Male Circumcision Reduces Human Papillomavirus Incidence and Prevalence: Clarifying the Evidence

Nicola Zetola, MD, MPH, and Jeffrey D. Klausner, MD, MPH†*

Male circumcision (MC) has been practiced for centuries by multiple cultures and ethnic groups. Many of its health benefits have been long recognized. However, it is only recently that well-designed studies and randomized clinical trials have proved those benefits.[1] A growing list of well-documented favorable health outcomes associated with this simple procedure has attracted significant attention. In particular, lifelong-lasting protection against acquisition of certain sexually transmitted diseases (STDs) has turned MC into a "vaccine" available for such diseases with calls for widespread availability.[2] Without any doubt, the most important clinical and public health benefit of MC is the ~75% risk reduction for human immunodeficiency virus (HIV) infection at the population level. This protective effect is comparable to and superior in certain instances (e.g., influenza vaccination) with the effect of vaccines currently recommended for other diseases. MC also confers a protective benefit against genital herpes simplex virus infections (HSV).[1] However, the effect of MC on the acquisition and natural history of human papillomavirus (HPV) infection has been less clear. As high-risk HPV infection is required for the development of almost all cervical cancers in women and genital, anal, and several other cancers in both, men and women, the question of whether MC has a favorable impact on the natural history of HPV infections in men is not trivial.

It is only natural to ask what is so different about HPV that makes it difficult to determine the effect of MC on its natural history, when studies of similar or same design have determined so conclusively the protective effect of MC on other viral STDs? The answer to this question is complex; nevertheless, we would like to highlight 3 main differences that will be of major importance when interpreting the results of those studies. First, given their increased feasibility and lower cost, most of the studies looking into the effect of MC on HPV infection have used a case-control or cross-sectional design and used prevalence of infection as the main outcome. As opposed to HIV and HSV, which are lifelong infections, HPV may be a transient infection in most cases. Therefore, if MC shortens the duration of infection, as has been suggested by several studies, the protective effect of MC would be underestimated. Second, contrary to HIV and HSV, which are usually diagnosed through a serologic test, most HPV studies use either clinical examination or molecular techniques for the direct detection of the virus. Given that MC is limited to the removal of the foreskin, it seems unlikely that MC will have any effect on the infections affecting the penile shaft, testicles, or perineum, which are frequently infected by HPV. Although the clinical significance of those infections is poorly understood, most studies have used aggregate outcomes that combine infections of >1 site, limiting the ability of those studies to identify a protective effect when one truly exists. Last, several behavioral factors, such as the number and gender of sex partners, frequency of sex, and type of sexual practices, might confound the relationship between MC and HPV and need to be considered. Lack of adjustment for those factors could lead to under- or overestimation of the true effect. As the design and quality of studies looking into the effect of MC on HPV genital infection vary significantly, the analysis and presentation of results vary as well. Many studies fail to account for those factors, making the results difficult to interpret.

In this issue of the journal, Albero et al assess the association between MC and genital HPV infection, including genital warts, by performing a meta-analysis of the relevant studies published between February 1971 and August 2010. Although meta-analyses can be very powerful and helpful tools to answer difficult questions, they are only as good as the data summarized, and their results need to be interpreted in that context. In fact, poorly performed meta-analyses could be highly misleading and potentially dangerous, as they may influence the opinion and practice of health care workers and policy makers. In their study, Albero et al recognize that complexities inherent to the

From the *University of Pennsylvania, Gabarone, Botswana; and †the University of California, San Francisco, CA
Correspondence: Jeffrey Klausner, MD, MPH, University of California, San Francisco, 1001 Potrero Avenue, San Francisco, CA 94110. E-mail: drklausner@hotmail.com.
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study of the relationship between MC and HPV genital infection may be magnified when pooled together and interpret their results in that context.

Randomized controlled trials (RCTs) are considered the strongest level of evidence to determine the causal association between an intervention and an outcome. Furthermore, the level of confidence that an association between intervention and outcome is causal increases when the results from several RCTs are consistent and supported by those of well-designed prospective studies. Thus, one of the major strengths of Albero et al's meta-analysis is the inclusion of data from 2 recently completed RCTs and several recent prospective observational studies.[3,4] Together, the 2 RCTs randomized 6667 participants to a control arm or MC (intervention). Of those, 1774 participants met the inclusion criteria (anatomical site-specific samples were reported) and were included in this meta-analysis. The authors found a consistent and strong inverse association between MC and prevalence of high-risk HPV infection (relative risk = 0.67, 95% confidence interval: 0.54–0.82). Those results were also supported by the pooled results of 14 observational studies that showed similar estimates (odds ratio = 0.57, 95% confidence interval: 0.42–0.77).

In addition, the authors are to be commended for the thorough categorization and analyses of studies by their design and outcome as well as the multiple sensitivity analyses which add substantially to the interpretation of their results. HPV incidence and clearance can only be assessed by study designs that allow the establishment of a temporal relationship between events. As such studies are costly and resource intensive, their number is significantly smaller than those looking into HPV prevalence. In this meta-analysis, the authors identified 1 RCT and 1 cohort study looking into both, acquisition and clearance of HPV infection, 2 cohort studies looking only into acquisition of HPV infection and 1 additional cohort study looking only into clearance of infection. Unfortunately, 3 of the 4 cohort studies used aggregate outcomes of HPV incidence or clearance that did not take into account the anatomical sampling site. Therefore, it is impossible to identify any effect of MC on the incidence or clearance of HPV infections in the glans (including the urethral meatus and, in uncircumcised men, the inside of the foreskin), the genital area MC is expected to protect.

The single study with anatomical specificity, the RCT, showed a significant reduction in the incidence and increased clearance of HPV infections among circumcised men.[5] Those findings are consistent with the other 2 RCTs that showed the protective effect of MC on HPV prevalence.[3,4] On the contrary, the pooled effect of the studies included in Albero et al's meta-analysis failed to show any protective effect of MC on either incidence or clearance of HPV infections, again which is not surprising, given the lack of specificity of the outcome measures. Altogether, those findings in total strongly suggest that to demonstrate the protective effect of MC, outcomes must be restricted to the glans and the areas covered by the foreskin.

Given the level of consistent evidence demonstrating the protective effect of MC in HIV, HSV, HPV acquisition and in pediatric urologic diseases like urinary tract infections, phimosis, paraphimosis, and balanitis as well as its protection against penile cancer, it's high time to move from research in causality to research in implementation. Albero et al's meta-analysis adds important conclusions to the rapidly growing evidence base supporting the benefits of MC. Recent CDC data show that about 50% of infants currently born in the United States undergo circumcision.[6] Unfortunately, the performance of that procedure is significantly impacted geographically by Medicaid coverage: states that cover infant circumcision have much higher levels of infant circumcision than states that do not.[7] For several years, now the US Government has dithered in developing and disseminating a national MC policy. Although a task force was convened in 2006, 5 years later, and counting, no recommendations have been put forward. Public health has always been a mixture of politics and evidence. But given the wealth of scientific evidence, such delays are unconscionable.

Recent data suggest that MC is not only cost-effective but in some settings, including the United States, is cost saving.[8,9] In sub-Saharan Africa, the drive to circumcise adult men within a package of combination HIV prevention programs has begun. Implementation is slow, however, and inconsistent. At the current rate of scale-up, it will take decades to reach a population-level prevalence of MC to realize a regional impact on HIV transmission. Local impact is attainable: one recent report demonstrated a significant 76% reduction in HIV incidence among circumcised men at the population level.[10]

There is now consistent evidence of the beneficial effects of MC on multiple STDs. It's time for scientists and public health researchers to use that evidence for advocacy.

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