COMMENTARY

Should Male Circumcision be Advocated for Genital Cancer Prevention?

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Abstract

The recent policy statement by the Cancer Council of Australia on infant circumcision and cancer prevention and the announcement that the quadrivalent human papillomavirus (HPV) vaccine will be made available for boys in Australia prompted us to provide an assessment of genital cancer prevention. While HPV vaccination of boys should help reduce anal cancer in homosexual men and cervical cancer in women, it will have little or no impact on penile or prostate cancer. Male circumcision can reduce cervical, penile and possibly prostate cancer. Promotion of both HPV vaccination and male circumcision will synergistically maximize genital cancer prevention.

Keywords: Cancer - men's health - women's health - infectious diseases - public health - sexual health - urology

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Introduction

The Cancer Council of Australia recently issued a policy statement entitled "Neonatal male circumcision and cancer" that addresses penile cancer and prostate cancer, concluding that it "does not recommend circumcision as a routine cancer-preventive procedure at this time" (Cancer Council of Australia, 2012). This policy was based on the infant circumcision policy of the Royal Australasian College of Physicians (2010) that ignored much of the compelling evidence concerning the medical benefits of male circumcision (Morris et al., 2012a). The American Academy of Pediatrics (2012) new policy statement and technical report concludes that the health benefits of male circumcision outweigh the risks. Here we evaluate the current evidence and provide additional information to convey a more complete assessment of the roles of male circumcision and HPV vaccines in reducing genital tract cancers in men and women.

Circumcision-related Cancer

The genital cancer for which infant male circumcision confers the greatest protection is cancer of the penis, a disease that is confined almost exclusively to uncircumcised men (Larke et al., 2011; Morris et al., 2011). Meta-analyses have confirmed findings of previous epidemiological studies, suggesting that phimosis, balanitis and the presence of smegma increase the risk of penile cancer by 12-, 4- and 3-fold, respectively (Morris et al., 2011). Each of these risk factors is either more common in, or exclusive to, uncircumcised men. Inflammation is a predisposing factor for many cancers, further supporting evidence that balanitis, defined as inflammation of the foreskin and head of the penis, may increase penile cancer risk (Chaux and Cubilla, 2012).

While it is clear that penile cancer is uncommon in the overall male population, with "an [annual population] incidence of 1 in 100,000", to quote the Cancer Council of Australia (2012) policy statement, the lifetime prevalence – 1 in 1,000 in uncircumcised men (Morris et al., 2011; American Academy of Pediatrics, 2012) – provides a more realistic picture.

A randomised controlled trial (RCT) showed that male circumcision provides 98% protection against the acquisition of flat penile lesions caused by a multitude of oncogenic HPV genotypes such HPV56 (29%; a type not targeted by vaccines), HPV16 (26%) and others that were less common (Backes et al., 2012). A meta-analysis of 21 observational studies and two RCTs has, moreover, shown that circumcision reduces by 43% and 33%, respectively, the risk of genital infection by high-risk HPV in men (Bosch et al., 2009). Circumcision affords 57% protection against high-risk HPV16 acquisition in men

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who predominantly practice insertive anal intercourse (Poynten et al., 2012). RCT data showed a 95% reduction in the viral load of high-risk HPV types 24 months after circumcision, and a 46% reduction in high-risk HPV signal strength in type-specific linear array quantitative polymerase chain reaction assays (Wilson et al., 2012).

The vaccination of girls with the quadrivalent HPV vaccine in Victoria, Australia that began in 2007 has already been associated with a very small (0.38%) reduction in the high-grade lesions that can precede cervical cancer (Brotherton et al., 2011). The recent announcement that the program will be extended to boys should, with time, further lower common low-risk and high-risk HPV types in both sexes, and anal cancer in men who have sex with men. However, although high-risk HPV has been implicated in over 99% of cervical squamous cell carcinomas (SCC), its presence in penile SCC varies by histological type and it is found on average in only 50% of SCCs (Mirralles-Guri et al., 2006). Moreover, oncogenic types not presently covered by current HPV vaccines can be common (Mirralles-Guri et al., 2006 ; Larke et al., 2011; Morris et al., 2011). Based on an assumption drawn from cervical SCC (Bosch et al., 2009; Morris et al., 2011)) of a 70% prevalence of high-risk HPV vaccine types 16 and 18 in the 50% of penile cancers that do contain HPV, we estimate that vaccination, under the most optimistic of scenarios, could reduce penile cancer by up to 35%. In vulval intraepithelial neoplasia (VIN) the prevalence of HPV is likewise approximately 50%, the effectiveness of the quadrivalent HPV vaccine in reducing HPV-related disease having been found to be 18.4% for VIN grade I or worse and 23.5% for VIN grade II or worse (Joura et al., 2012).

In summary, penile cancer is certainly uncommon though not rare and it occurs almost exclusively in uncircumcised men. Men who are circumcised are protected against multiple foreskin-related risk factors and are less likely to acquire oncogenic HPV infections. Given the mixed array of etiological factors, HPV vaccines are likely to have only a partial effect in reducing penile cancer incidence.

Cervical cancer, which still affects 700 women and causes 200 deaths in Australia every year (Canfell et al., 2006; Australian Institute of Health and Welfare, 2011), is less common in female sex partners of circumcised males (Albera et al., 2012), making circumcision worthy of consideration. In a RCT, female partners of circumcised men had a 28% lower prevalence of high-risk HPV compared to female partners of uncircumcised men (Wawer et al., 2011). This may be explained by the decreased penile high-risk HPV shedding observed among infected circumcised men (Wilson et al., 2012). A large study in the New England Journal of Medicine found that the risk of cervical cancer in monogamous women whose male partner had had 5 or more previous sexual partners was 6-fold lower when their male partner was circumcised, and was 2-fold lower for female partners of circumcised males with an intermediate sexual behaviour risk index (Castellsague et al., 2002). Risk reduction was also reported in a meta-analysis of 14 studies (Albero et al., 2012) and a recent European study of 3,261 women found that in women with two or more lifetime sexual partners, male circumcision was associated with a 40% lower risk of HPV (Rora et al., 2011). Condoms offered only slight protection (Castellsague et al., 2002; Wawer et al., 2011; Rora et al., 2011). The quadrivalent HPV vaccine was found to reduce cervical intraepithelial neoplasia (CIN) grade I or worse by 46.3% and CIN II or worse by 40.8% (Joura et al., 2012). While prophylactic HPV vaccines should reduce cervical cancer incidence and deaths, they do not cover the full spectrum of oncogenic HPV types. In contrast, circumcision partially protects against all oncogenic HPV types (Wawer et al., 2011). Circumcision and vaccination should therefore be seen as synergistic interventions.

Cancer of the prostate is one of the most common cancers in men. A recent large study in Seattle showed a 12-18% reduction in prostate cancer in men circumcised in childhood compared to uncircumcised men (Wright et al., 2012). The study also found that there was no significant reduction in prostate cancer associated with circumcision performed after sexual debut. The protective effect was not affected by socioeconomic status. These new findings add to numerous previous studies that have shown a 30-50% lower prevalence of prostate cancer in circumcised men (Morris et al., 2007; 2011). Although a history of sexually transmitted infections is a risk factor, the evidence does not support a role for HPV infection (Morris et al., 2007; 2011; Wright et al., 2012). We agree with the Cancer Council of Australia that "more research is needed before there is sufficient evidence to recommend population-level circumcision to help reduce prostate cancer incidence" (Cancer Council of Australia, 2012). It should, however, be recognised that even a small reduction in prostate cancer incidence has the potential to represent enormous savings in lives and costs (Morris et al., 2007).

Cost Benefit

In the USA infant male circumcision has been shown to be a cost-saving intervention due to it reducing the risk of multiple infections among men and their female sexual partners (Schoen et al., 2006; Kacker et al., 2012). If male circumcision rates in the USA were to decrease to levels of 10% seen in Europe, the additional costs of infections among 10 annual birth cohorts would amount to more than US$4.4 billion, even after accounting for the procedure's cost (Kacker et al., 2012). Each forgone male circumcision procedure is estimated to lead to US$313 in increased direct medical expenses. While heterosexually-acquired HIV infection drives the majority of the costs, the increased costs of HPV-associated cervical cancer and penile cancer account for 8% of the total increase in expenses.

In the absence of a comprehensive cost-benefit analysis of male circumcision in Australia, we considered it instructive to provide preliminary, approximate calculations, which should be regarded as hypothesis generating only. The current male birth rate in Australia (total population 22 million) is 12 per 1,000 population per year, i.e, 0.25 million. The cost of circumcision of a male aged less than 6 months ranges in private practice from

A$300-800, even though the scheduled fee is A$45.65. The Medicare rebate for an infant circumcision is A$38.85 (85%) or A$34.25 (75%). Should the circumcision of infant males become universal the total annual cost to the Australian Federal Government via the Medicare rebate would be approximately A$9 million, with the out-of-pocket 'gap' paid by parents to cover the shortfall being A$70-200 million.

The direct medical and hospital costs of cancer treatment and care vary according to type of cancer and individual patient. The Cancer Council of Australia (2011) reported that in 2010 there were 114,000 new cancer diagnoses, 43,000 deaths and an annual direct health system cost of $3.8 billion, representing $33,000 per patient. Amongst these there were 16,000 prostate cancers, 700 cervical cancers and 70 penile cancers. For approximate risk reductions conferred by male circumcision of 15–50%, 50% and 95% for each cancer type, respectively, the lack of circumcision factor alone would contribute to approximately 3,000–6,000 fewer cancers when comparing 100% male circumcision prevalence versus zero. Since overall infant male circumcision prevalence in Australia is currently 10–20%, a shift to 80% would mean a total saving to the Government in direct medical costs of 0.8 x $33,000 x (2500–5000) = approximately A$1–2 million, unadjusted for inflation. This does not include other measures such as quality-adjusted life years (QALYS) or disability-adjusted life years (DALYS). Less-easily ascertained direct and indirect costs to society include those caused by loss of a mother as caregiver and of an employee by death and sick leave, as well as the psychological consequences of disease.

The predicted cost to the Government of universal infant male circumcision ($9 million) is far less than the $89 million annual expenditure budgeted for the HPV vaccination programme (Parliament of Australia, 2007). The quadrivalent HPV vaccine is currently offered to 12- and 13-year old girls, and, as announced recently, will soon be offered to boys as well.

Moreover, considering that, if uncircumcised, up to half of males may suffer not just these but various other adverse medical conditions over their lifetime (Morris et al. 2012c), infant male circumcision should have a positive overall cost-benefit in Australia just as estimated for the USA by Schoen et al. (2006) and Kacker et al. (2012).

Conclusion

In the Asia-Pacific region most males in Korea, the Philippines, Pacific Island nations and countries with large Muslim populations such as Indonesia are circumcised by the time they reach adulthood. Since the region accounts for half of the global population, improvements in public education about male circumcision and methods to provide training in the technique of affordable medical male circumcision, ideally performed in infancy (Morris et al., 2012b), could have substantial benefit. Cost-effectiveness studies should be commissioned to estimate costs and benefits in Australia and other countries in the region.

Based on the evidence presented above, we believe that male circumcision has an important role in reducing penile cancer, and possibly prostate cancer, in men, as well as cervical cancer in women. Given (1) the biological and other limitations of vaccination programmes in girls and boys and of current vaccines, (2) the fact that condoms provide only marginal protection against HPV acquisition, and (3) that factors related to the foreskin but not to HPV appear to contribute to the etiology of penile cancer and possibly prostate cancer in males, a multi-pronged approach is needed. An effective strategy would involve reducing financial and other barriers to uptake of male circumcision, as well as improving parent and provider education about the pros and cons of circumcision of infant males. Supporting access to procedures among infant males when the lifetime benefits, convenience, ease of operation, costs and cosmetic outcome are greatest, and the risks are lowest (American Academy of Pediatrics, 2012; Morris et al., 2012b), should be a part of the public health response to genital cancers in Australia (Morris et al., 2012c) and Asian Pacific countries.

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