

## INTRODUCTION

It is now 20 years since the first clues emerged that circumcised men had a lower risk of developing HIV infection [1–3], and 4 years since the first of three randomized trials [4] were reported. They involved 11 054 men and showed that circumcising males aged 15–49 years reduced their risk of HIV infection after up to 2 years of follow-up by 48%, 53% and 60% [4–6]. Since then there has been considerable correspondence, both in medical journals [3,7] and newspapers, showing a considerable lack of consensus and a suspicion that such a solution is not being implemented widely because the health service resources needed are not readily available. In miniature, these debates mirror the long-standing debate about whether circumcision is necessary to eliminate penile cancer and reduce UTI in childhood. The strongest arguments against circumcision come from four countries where penile cancer has reduced substantially without implementing circumcision. In Denmark, penile and cervical cancer decreased by 28% and 24%, respectively, between 1940 and 1990, coincident with an increase from 35% to 90% in the proportion of dwellings having a bath [8]. In India, high caste and better educated uncircumcised men have less penile cancer than less-educated circumcised Muslims, and the prevalence of cervical cancer in equivalent females mirrors this trend [9]. In Brazil, where there has been considerable investment in sanitation facilities [10], there is a gradient of increasing penile and cervical cancer in the areas of the country that have least provision of sanitation. In China, where before 1951 penile cancer was the most frequent urological malignancy, accounting for 39.5% of cases, it had declined to the least frequent, and only accounted for 1.6% of urological malignancies by 2000 [11], due at least in part to the better domestic sanitation facilities for a larger proportion of the population.

## CIRCUMCISION AND/OR VACCINATION AGAINST HUMAN PAPILLOMAVIRUS IN THE MALE TO PREVENT INFECTION WITH HUMAN IMMUNODEFICIENCY VIRUS: AN EARLY SURROGATE ENDPOINT FOR THE LATER PREVENTION OF PENILE, PROSTATE, ANAL AND ORAL CANCER? R.T.D. Oliver – Institute of Cancer, St Barts &

The London School of Medicine, Queen Mary University of London, London, UK

Accepted for publication 13 March 2009

For cervical, penile, vulval, anal, oral and to a lesser extent prostate cancer, there is evidence of a proportion of cases in which human papillomaviruses (HPV) are known to be involved. Those tumours that are positive tend to be in younger patients, have a lower frequency of *p53* mutation and have a lower frequency of carcinogen (mostly smoking) exposure [12]. These observations have led some authors to speculate as to whether the HPV-negative tumours have arisen after the virus has played a 'hit and run' role in their initiation being lost from the tumour cell when carcinogen exposure had mutated one or other of the blocked tumour suppressor genes, while the HPV-positive tumours are in patients whose MHC phenotype puts them at increased susceptibility to viral persistence [13–15]. In addition, the virus-positive patients have a better prognosis in terms of survival and response to chemotherapy [12]. If a population-based HPV vaccine trial with adequate follow-up were to show a reduction of HPV-negative tumours, this would be evidence that 'hit and run' actually could be a factor in the initiation of these tumours, as has been reported in cell-lines infected with HPV 18 and serially passaged in nude mice [16].

To date, the two first-generation vaccines [17,18] have been used in trials of prevention of cervical cancer, and both vaccines have been licensed for use in women only, despite men being known to be the responsible vector. Apart from recent funding of small-scale trials, the two companies involved have been

resistant to the idea of including males in the trials of HPV vaccines, despite considerable pleading [19–21], essentially because there is no tumour type in males that is totally HPV-related, and with an early stage that is easily detected and the changed incidence of which would lead to a licence after a short follow-up of 3–4 years, rather than the 30–40-year period which would be required for any of the tumours currently having a subset which are HPV-positive. The increasing incidence of the oropharyngeal HPV-positive tumour [22] particularly in non-smokers and in association with oral sex [23], have in part increased the call for trials to be conducted in men as part of the development of second-generation HPV vaccines with a broader range of HPV subtypes.

The relationship of HPV and HIV has been extensively investigated and confirms that HIV infection increases the risk of persistent HPV infection [24], and progression to malignant transformation [25,26]. More critically, from the point of view of use of HPV vaccines, is the question of whether persistent, highly vascular HPV lesions increase the rate of HIV acquisition. This is something that could be answered by including males in the 'roll-out' phase of the HPV vaccines in an area of high HIV prevalence.

In South Africa, the two main tribal groups have opposing attitudes to circumcision, the Xhosa advocating it as part of the puberty/coming-of-age ceremony, while the Zulu

oppose it. The country provides the ideal place to do a 2 × 2 patient-preference trial that seeks a consensus as to how to integrate the two observations, i.e. circumcision and HPV in a low healthcare environment. The increasing incidence of prostate cancer being seen in these groups, with mainly supportive [27,28], although sometimes conflicting [29] evidence for the role of circumcision preventing, and HPV infection promoting, prostate cancer provides an additional interest in conducting the trial. Such a trial should randomize (allowing patients to opt out, or as is their preference, election) between immediate vs deferred circumcision (that would only take place at the time of first sexually transmitted disease, STD, or development of foreskin problems) and HPV vaccination or placebo (also allowing a patient opt-out or in preference, election) in males in a population where the females were also being randomized to assess the impact of the second-generation HPV vaccination vs first-generation vaccine. Ideally this would be conducted in 9–15-year-olds, who would also be given focused education about safe sex, genital hygiene and the role of violence [30,31] in the current state of the AIDS epidemic in their area, where close to 20% of pregnant women are HIV-positive. The advantage of a patient-preference method is that it allows for tribal and religious sensibilities to be addressed.

The endpoints for the study would primarily be HIV and HPV incidence at age 20 years, although secondary endpoints would be monitoring throughout the duration of the trial for episodes of orogenital infection by an annual messaging/text-administered questionnaire. Questionnaires to determine the outcome for the chosen or randomized selection of foreskin management would also be developed, and at the end of the trial a visual inspection would be made for a full assessment of genital health.

Finding funding for what could be a large trial might take some time to organize. Increasing funding for the current small-scale observational studies of the natural history of HPV in the male to explore low-cost ways of delivering the intended endpoints for such a trial, and allow an assessment of the proportion of people who would accept randomization or participation in one or other of the options would help to give an idea of what numbers might be necessary (vis the Protect trial of surgery vs radiotherapy in

prostate cancer [32]). The PSA level could also be measured, as in this age group it is a good measure of exudative STD urethritis and prostatitis [2], and therefore provides a possible early surrogate endpoint that if reduced in the patients receiving HPV vaccine, would suggest that the vaccine could ultimately contribute to cancer prevention at a later point.

CONFLICT OF INTEREST

None declared.

REFERENCES

- 1 Cameron DW, Simonsen JN, D’Costa LJ *et al.* Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. *Lancet* 1989; **2**: 403–7
- 2 Oliver J, Oliver R, Ballard R. Influence of circumcision and sexual behaviour on PSA levels in patients attending a sexually transmitted disease (STD) clinic. *Prostate Cancer Prostate Dis* 2001; **4**: 228–31
- 3 Oliver R, Oliver J, Ballard R. Male circumcision and HIV prevention. More studies need to be done before widespread circumcision is implemented. *BMJ* 2000; **321**: 1468–9
- 4 Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med* 2005; **2**: e298
- 5 Gray RH, Kigozi G, Serwadda D *et al.* Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007; **369**: 657–66
- 6 Bailey RC, Moses S, Parker CB *et al.* Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 2007; **369**: 643–56
- 7 Fitzpatrick JM. Editor’s comment. *BJU Int* 2008; **101**: i
- 8 Madsen BS, van den Brule AJ, Jensen HL, Wohlfahrt J, Frisch M. Risk factors for squamous cell carcinoma of the penis – population-based case-control study in Denmark. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 2683–91
- 9 Gajalakshmi CK, Shanta V. Association between cervical and penile cancers in

Madras. *India Acta Oncol* 1993; **32**: 617–20

- 10 Barreto ML, Genser B, Strina A *et al.* Effect of city-wide sanitation programme on reduction in rate of childhood diarrhoea in northeast Brazil: assessment by two cohort studies. *Lancet* 2007; **370**: 1622–8
- 11 Gu F. Changing constituents of genitourinary cancer in recent 50 years in Beijing. *Chin Med J* 2003; **116**: 1391–3
- 12 Kumar B, Cordell KG, Lee JS *et al.* EGFR, p16, HPV Titer, Bcl-xL and p53, sex, and smoking as indicators of response to therapy and survival in oropharyngeal cancer. *J Clin Oncol* 2008; **26**: 3128–37
- 13 Slater S, Oliver RT. Testosterone: its role in development of prostate cancer and potential risk from use as hormone replacement therapy. *Drugs Aging* 2000; **17**: 431–9
- 14 Oliver R. Medical Interventions relevant to management of early prostate cancer and its prevention: a new potential role for general practitioners, schools and works medical officers as well as STD and Infertility clinics. In Wallace DMA, Oliver RTD, eds, *UK Key Advances in Clinical Practice Series the Effective Management of Prostate Cancer*. London: Aesculapius Medical Press, 2002: 117–38
- 15 Oliver T, Lorincz A, Cuzick J. Prostate cancer prevention by short-term anti-androgens: the rationale behind design of pilot studies. In Senn H-J, Kapp U, Otto F eds. *Cancer Prevention II. Recent Results in Cancer Research*, Vol I. Berlin: Springer Verlag, 2008: 195–205
- 16 Iwasaka T, Hayashi Y, Yokoyama M, Hara K, Matsuo N, Sugimori H. ‘Hit and run’ oncogenesis by human papillomavirus type 18 DNA. *Acta Obstet Gynecol Scand* 1992; **71**: 219–23
- 17 Harper DM, Franco EL, Wheeler CM *et al.* Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet* 2006; **367**: 1247–55
- 18 Ault KA. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. *Lancet* 2007; **369**: 1861–8
- 19 Svare EI, Kjaer SK, Worm AM, Osterlind A, Meijer CJ, van den Brule AJ. Risk

- factors for genital HPV DNA in men resemble those found in women: a study of male attendees at a Danish STD clinic. *Sex Transm Infect* 2002; **78**: 215–8
- 20 **Elbasha EH, Dasbach EJ, Insinga RP.** Model for assessing human papillomavirus vaccination strategies. *Emerg Infect Dis* 2007; **13**: 28–41
- 21 **Kubba T.** Human papillomavirus vaccination in the United Kingdom: what about boys? *Reprod Health Matters* 2008; **16**: 97–103
- 22 **Fakhry C, Gillison ML.** Clinical implications of human papillomavirus in head and neck cancers. *J Clin Oncol* 2006; **24**: 2606–11
- 23 **D'Souza G, Kreimer AR, Viscidi R et al.** Case-control study of human papillomavirus and oropharyngeal cancer. *New Engl J Med* 2007; **356**: 1944–56
- 24 **Marais DJ, Carrara H, Ramjee G, Kay P, Williamson AL.** HIV-1 seroconversion promotes rapid changes in cervical human papillomavirus (HPV) prevalence and HPV-16 antibodies in female sex workers. *J Med Virol* 2009; **81**: 203–10
- 25 **Jong E, Mulder JW, van Gorp EC et al.** The prevalence of human papillomavirus (HPV) infection in paired urine and cervical smear samples of HIV-infected women. *J Clin Virol* 2008; **41**: 111–5
- 26 **De Vuyst H, Lillo F, Broutet N, Smith JS.** HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. *Eur J Cancer Prev* 2008; **17**: 545–54
- 27 **Morris BJ, Waskett J, Bailis SA.** Case number and the financial impact of circumcision in reducing prostate cancer. *BJU Int* 2007; **100**: 5–6
- 28 **Dillner J, Knekt P, Boman J et al.** Sero-epidemiological association between human papillomavirus infection and risk of prostate cancer. *Int J Cancer* 1998; **75**: 564–7
- 29 **Korodi Z, Dillner J, Jellum E et al.** Human papillomavirus 16, 18, and 33 infections and risk of prostate cancer: a Nordic nested case-control study. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 2952–5
- 30 **Oliver R.** Though HIV is the main cause of AIDS, other factors play a role. *Nature* 2000; **406**: 673
- 31 **Dunkle KL, Jewkes RK, Brown HC, Gray GE, McIntyre JA, Harlow SD.** Gender-based violence, relationship power, and risk of HIV infection in women attending antenatal clinics in South Africa. *Lancet* 2004; **363**: 1415–21
- 32 **Donovan J, Hamdy F, Neal D et al.** Prostate testing for cancer and treatment (protect) feasibility study. *Health Technol Assess* 2003; **7**: 1–88

**Correspondence:** Tim R. Oliver, Institute of Cancer, St Barts & The London School of Medicine, Queen Mary University of London, London EC1M 8BQ, UK.  
e-mail: r.t.oliver@qmul.ac.uk

**Abbreviations:** HPV, human papillomavirus; STD, sexually transmitted disease.