Human Papillomavirus and Circumcision: The Story Beyond the Tip
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Abstract
Genital infections with human papillomavirus (HPV) may be the most common sexually transmitted infections, but most infections with HPV are transient. While HPV infections may cause cervical cancer, only a handful of the hundred or so types of HPV are carcinogenic. Some have claimed, using a selective bibliography, that circumcision in males reduces the risk of HPV infections and the risk of cervical cancer in female sexual partners. The breadth and the quality of the epidemiological research regarding any association between male circumcision and HPV infections in general, and carcinogenic HPV in particular, will be considered. It will also be explored whether associations found in some studies can be attributed to other factors.

Introduction
The connection between male circumcision and the risk of genital human papillomavirus (HPV) infections is a tar baby of sorts. It is a complex, multifaceted issue that is not well understood. It has become the source of pro-circumcision hyperbole in the recent past. It works well for them as it combines the fear-mongering of sexually transmitted diseases with the fear-mongering of cancer.

Part of the confusion is that not all HPV is the same. There are over 100 different types, some of which cause common warts while others cause genital warts. The major concern with HPV is over the types of HPV that have been linked to cancers. Too often the conversations about HPV do not make a distinction between those that cause cancer and those that do not. Even among the oncogenic HPV types, some have a greater propensity to be cancer-causing than others. For example, the DNA of HPV 16 and HPV 18 are found in 70% of the cases of cervical cancer in women.

The fear-mongering around HPV has also been fueled by the misperception that these infections are permanent. The truth is that 80% of these infections resolve spontaneously within a year and 90% will resolve spontaneously within two years. HPV infections in women are fairly common and will affect four out of five women at some point during their lifetime.

This should not diminish the fact that these viruses can be deadly. There is a strong link to cervical cancer in women with nearly all (91%) of cervical cancers having HPV DNA within their cancer cells. HPV DNA is also found in about half of the cancer cells in men who have penile cancer.[1,2] The other half of cases of penile cancer in men may be the result of balanitis xerotica obliterans, the most common cause of pathologic phimosis, which may explain the strong link between phimosis and penile cancer.[3-16] Smoking has been shown to be an effects modifier for these forms of cancer as these cancers are seen significantly more commonly in individuals who smoke.

Evaluation of the impact of circumcision on genital HPV infections is confused further by the variety of reporting the link between the two. Some studies have reported specifically on genital warts. Other studies have looked at all HPV types. Some studies have reported on only high-risk HPV types. And finally, some studies have reported low-risk and high-risk HPV results separately within their populations.

Many of these studies have serious forms of bias built into their design that make their reported results suspect. The most common of these is sampling bias, misclassification bias, and geographical bias.

Sampling bias

Sampling bias occurs when only selected portions of the genitals are sampled for the presence of HPV. Selective sampling would not be a problem if doing so provided similar results to comprehensive sampling. For HPV on the male genitals, however, this is not the case. Several studies have shown that circumcised men who have HPV somewhere on their genitals are more likely to harbor the virus on the shaft of the penis.[17-22] Other studies have shown that genital warts are more likely to be found on the shaft of the penis in circumcised men than in intact men.[23] As shown in Table I, two studies out of the University of Washington found that if only the glans is sampled 45 to 47% of circumcised men with genital HPV will be detected.[17,18] In contrast sampling only the glans of intact men will identify 65 to 66% of intact men who have HPV on their genitals. As a consequence, sampling only the glans of the penis will miss more HPV infections in circumcised men than it will in intact men. For example, in the randomized clinical trial performed in Uganda that only considered HPV detected from swabbing the glans of the penis, it was reported that intact men had a greater incidence of genital HPV than in the men who underwent circumcision.[24] If the numbers from Van Buskirk et al.[18] are correct, the number of intact men expected to be infected with HPV infection would be expected to be the number of men identified by sampling only the glans increased by a factor of 1.514. Similarly, for the men who underwent circumcision, the number identified in the trial would be increased by a factor of 2.212.

When the adjustment for sampling bias is made, the relative risk ratio (risk of intact men versus circumcised men) was reduced from 1.54 (95%CI=1.11-2.17) to 1.20 (0.81-1.79), with the difference no longer being statistically significant. As a consequence, the difference in incidence between intact and circumcised men reported by the Johns Hopkins team can be completely explained by their failure to sample beyond the glans of the penis.[25] Likewise, in the randomized clinical trial in South Africa,[26] which also only sampled the glans, the relative risk after adjusting for sampling bias goes from 1.52 (95%CI=1.16–1.96) to 1.15 (95%CI=0.81-1.79), with the difference no longer being statistically significant.[27]

These were not the only two studies to sample only the glans. When an analysis of the entire medical literature is performed using meta-regression,[28,29] studies that sampled only the glans were demonstrated to have stronger associations between having a foreskin and HPV infections. This finding was statistically significant, suggesting that

sampling only the glans of the penis consistently overestimates the association between having a foreskin and genital HPV.

The story on sampling bias, however, goes deeper. In 2007, researchers from Johns Hopkins reported at the beginning of their randomized clinical trial that, "Two subpreputial and shaft swabs were also obtained for future testing human papillomavirus infection."[30] In the 2009 report of their findings, only the results from swabbing the glans were reported. The results from swabbing the shaft of the penis were not included in their report.[24] In 2011, the same team reported the results of HPV cultures from the glans *and* the penile shaft collected at the 12 month follow-up visit of the randomized clinical controlled trial participants.[31] It remains unclear why the researchers from Johns Hopkins would selectively report the results in this fashion, especially given the fact that Weaver at al. had published their findings of a differential in HPV acquisition based on the site of the sampling on male genitals in 2004.[17] A justification for the selective reporting of their data is warranted.

The other wrinkle in the sampling bias problem is that the penile shaft is the portion of the penis with the highest viral loads for HPV. It is also the preferred location for HPV 16, the most pathogenic HPV type.[32] This would suggest that circumcised men would be even more likely to pass on HPV 16 to their partners.

Misclassification Bias

Misclassification bias occurs when individuals within the study are placed in the incorrect category. This can happen when men are asked to identify their circumcision status and they do so incorrectly. Perhaps the most egregious example of this is a 2005 study out of Mexico in which 95 men reported being circumcised while only 8.3% of them were actually circumcised on physical examination.[33] While the authors of this study had determined the circumcision status of the study participants based on physical examination, they instead reported their results based on the circumcision status as reported by the men. In effect, the study demonstrated that HPV risk was lower in men who thought they were circumcised rather than whether they were actually circumcised or not[34]

Evaluating the entire medical literature, meta-regression has demonstrated that studies that relied on patient report to determine circumcision status consistently and systematically significantly overestimated the association between having a foreskin and genital HPV.[28,29] This finding was also statistically significant, suggesting that patient self-report of circumcision status consistently overestimates the association between having a foreskin and genital HPV.

Geographical Bias

The geographical location in which data are collected can impact the results reported in studies that use more than one country to collect data. I like to refer to this as the "Brazil effect." Brazil has a very high prevalence of HPV and also a very low circumcision prevalence. While multi-country studies have included Brazil, they have failed to stratify by country. As a consequence, an association between having a foreskin and genital

HPV may be demonstrated-, when no such association exists. The Brazil effect may be present in at least two studies.[35,36] The same effect may be present in a study from Texas that failed to consider Hispanics, blacks, and whites as separate strata.[37]

Statistical Nightmare

The Brazil effect may be partially to blame for a statistical nightmare that was published in the *New England Journal of Medicine*.[36] This study combined the data from seven studies in five countries on three continents. The problem with the study is that there was a small number of circumcised men in four of the five countries and a small number of intact man in the fifth country. In order for asymptotic statistical methods, which rely on the assumption that values follow a normal distribution, to provide accurate results there needs to be more than 5 (some say more than 10) subjects who conform to each classification. Looking at Table II, seven of the twenty classifications have 5 or few subjects in them. The authors used asymptotic statistical methods, even though this would not yield valid results. They should have used exact statistical methods instead. In other words, the small number of circumcised men in Brazil, Columbia, Spain, and Thailand, and the small number of intact men in the Philippines made for an unstable statistical model.

The Big Lie

The Big Lie that is being put forth by circumcision enthusiasts and apologists is that circumcision "prevents" or reduces the risk of cervical cancer in female partners. Following the release of their 2012 Task Force report, the AAP provided Academy potential spokespeople with this talking point: "The health benefits include … lower risk of cervical cancer in sexual partners." If submitted to a fact checker, this statement would get four "Pinocchios". There have been 16 studies that have looked for an association between the circumcision status of the male sexual partner and the risk of cervical cancer in women. None of these studies have found a statistically significant association.[36,38-52] (One study reported that they did report a statistically significant association, but when their numbers are used to calculate a Fisher's exact test, their findings were not statistically significant.[48]) When I attended the 2012 International AIDS Conference in Washington, DC, I heard this lie repeated so many times it nearly made my head spin off. One person putting forth this lie was Tim Farley of the World Health Organization. When asked how he could justify making this claim in the face of no support for it within the medical literature, he quickly, in his own bombastic style, changed the topic.

Other than a sense of desperation, where is this lie coming from? Circumcision enthusiasts often will cite a 2002 study in which there was one substrata of women in which cervical cancer was significantly linked to the male sexual partner's circumcision status, but overall the study was not able to demonstrate a significant association.[36] But as seen in Table II, it would be hard, if not impossible, for the data to be stratified by country and then be further stratified by the number of sexual partners and have enough data from which to produce anything meaningful. Most of the hopes of circumcision enthusiasts have been hitched to one poorly done study that has suggested an increase

of genital HPV infections in women who have intact men for sexual partners.[53] As will be discussed below, people making this leap of faith are assuming that there is an equivalency between HPV and cervical cancer when they are not equivalent. The age-adjusted risk of cervical cancer in women is 8.1 per 100,000 person-years.[54] This corresponds to a lifetime risk of one in 147. The prevalence of high-risk HPV and women in the United States is 15.2%. So approximately one in 22 women with high-risk HPV will get cervical cancer. While this is a high rate of cancer for these women, it does not mean that every woman who becomes infected with a high-risk HPV will get cervical cancer. Also, as will be discussed below, not all oncogenic HPV types are created equal. Some HPV types, such as 16 and 18, have a higher propensity to cause cervical cancer.

Only two studies have looked for the association between HPV infections in women and the circumcision status of their male sexual partners. The first was out of the University of Washington and published in 2003.[55] The study did not report specific numbers, but stated that circumcision status of the male partner was not a risk factor for HPV in the women in the study. The second study was part of the randomized clinical trial in Uganda.[53] This study is the basis for the claims that circumcision prevents cervical cancer even though cervical cancer was not an outcome of interest or even measured as an outcome in the study. This study suffered from serious methodological problems. As with the HIV infections measured in the men in this trial, there was no attempt to determine the source of infection, more specifically whether a husband had the same HPV strain as his wife who acquired HPV during the trial. These women also may have been unduly influenced as they were paid $1.50 for each visit. This may not sound like a substantial amount of money, but $1.50 is equivalent to three days wages in Uganda. Participation for the entire trial for these women would pay them the equivalent of $1296 if the trial had taken place in the United States. This level of compensation for participants of a clinical trial in the United States would never be approved by an institutional review board because it would be deemed as having an undue influence over the participants.

The women in this trial were not particularly promiscuous. Only 2.5% of them reported more than one sexual partner and only 1.02% reported having had an extramarital relationship. Despite this level of fidelity, a high percentage of women were found to have high risk HPV.

The study relied on self-collected vaginal swabs from participants as the source of their data. The authors of the study noted, “Studies have shown that self-collected vaginal swabs are as effective as physician-collected cervical swabs for HPV detection.” However, the citation given for this statement does not bear this out.[56] The gold standard for assessing genital HPV infections in women is a clinician-obtained cervical swab. When compared to the gold standard, a self-collected vaginal swab has a sensitivity of only 74% (95%CI=61%-84%) and a specificity of only 88% (95%CI=83%-92%). This means that nearly a quarter of the HPV infections would be missed using this collection method. It also means that there would be high rate of false positives. The positive likelihood ratio for the test is 6.16, making a moderately poor diagnostic

test. (Positive likelihood ratio means that someone with a disease is only 6 times more likely to have a positive test than someone without the disease. A good diagnostic test will have a positive likelihood ratio of 10 or greater. A diagnostic test with a positive likelihood ratio of 5 or lower is considered a poor test.) It is amazing that such striking pronouncements regarding the results of this trial have been made considering that the data were collected using a marginally reliable testing method. The researchers from Johns Hopkins should have used the gold standard, especially if they were to make such outrageous claims based on the results of this trial.

Another striking finding of this trial is that HPV types 16 and 18, which account for 70% of the cases of cervical cancer, were not associated with the male sexual partner's circumcision status. In other words, this study fails the "So What" test. If HPV 16 and 18 are not affected by circumcision then it is unlikely that circumcision has much of an impact on cervical cancer. What the study does provide is a link to the many HPV types that have been shown to have some carcinogenic qualities. Of the high-risk HPV isolates identified in this trial, HPV 16 and 18 account for only 19.4%, but are expected to account for 70% of cervical cancers. As the results of this trial were reported, there was an overemphasis on the presence of carcinogenic HPV types that are less likely to cause cancer than HPV 16 and 18.

Like the other randomized clinical trials, the rate of those lost to follow-up rate was fairly high (17.1%) and the trial failed to adjust for lead-time bias. Failing to adjust for lead-time bias may sound like a trivial matter, but avoiding lead-time bias is something that is taught at the most rudimentary level when learning how to design a cohort study.[57] It is astounding that researchers from one of the top schools of public health in the world would make this rookie mistake.

Strikingly missing from the publication of these results is any reference to the study from the University of Washington that found no difference in HPV risk in women on the basis of the male partner's circumcision status.[55] Considering that it was the only other study to look at this question, and it was published in 2003 in an easily accessible journal, even a cursory review of the medical literature would have found it. So either the Johns Hopkins team did not do a cursory medical literature review or they purposely left it out of their discussion section. Either would represent a failure to meet commonly accepted academic standards.

Finally, one of their results does not make sense. Women who reported high condom use had a higher incidence of HPV infection than women who reported not using condoms at all. This is consistent with the same trial finding that the incidence of HIV infection was similar in men who reported using condoms consistently compared to men who reported not using condoms at all.[30]

The bottom line is that HPV 16 and 18 infections in women are not associated with the circumcision status of the male sexual partner. Consequently, based on these two studies and the 16 studies that have failed to find an association between cervical

cancer risk and male circumcision status, it is safe to say that cervical cancer has no appreciable link to male circumcision status.

Genital HPV in Men

The link between genital HPV infections and circumcision status in men has been assessed in a number of meta-analyses.[28,29,58,59] The problem with meta-analyses is that they are only as strong as the studies that contribute to the analysis. Far too often the selection criteria by which studies are included in the analysis can also often predict the results of the meta-analysis. The question arises of what to do with studies that have either a clear sampling bias, a clear misclassification bias, or both. In the case of sampling bias, the studies can either be excluded from the analysis or data can be adjusted based on the data from the University of Washington studies[17,18] or using meta-regression.[60] Analyses have used all three approaches.[28,29] The most recent and up-to-date meta-analyses were published in 2013.[29] Since that time only one new study on HPV and circumcision status has appeared.[61] Rather than replicate the meta-analyses, I will provide an updated summary of their findings.

One analysis looked specifically at the thirteen studies that assessed the prevalence of genital warts based on circumcision status. The overall random-effects summary odds ratio showed a trend toward a lower risk in intact men (OR=0.82, 95%CI=0.65-1.04) with a significantly lower risk when only studies of general populations were considered (OR=0.78, 95%CI=0.63-0.96).

Nineteen studies that reported on 25 separate populations have assessed the prevalence of HPV as it relates to circumcision status. Five of these studies provided data on any type of HPV being isolated as well as high-risk HPV being isolated. Because we are more interested in high-risk HPV, this data was used in the meta-analysis. For these 25 populations, the random-effects summary odds ratio found no statistically significant difference (OR=1.16, 95%CI=0.94-1.45). This analysis included studies that were known to have either sampling bias or misclassification bias. When adjusted for sampling bias using meta-regression, the random-effects summary odds ratio was 1.10 (95%CI=0.88-1.37). For studies that sampled only the glans, the random-effects summary odds ratio is much greater (OR=1.86, 0.99-3.46). When adjusted for misclassification bias using meta-regression, studies that relied on physical examination to determine circumcision status had a random-effects summary odds ratio of 1.08 (95%CI=0.88-1.32), which was not statistically significant. Studies that relied on patient report had a much greater random-effects summary odds ratio (OR=2.16, 95%CI=1.18-3.99). The influence of misclassification bias on a study's reported odds ratio was statistically significant (t=2.24, p=.0251). When a meta-regression model included both factors, both sampling bias (t=1.92, p=.0549) and misclassification bias (t=2.47, p=.0135) were shown to influence a study's reported odds ratio. In studies that used appropriate sampling and relied on physical examination to determine circumcision status, the random-effects summary odds ratio was 1.01 (0.84-1.22), indicating that there is no difference in the risk of genital HPV in intact and circumcised men. If, however, only the glans is sampled and circumcision status is based on patient report, the random-effects summary odds ratio is much greater (OR=3.45, 1.60-7.42).

An alternative, which is completely acceptable, is to exclude the nine populations in which either only the glans was sampled and/or the investigators relied on patient report for circumcision status. A meta-analysis of remaining populations found a random-effects summary odds ratio of 1.01, (95%CI=0.80-1.28). This suggests that with a properly performed study there is no difference in a risk of genital HPV based on circumcision status in men.

The 2013 meta-analysis included seven prospective studies that assessed the incidence of HPV in men based on circumcision status. This analysis did not include the data from the randomized clinical trial in Kenya as the investigators have not been forthcoming with their data.

In 2012, Bailey and Moses's group published the results of their randomized clinic trial data on high-risk HPV, but they did not report their data directly: at no point in the report do they give the number of circumcised men who became infected with high-risk HPV or the number of intact man who became infected with high-risk HPV. Instead they reported that intact men developed more flat lesions that were more likely to harbor high-risk HPV.[62] On the face of it, and from the title of their publication, it may sound like intact men were at greater risk for an infection with high-risk HPV, but this is not the case. While intact men were at greater risk for flat lesions, circumcised men were at greater risk for papular and pearly lesions. While the papular and pearly lesions are less likely to harbor high-risk HPV, they are much more common than the flat lesions. For example, 33 men in the study had flat lesions, while 133 and 187 men had papular and pearly lesions, respectively. Of the men with flat lesions, one was circumcised and 32 were intact. Of the flat lesions 22 were found to harbor high-risk HPV. Papular lesions were found in 91 circumcised men and 42 intact men. Of the 133 papular lesions, 28 harbored high-risk HPV. Pearly lesions were found in 112 circumcised men and 75 intact men. Of the 187 pearly lesions, 49 harbored high-risk HPV. Based on these numbers, one can back-calculate and estimate the number of men expected to have been infected with high-risk HPV based on circumcision status (See Table III). Considering there were 124 intact men and 151 circumcised men, the odds ratio was 1.45 (95%CI=0.89-2.38), but the difference was not statistically significant. This should not be a surprise as this study sampled both the glans and penile shaft of the study participants and reported the results on all of the samples they collected. What is surprising is that, when I wrote a letter to the editor asking for the authors of the study to supply the number of men found to have high-risk HPV, irrespective of lesion type, by circumcision status, which many would consider important information, the editors refused to publish my letter. One can only speculate as to why this most basic finding of their trial was not revealed.

Since publication of the 2013 meta-analysis, the results of the HPV Infection in Men (HIM), a prospective study of HPV in men that looked at risk of new HPV infections by circumcision status, was published.[61] This was to be the ultimate prospective cohort study on the topic. Preliminary reports from the study appeared in such high-profile journals as the *International Journal of Cancer* and *The Lancet*.[63,64] The study included

4033 participants aged 18 to 70 years. In the study, they sampled the glans, the penile shaft, and the scrotum. Men were evaluated every six months for a median of 17.5 months. Participants came from Florida, Mexico, and Brazil and the results were stratified by country of origin to avoid the Brazil effect. The results must have been a great disappointment for the authors of the study who in the past had lobbied in favor of the protective effects of circumcision.[65-75] The hazard ratio for oncogenic HPV was 0.90 (95%CI%=0.76–1.06) indicating a non-significant trend for circumcised men to have a higher incidence of HPV infections. No difference was seen for HPV 16. Even more disappointing for them was the finding that oncogenic HPV, and HPV 16 in particular, cleared significantly more quickly from the intact penis then the circumcised penis. These results were the exact opposite of what the authors had hoped for. As Morton Frisch noted, the authors "tortured the data but could not get them to confess." Instead they tried to put an interesting spin on the results by noting, "The use in this study of a single combined sample from the penis and scrotum likely limited our ability to identify a true effect at the distal penis." There is no evidence to suggest that transmission of HPV from a male to female during intercourse is impacted by where HPV is located on the penis.

One cannot help but notice that this study was published in a journal with an impact factor of 2.56, while preliminary results of this trial were reported in *International Journal of Cancer*, which has an impact factor of 5.007 and *The Lancet*, which has an impact factor of 39.207. I cannot help but wonder whether the authors were required to publish their results by their funding agency and a low-impact journal was chosen to avoid the attention of the lay press, which has been complicit in spreading propaganda about circumcision's purported health benefits.

With a new prospective study of the incidence of HPV based on circumcision, the numbers need to be updated. Before doing so, it is interesting to note that the only prospective studies that found a significant difference are those that sampled only the glans.

With all eight prospective studies considered in the analysis, the fixed-effect relative risk is 1.05 (95%CI=0.88-1.25), indicating no statistically significant difference. But we know that the two randomized clinical trials suffered from both lead-time bias and sampling bias. When these two factors are adjusted for, the fixed-effect relative risk is 0.97 (95%CI=0.91-1.04), which is also not statistically significant.

Conclusion

To get to the truth, one needs to look beyond just the tip of the penis to get the full picture of the impact of circumcision on the risk for genital HPV infections. For all the hyperbole surrounding the propaganda of repeating the lie that circumcision reduces the risk of genital HPV infections in both men and women, the medical evidence simply does not support this claim. Anyone who makes these claims should be called out as a fraud.

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Table I: Percentage of men with genital human papillomavirus infections that would be identified if only the glans of penis is sampled or only the shaft of the penis is sampled.[17,18]

	Glans only	Shaft only
Circumcised - Weaver	47.6%	37.8%
Circumcised - Van Buskirk	45.2%	50.2%
Intact - Weaver	64.7%	5.9%
Intact - Van Buskirk	66.1%	29.7%

Table II: Genital human papillomavirus infections in men based on country and circumcision status.[36]

Country	Intact positive	Intact negative	Circumcised positive	Circumcised negative
Brazil	40	63	1	5
Columbia	52	183	0	4
Spain	37	278	1	36
Thailand	35	136	2	35
Philippines	2	20	12	221

Table III: Number of human papillomavirus positive lesions by type of lesion and circumcision status determined by back-calculation.[62]

Type of lesion	Circumcised	Intact
Flat HPV positive	1	22
Papular HPV positve	19	9
Pearly HPV positive	29	20
Total HPV positive	49	51

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