Male circumcision, human papillomavirus and cervical cancer: from evidence to intervention

F Xavier Bosch, Ginesa Albero, Xavier Castellsagué

Introduction
The relationship between male circumcision and genital human papillomavirus (HPV) infection and cervical cancer has been greatly clarified in recent years. Along with the strong evidence from both observational studies and three randomised clinical trials (RCTs) consistently showing that male circumcision reduces the risk of HIV infection,1–4 the rapidly accumulating evidence for a protective effect of male circumcision on HPV and cervical cancer has prompted the suggestion that male circumcision could be considered a major intervention measure to prevent the incidence of both diseases. Thus, the introduction of safe male circumcision, if widely accepted and implemented, might be in particular relevant in developing countries in which no other measures to curtail AIDS and cervical cancer are available.

This commentary examines the evidence on the protective effect of male circumcision on penile HPV through a meta-analysis on the association between male circumcision and penile HPV and also summarises the authors’ own research data from a large multicentre case-control study that assessed the relationship between male circumcision and cervical cancer. Both pieces of evidence strongly suggest that male circumcision may indeed have an additional protective value against HPV and cervical cancer to the already established benefit for HIV prevention.

Circumcision and penile HPV: an updated meta-analysis
We have recently published results from a systematic review and meta-analysis of published studies reporting on the association between male circumcision and penile HPV or genital warts up to March 2006.2 Here we present an update that includes published studies on the topic up to September 2007. The details of the studies included in the first meta-analysis in terms of study design, type of study population, anatomical sites sampled, and the HPV DNA detection methods used have already been described. This update adds three additional studies6–8 that increase the number of subjects to a total of 5880 circumcised and 4257 uncircumcised men.9 These subjects were recruited in 14 studies conducted in the USA (five studies), Mexico (two studies), Australia (two studies), South Korea, Denmark, England, Kenya, and in a multinational study conducted in Brazil, Colombia, Spain, Thailand and The Philippines. Most studies were of cross-sectional nature. The study populations were very heterogeneous across studies and included university students, sexually transmitted infection (STI)/vasectomy clinic patients, military men, subjects from the general population, truck drivers or husbands of women with and without cervical cancer. Age at circumcision was only reported in two studies, thus its overall potential effect on penile HPV could not be appropriately assessed.

After taking into account the key potential sources of heterogeneity and publication bias, we found inverse associations between male circumcision and penile HPV and, to a lesser extent, genital warts. Thus, male circumcision was associated with a statistically significant reduced risk of penile HPV [odds ratio (OR) 0.52, 95% CI 0.33–0.82; Figure 1]. This inverse association was not as strong, but still statistically significant, when penile HPV and genital warts were combined into a single outcome variable (OR 0.63, 95% CI 0.45–0.90). In contrast, the inverse association between male circumcision and genital warts did not reach statistical significance (OR 0.89, 95% CI 0.59–1.33). It is well established that genital warts are highly accurate. The lack of a strong effect of male circumcision on genital warts might be due to the fact that in addition to the urethra, glans and prepuce, these lesions frequently occur in the penile shaft, a site for which circumcision is unlikely to exert an effect.

Circumcision and cervical cancer
A recent solid piece of evidence confirming the potential impact of male circumcision on HPV transmission and cervical carcinogenesis comes from the International Agency for Research on Cancer (IARC) multicentre case-control study on cervical cancer conducted in Spain,

Figure 1 Meta-analysis for the association between male circumcision and penile human papillomavirus (HPV) DNA.

OR (95% CI)  
Baldwin 2004 0.34 (0.20–0.57)  
Castellsagué 2002 0.37 (0.16–0.85)  
Lajous 2005 0.48 (0.26–0.87)  
Shin 2004 1.00 (0.40–2.10)  
Svens 2002 0.29 (0.06–1.24)  
Weaver 2004 0.95 (0.56–1.69)  
Vaccarella 2006 0.20 (0.10–0.41)  
Nielson 2007 1.24 (0.75–2.05)  
Partridge 2007 0.67 (0.35–1.28)  
All studies combined 0.52 (0.33–0.82)  

0.05 0.10 0.50 1.00 5.00  
Odds Ratio  
©FSRH J Fam Plann Reprod Health Care 2009: 35(1)

©FSRH J Fam Plann Reprod Health Care 2009: 35(1)
Husbands’ sexual practices:

<table>
<thead>
<tr>
<th>All combined</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first intercourse</td>
<td></td>
</tr>
<tr>
<td>≥ 17</td>
<td>0.75 (0.49-1.14)</td>
</tr>
<tr>
<td>≤ 16</td>
<td>0.89 (0.56-1.40)</td>
</tr>
<tr>
<td>Lifetime number sexual partners</td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>0.30 (0.09-1.06)</td>
</tr>
<tr>
<td>≥ 6</td>
<td>1.40 (0.76-2.57)</td>
</tr>
<tr>
<td>Sexual intercourse with prostitutes</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>0.42 (0.23-0.79)</td>
</tr>
<tr>
<td>Ever</td>
<td>1.39 (0.70-2.74)</td>
</tr>
<tr>
<td>Sexual behaviour risk index</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.53 (0.30-0.94)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.61 (0.86-3.02)</td>
</tr>
<tr>
<td>High</td>
<td>0.50 (0.27-0.94)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.18 (0.04-0.89)</td>
</tr>
</tbody>
</table>

Our finding that male circumcision may reduce the risk of cervical cancer in female sex partners is highly plausible for several quantitative reasons derived from further data analyses of the same IARC case-control study. First, because circumcision was found to be associated with a significant reduction in the risk of penile HPV infection; second, because penile HPV was also associated with a four-fold increased risk of cervical cancer in monogamous women overall and according to husbands’ sexual behaviour characteristics. The black square and horizontal line represents the odds ratio (OR) and 95% confidence interval (95% CI) for that stratum. The area of the black squares is proportional to the estimate’s precision. The diamond represents the combined OR and 95% CI. Husbands with a high sexual behaviour risk index were those with a later sexual debut before 17 years of age and six or more lifetime number of sexual partners. Husbands with a low sexual behaviour risk index were those with a later sexual debut and a lower number of sexual partners. The remaining husbands were considered to have an intermediate sexual behaviour risk index. For all models reference group is wives of uncircumcised men in that stratum. Models were adjusted by study, male’s and female’s age, male’s education attained, male’s age at first sexual intercourse, male’s frequency of genital washing after sex, male’s lifetime number of sexual partners and female’s age at first intercourse.
HPV infection in the female partner; and finally, because cervical HPV infection was also associated with a 77-fold increase in the risk of cervical cancer. Thus, within the same study data we consistently found strong associations in the three key steps occurring from male circumcision to cervical cancer development: (1) male circumcision reducing the risk of penile HPV, (2) penile HPV increasing the risk of cervical HPV and (3) cervical HPV increasing the risk of cervical cancer. Thus, circumcision can be considered an important co-factor in the natural history of HPV infection, since it may influence the risk of HPV acquisition and transmission as well as of cervical cancer development.

In conclusion, this IARC study proves strong epidemiological evidence that male circumcision is associated with a reduced risk of genital HPV infection in men and with a reduced risk of cervical cancer in women, notably among women with high-risk partners.

From evidence to intervention

The inverse associations found between male circumcision, HPV and cervical cancer are consistent with the current rapidly accumulating scientific evidence associating adult male circumcision with a reduced risk of acquiring and transmitting a number of STIs.\(^1\) In particular, the strong evidence from RCTs\(^2-4\) showing that male circumcision may substantially reduce the risk of HPV infection (Figure 3).

Taking into account the overall evidence of the protective role of male circumcision on HIV, HPV and other STIs, male circumcision could be regarded as a potential one-time, single, affordable and safe global preventative option, acting like a global vaccine to reduce the burden of a number of STI-related diseases. Male circumcision should in particular be considered in adult men in high-risk countries that cannot afford the implementation of primary and secondary prevention strategies to control HIV, HPV and HPV-related cancers both in men and women.

Most routine circumcision procedures in developed countries occur almost exclusively in infancy or early childhood. A very small percentage of men require or request the procedure as adults. In contrast, in the clinical trials of male circumcision and HIV, the procedure is performed during adulthood. Thus, it remains to be better assessed whether infant circumcision also may exert long-term protective effects for HIV and HPV during adulthood, many years after the removal of the prepuce occurs.

In the context of the urgent need for initiatives to prevent AIDS and cervical cancer, the conclusive evidence that male circumcision reduces the risk of HIV and HPV acquisition is both promising and challenging. The evidence is solidly available and further data from intervention RCTs on circumcision and HPV should be available shortly. The challenge now is translating this evidence into public health policy: a complex task that will need to be context specific. The fact that the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) are endorsing the introduction or expansion of male circumcision programmes for HIV prevention should increase the demand for safe adult male circumcision services in populations with a high STI-related disease burden.\(^1\)

International funding agencies such as the US President’s Emergency Plan For AIDS Research (PEPFAR), the Agence Nationale de Recherche sur la SIDA (ANRS), the Bill and Melinda Gates Foundation and the US National Institutes of Health are also supporting this initiative with further operational research. The scaling-up of the procedure taking into account its feasibility, cultural acceptability and the local epidemiology of HPV and HIV may result in a substantial reduction of the burden of both AIDS and cervical cancer in years to come. Close monitoring and evaluation of these programmes will certainly be needed to ensure that the procedure is well implemented and accompanied by counselling and follow-up to demonstrate that the intervention brings benefit and no harm.

Statements on funding and competing interests

Funding

The work was partially supported by grants from the European Community [CI-0371-F-C(DD)]; the Fondo de Investigaciones Sanitarias (FIS), Spain (86/753, 87/1513, 88/2043, 90/0901, 95/0955, 01/1237, 01/1236, and BAE 01/5013); Programa Interministerial de Investigación y Desarrollo, Spain (SAF 96/0323); Spanish public grants from the Instituto de Salud Carlos III (grants FIS PI030240, FIS PI061246, RCEPS P03/09, RTICESP C03/10, RTIC ESP C03/10, RTIC RD06/0200/0095 and CIBERESP), from the Agencia de Gestió d’Ajuts Universitaris i de Recerca (AGAUR 2005SGR 00695), and from the Marató de TV3 Foundation (051530), all of which had no role in the data collection, analysis or interpretation of the results.

Competing interests

The authors have received educational, research or travel grants from the pharmaceutical industry as indicated: F Xavier Bosch – GlaxoSmithKline, Merck Sharp & Dohme, Sanofi Pasteur MSD; Gi raises Albero – GlaxoSmithKline; Xavier Castellsagué – GlaxoSmithKline, Merck Sharp & Dohme, Sanofi Pasteur MSD.

References