable that the optimal assays for penile HPV detection are either of the 2 commercially available consensus polymerase chain reaction methods, PGMY 09/11 L1 consensus primers with the Roche Linear Array genotyping assay or SPF10 consensus primers with the LiPA25 genotyping assay. Ideally, these should become the standard methods for assessment of HPV infection in men. In addition, it would be highly desirable to use PRRs or incidence rate ratios rather than ORs in statistical analyses, to avoid the bias associated with ORs and to permit more informative comparisons between observational and trial data.

What are the public health implications of these findings?

Given the range of estimates of the protective effects from observational studies and the fact that we have data from only 1 randomized trial, it would be premature to promote circumcision as a way to prevent HPV infection in men and a possible way to protect their female sex partners from infection [14]. It is likely that the efficacy of male circumcision for preventing HPV infection in men will remain unclear until HPV results are reported from 2 other trials of male circumcision for the prevention of HIV infection in Kenya and Uganda [15, 16].

The lack of clarity in the studies of circumcision and HPV infection stands in sharp contrast to the consistency of evidence that circumcision reduces HIV acquisition in men, which has been demonstrated in 3 randomized trials [15–17] and in multiple observational studies [18], predominantly conducted in sub-Saharan Africa. This consistency of evidence prompted the World Health Organization and UNAIDS to recommend circumcision as a strategy for preventing HIV infection. However, research on circumcision and HIV infection in the United States is very limited and has largely focused on men who have sex with men, among whom insertive and receptive anal intercourse practices may confuse findings. It is therefore encouraging that this issue of the *Journal* also includes an article by Warner et al. [19] on male circumcision and prevalent HIV infection among heterosexual African American men with known exposure to HIV. The authors found a PRR of 0.49 (95% CI, 0.26–0.93) for the association between HIV infection and circumcision, which is close to estimates of efficacy from the trials [15–17] and from a meta-analysis of the observational studies [18]. This suggests that the findings from international studies are applicable to HIV-exposed men in the United States. Here, circumcision is less common among African American and Hispanic men, who are also the subgroups most at risk of HIV infection [20, 21]. Thus, circumcision may afford an additional means of protection against HIV infection in these at-risk minorities.

In 2007, the American Academy of Pediatrics (AAP), while “recognizing potential medical benefits of newborn male circumcision,” concluded that the “data are not sufficient to recommend routine neonatal circumcision” [22]. The statement was similar to prior AAP recommendations. Because of this decision, Medicaid does not cover circumcision costs, which is particularly disadvantageous for poorer African American and Hispanic boys who, as adults, may face high risk of HIV exposure. It is also noteworthy that circumcision rates have been declining in the United States, possibly because of a lack of Medicaid coverage [20]. It is to be hoped that the findings reported by Warner et al. [19], in conjunction with the weight of evidence from international studies, will persuade the AAP to recognize the public health importance of this surgery for the prevention of HIV infection in minority US populations.

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