Reviewer's report

Title: Risk of human papillomavirus-related cancers among patients with end-stage renal disease - an observational cohort study

Version: 1 Date: 9 April 2013

Reviewer: Andrew Grulich

Reviewer's report:

The authors answer a well-defined question, and the methods are generally appropriate and well described. With the exception of the issue outlined below (adjustment for a comorbidity index and cause of ESRD), the data are sound. Apart from the issue of claimed lack of difference in rates between transplantation and dialysis, which I do not believe is justified, the discussion and conclusions are otherwise well balanced and adequately supported by the data. The limitations of the work are clearly stated.

Major compulsory revisions

1. Methods, Risk factor analysis: no justification is given for adjusting for the co-morbidity index (CMI). Unless this is an accepted risk factor for HPV-related cancer, then there is no need to adjust for it, and in fact adjusting for it may be inappropriate to me. Eg Could a higher CMI be the result (not a cause) of HPV-related cancer? Later in the paper, in the analysis of the effect of transplantation, cause of ESRD is also adjusted for. Again, there is insufficient justification for why that is necessary, and it may be inappropriate to adjust for cause of ESRD. The authors should justify why this adjustment is necessary, or delete the results from the paper that are based on adjusting for CMI/cause of ESRD.

2. Results, Page 13. The authors state: “Among ESRD patients, transplant recipients with functioning grafts had an unadjusted 1.83 (95% CI, 1.11-3.01) fold higher risk of HPV-related cancer compared to dialysis patients. When adjusted for age, comorbidity and cause of ESRD the IRR fell to 1.44 (95% CI, 0.84-2.48) comparing transplant recipients to dialysis patients (table 4).” As I have outlined above, I do not believe sufficient justification for adjusting for comorbidity and ESRD cause has been presented. As it stands, I think the unadjusted result may be more valuable.

3. Discussion, First paragraph. The authors state: “Surprisingly, transplant recipients (with a functioning graft) did not have a significantly increased risk of HPV-related cancer compared to dialysis patients when adjusted for age, cause of renal failure, and co-morbidity”. As stated above, I am not sure this is the most relevant result. When not adjusted for these variables, there was an association. The difference is unlikely to be due to age, as the two cohorts were closely matched for age. In the Vajdic paper, rates at most HPV-related sites were significantly higher during periods of transplant function.
Minor Essential Revisions

1. Background. The following sentence is not totally correct and should be revised. “Among persons infected with human immunodeficiency virus (HIV), the immunosuppression caused by HIV is considered responsible for the well described excess risk of HPV-related cancers in this group”. Immune suppression is not the only reason for increased HPV-related cancer in this population. Increased exposure to HPV through confounding is also present, as in most cases, HIV, like HPV, is sexually transmitted. In 1993, cervical cancer was added to the list of AIDS-defining conditions simply because of the recognition that it occurred at increased rates – not because there was any agreement about its association with immune deficiency.

2. Background. The authors state “the total burden of HPV-related cancers is uncertain”: This phrase is not quite correct. At least one paper (Vajdic et al, JAMA 2007) has separately presented data on incidence of cancers of the anus, cervix, vulva, penis and mouth. The current paper is an important contribution to expanding the body of knowledge on HPV-related cancer.

3. Results, Page 13 and elsewhere. Since there has been restriction to HPV-associated head and neck sites it would be preferable to refer to these as “HPV-related head and neck subsites” or similar. Most cancers of the “head and neck” are not HPV-related and it is a strength of this paper that analysis has been confined to HPV-related sites.

4. Page 17 “In a more recent study, Van Leeuwen et al reported a rapid decline in cancer risk among kidney transplant recipients”. In fact the decrease only occurred in certain cancer sites including NHL, KS and melanoma.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests