Reviewer's report

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

Version: 1 Date: 20 March 2013

Reviewer: Eric Engels

Reviewer's report:

Risk of HPV related cancers in ESRD, Dalgaard et al. for BMC Nephrology

Major compulsory revisions

1. The authors compare the incidence of HPV-related cancers in ESRD patients to that in the general population. One of the challenges here is that the authors mostly consider two separate groups as one group: people on dialysis, and kidney transplant recipients. Usually, when the term “ESRD patients” is used, readers interpret this to include only people on dialysis. Considering these two groups together, especially without clearly calling attention to the approach, is confusing. Also, it is plausible that cancer risk differs between them, since immunosuppression is much greater for transplant recipients than people on dialysis.

In order to address this issue, the authors need to substantially edit the paper. One set of changes has to do with clarifying for the reader when the authors are considering dialysis patients, when they are considering transplant recipients, and when they are considering both. The title needs to be edited to reflect that both groups are included in the paper. The Introduction and Discussion need to better distinguish which biological considerations relate to each, and distinguish between prior published studies on these two groups.

2. In terms of the analyses, the ESRD subjects consist of two groups: people on dialysis, and transplant recipients. Were these groups defined by their status at the start of follow-up? That should be stated more clearly. In order to compare cancer risk for dialysis patients with transplant recipients, it would be best to transition people from the dialysis group to the transplant group when they receive a transplant, dividing the person-time and events appropriately—in effect, treating transplant as a time-dependent covariate. However, it is not clear that that was done. The authors should clarify the approach.

What proportion of people who started out in the dialysis group eventually received a transplant? If this proportion is high, and/or if many of the HPV-related cancers in the dialysis group actually occurred after the patients received a transplant, then it would be incorrect to attribute the cancers to dialysis. The approach therefore has an impact on the conclusion that transplantation does not increase risk for HPV-related cancers above that seen for dialysis.
3. The authors found a non-significantly increased risk of HPV-related cancers in transplant recipients compared to dialysis patients (adjusted IRR 1.44). It would be important to mention in the Discussion that the confidence interval does not rule out an increased risk (IRR as high as 2.48). Therefore, one potential reason why transplant recipients do not appear to have especially high risk is low power to make this comparison.

4. It appears from the Discussion (page 16) that the Danish National Registry of Patients was used to help identify cancer cases, supplementing the Danish Cancer Registry. Is that the case? If so, it should be mentioned in the Methods. How many cancers were identified through each approach? Is it likely that cases found only in the DNRP are valid?

5. Figure 2 appears to show Kaplan-Meier estimates for the proportion with cancer, by age. No method is described, but I have concerns that these results are valid. First, a Kaplan-Meier curve treats people who die as censored and therefore still at risk for developing cancer. This approach leads to an estimate of the cumulative incidence of cancer that is too high, especially for the ESRD group, who have a high mortality. Second, the Kaplan-Meier approach assumes that all people are under follow up at the baseline on the time scale—here, at age 0. That is not the situation however, because people in each group enter follow-up at different ages (delayed entry). For these reasons, the Kaplan-Meier approach cannot be used here.

6. The authors argue (first in the Introduction, then in the Discussion) that HPV vaccination might help reduce the high risk of HPV-related cancers. However, the utility of this vaccine would likely be low in the ESRD population, because: 1) many people with ESRD would already be infected, and 2) their weakened immune status might make the vaccine less immunogenic. Instead of emphasizing the potential benefits of the vaccine, the authors should focus on screening for HPV-related cancers. In the HIV setting, some have advocated for use of anal Pap smears, analogous to cervical Pap smear. This topic could be added to the discussion of cancer prevention.

Minor comments

Page 9. “Ren contractus” is not a standard term.

Page 13. The authors comment on an increasing trend over time for ESRD patients (Figure 1). This comment should be supported by a statistical test of trend.

Page 15. The authors mention exclusion of prevalent HPV-related cancers as a strength of their study. However, because these cancers are not common, very few people would need to be excluded, so this approach does not result in a great advantage here.
The authors may want to cite the recent paper below, which found an elevated risk of cervical cancer among elderly ESRD patients.


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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests