Letters to the Editor

Human Papillomavirus Link to Circumcision Is Misleading

To the Editors: Physical examination is the consensus gold standard for determining circumcision status in men. In their study of Mexican military men, Lajous et al. (1) found that self-report of circumcision status had a sensitivity of 57.14% and a positive predictive value of 8.33% when compared with physical examination. In other words, of the men who were considered circumcised, only 8.33% of them actually were. If the authors had physical examination data on their subjects, why did they use self-report as measure of circumcision status when they knew it could not be as accurate as the physical examination data? The increase in statistical power using the 95 men who reported themselves as circumcised as opposed to using the 14 men who were actually circumcised is more than offset by using an invalid measure. It would have been helpful if the authors had presented their analysis using the gold standard. As it stands, the authors' conclusion that circumcision was protective against human papillomavirus (HPV) infection is misleading. The more appropriate conclusion is that the mistaken belief of being circumcised is protective.

Can the extremely low positive predictive value of self-report of circumcision status be a result of lack of familiarity with the term ''circumcision'' that has been reported in Spanish speakers in the United States (2)? Does this mean that the 88 men who misidentified themselves as circumcised were less educated or less literate than men who correctly identified themselves, or did they have a ''short'' foreskin as described in South America mestizos (3)?

Finally, the authors should be congratulated on obtaining cultures from a broad array of genital sources. One large study of HPV prevalence failed to obtain specimens from the shaft of the penis (4), which has subsequently been found to be the only location to yield evidence of HPV in the majority of circumcised men with the infection (5). The failure to obtain shaft samples renders the results of this highly publicized *New England Journal of Medicine* study meaningless. Newer studies have found HPV DNA in the seminal vesicles, epididymis, vas deferens, Leydig cells, Sertoli cells, and probably germinal cells (6). Consequently, the validity of any future study of HPV infection in male genitalia will depend on the thoroughness of search for evidence of HPV.

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References

1. Lajous M, Mueller N, Cruz-Valdez A, et al. Determinants of prevalence, acquisition, and persistence of human papillomavirus in healthy Mexican military men. Cancer Epidemiol Biomarkers Prev 2005;14:1710–6.
2. Berger LR, Rose E. The prenatal pediatric visit revisited. Clin Pediatr (Phila) 1983;22:287–9.
3. Velazquez EF, Bock A, Soskin A, Codas R, Arbo M, Cubilla AL. Preputial variability and preferential association of long phimotic foreskins with penile cancer: an anatomic comparative study of types of foreskin in a general population and cancer patients. Am J Surg Pathol 2003;27:994–8.
4. Castellsagué X, Bosch FX, Muñoz N, et al; for the IARC Multicenter Cervical Cancer Study Group. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med 2002;346:1105–12.
5. Weaver BA, Feng Q, Holmes KK, et al. Evaluation of genital sites and sampling techniques for detection of human papillomavirus DNA in men. J Infect Dis 2004;189:677–85.
6. Martorell M, Gil-Salom M, Pérez-Vallés A, Angel Garcia J, Nuria Rausell N, Senpere A. Presence of human papillomavirus DNA in testicular biopsies from nonobstructive azoospermic men. Arch Pathol Lab Med 2005;129:1132–6.

In Response: We appreciate Drs. Van Howe and Cold's interest in our article. They suggest that our conclusion that circumcision may lower the risk of human papillomavirus (HPV) persistent infection is misleading and that the observed association in the literature is rendered meaningless by differential misclassification of HPV status. However, we consider their assessment of the validity of our conclusions to be inaccurate. For our study, we considered circumcision assessed by physical examination by male nurses to be unreliable and rather chose self-reported circumcision to assess the relation with HPV infection in Mexican military men. Even though physical examination has been shown to be more accurate than patients' reports, misclassification of male circumcision by clinicians is common. A study on the reproducibility of clinician's report of patient circumcision status showed a 16% disagreement between baseline and follow-up reports and close to 14% of clinicians did not agree with their own original assessment (1). Prevalence of circumcision, clinician training and different lengths in foreskins may explain inaccurate circumcision status classification.

Circumcision is not usually performed by public sector health care providers in Mexico and we estimate the prevalence to be 10% to 31%, depending on the population. Male nurse assessment of circumcision in our study may have been rendered unreliable by the very low prevalence of circumcision in this population and the lack of specific training regarding circumcision and foreskin length. We believe that circumcision as reported by our study participants is by no means ''an invalid measure.'' Participants were not aware of their HPV status. Thus, even if the subjects had misclassified their own circumcision status, the type of misclassification would have been nondifferential, which would have biased the results towards the null. This means that in the worst-case scenario, our protective estimate would have been underestimated and that the true inverse association could be even larger than reported.

Obtaining adequate specimens for HPV detection from male genitalia has proved to be challenging. As noted, sampling from different genital areas may reduce the possibility that the detection of an HPV infection may be accounted for by circumcision status. Castellsagué and colleagues published results from seven case-control studies, which concluded that circumcision reduced the risk of penile HPV infection (2). Their study used samples from the urethra, glans, and coronal sulcus of the penis to detect HPV infection. In addition to that of circumcision and penile HPV infection, the Castellsagué study design allowed for an evaluation of the association between circumcision and cervical

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cancer. The authors found an inverse association between circumcision and cervical cancer among women whose husbands had engaged in high-risk sexual behavior. These results are consistent with the HPV link to circumcision and support their conclusion of an inverse association between circumcision and penile HPV infection. It is obvious that circumcision cannot reduce the risk of acquiring or transmitting HPVs in or from the penile shaft or the scrotum. However, by removing the foreskin, the potential sites for HPV entry and/or transmission are reduced. Furthermore, it is likely that the risk of transmission to the cervix of HPVs in the mucosal part of the prepuce, and in the coronal sulcus and glans is higher than that of HPVs detected in the skin of the shaft or the scrotum. For all these reasons, failure to collect samples from the skin does not invalidate the results of a reduced risk of cervical cancer linked to the circumcision status of the husband. What Castellsagué et al.'s results may imply is that HPVs, as detected in the penile shaft and scrotum, are not that relevant to transmission or that they do not increase the risk of cervical cancer in the female partner. If they did, their study would not have detected such a strong protection.

Correct classification of exposure and outcome categories is essential in epidemiologic studies. We concur with the suggestion that clinicians who participate in future studies on sexually transmitted diseases should be specifically trained to classify the lengths of foreskins (1), and we consider that visual aids should be encouraged to standardize the procedure. Similarly, genital sampling schemes in epidemiologic HPV studies in males should aim at being accurate yet efficient. An overzealous evaluation of the genital area may be invasive to the participant, burdensome to the investigator, costly, and it may prove to be unnecessary.

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References

1. Diseiker RA, Lin LS, Kamb ML, et al. Fleeting foreskins: the misclassification of male circumcision status. Sex Transm Dis 2001;28:330–5.
2. Castellsagué X, Bosch FX, Munoz N, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med 2002;346:1105–12.

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