Author's response to reviews

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

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Author's response to reviews: see over
Dear Editors at BMC Nephrology

Thank you very much for your comments and this opportunity to revise our manuscript. We found that the comments raised some very interesting issues that significantly added to the quality of the paper. In revising the manuscript we have done our best to comply with the comments and suggestions. All comments have been emphasized and assigned a number from 1-17 (C1-C17)) and all answers following each question (A1-A17).

Please find the comments and answers enclosed below in this document.

A revised manuscript and a supplementary table have also been submitted.

Word count for the abstract: 255 and for the manuscript: 3600

Please, do not hesitate to contact us if you have any other question or further explanations are needed.

Sincerely,

Lars Skov Dalgaard
Eric Engels:

Major compulsory revisions

C1

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.

A1

The title has been changed to clarify that both dialysis patients and transplant recipients are included in the study. We have revised the introduction and discussion to clarify that both groups are included and to better distinguish between studies on the two groups. Table 4 has been expanded with anatomical site specific cancer incidence rates to clarify the contribution from persons on dialysis and persons with functioning graft, respectively. We have also described which biological considerations relate to each group in the introduction.

C2

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:

A2

The type of renal replacement therapy was treated as a time-dependent covariate. We have clarified this in the text (methods)

C3

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

A3

Good point, which we have now added to the discussion.

C4.

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?

A4

To address this point we have randomly sampled 100 persons from our study population with HPV-related cancer. Among these, 25 were identified in the DNRP only. We added this to the text in methods. In the Danish cancer registry ICD-7 diagnoses were used until 2004. Subsequently diagnoses have been electronically recoded from ICD-7 to ICD-10. In terms of HPV-related head and neck sites, this might cause some misclassification during the recoding process due to the very specific cancer sites (ICD10) used to identify these cancers. Six HPV-related neck cancers were identified solely in the DNRP before 2004 in the sample and in these cases DNRP may actually be more accurate. In the remaining cases the validity of DNPR may be slightly lower than cancer diagnosis from the cancer registry. We have added this to Methods and Discussion

C5:

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.

A5
We have deleted figure 2 and instead compared the mean age at first HPV-related cancer. The result section has been changed accordingly.

C6

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.

A6

This is a very relevant comment. Previous studies have shown protective effect of HPV vaccines among seropositive but PCR negative healthy individuals. Whether these persons actually have latent HPV infection is to our knowledge unknown. Whether HPV-related cancers among ESRD patients develops through reactivation of latent infections or progression of active infections is to our knowledge unknown and will be of importance for the efficacy of the vaccines among ESRD patients. Studies of quadrivalent HPV vaccination among HIV infected men and children have shown high rates (>95 %) of seroconversion and antibody titers [1, 2]. HPV vaccines are immunogenic in this group of immunocomprised individuals and may therefore also be protective in ESRD patients. However, studies are indeed needed to clarify the benefit of HPV vaccination among ESRD patients as stated in the text. We have added “proportion of persons with active HPV infection” in the introduction as this also is an important factor for vaccine efficacy and expanded the discussion of vaccine efficacy.

Minor comments

C7

Page 9 "ren contractus" is not a standard term.

A7

Changed to “chronic renal failure without specification”
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.

This has been added to the text.

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 sentence has been deleted.
Andrew Grulich

Major compulsory revisions

C10
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.

A10
This is a very relevant question. We agree that CCI in general is not an established risk factor for HPV-related cancer. Most reports of risk factors for HPV-related cancer have identified parameters like smoking, number of sexual partners, parity and use of oral contraceptives[3]. While we were unable to adjust directly for these factors due to lack of available data, using CCI is an indirect way to adjust for these risk factors due to their well known association with many of the conditions included in the CCI. For example, smoking is a risk factor for cervical cancer [4], vulvovaginal cancer [5] and HPV-related head and neck cancers[6] and is also a risk factor for numerous conditions included in the CCI, which may explain our findings. Further alcohol intake may also increase the risk of cancer at HPV-related head and neck sites. Immunosuppressive therapy is widely used for treatment of connective tissue disease and this may cause an increased risk of HPV-related cancer.

Indeed, we found increasing risk of HPV-related cancer among population controls increasing CCI. We consider this an important and novel finding and have mentioned this in the paper. Conversely, the apparent protective effect of high comorbidity among ESRD patients is likely caused by high mortality in this group and should therefore be interpreted with caution.

Adjusting for comorbidity and cause of renal failure in the comparison of dialysis patients and transplant recipients only had minor effect on the cancer risk and these factors have now been omitted from the analyses. In the result section we
have added a IRR adjusted for age and sex only in the comparison of ESRD patients and population controls.

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

A11

We have changed the analysis and now only adjust for age.

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.

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.

A12

The type of renal replacement therapy was treated as a time varying covariate and ESRD patients were matched on sex and gender with population controls. Therefore age can differ among persons on dialysis and persons with graft function. We have omitted cause of ESRD and comorbidity from this analysis. We further added the incidence rates at each anatomical region by type of renal replacement therapy in table 4 We have edited the text in the discussion.

Minor Essential Revisions

C13

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.

A13

The sentence has been revised.

C14

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.

A14

We deleted the sentence.

C15

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.

A15

We have revised the sentence.

C16

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”.

A16

We have changed this in the paper.

C17

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.

A17

We have clarified this in the text.


