Author's response to reviews

Title: Mortality in cancer patients with a history of cutaneous squamous cell carcinoma - a nationwide population-based cohort study

Authors:

Sigrun A Johannesdottir (saj@dce.au.dk)
Timothy L Lash (tl@dce.au.dk)
Annette Ø Jensen (aoj@dce.au.dk)
Dóra K Farkas (df@dce.au.dk)
Anne B Olesen (anneolse@rm.dk)

Version: 2 Date: 13 March 2012

Author's response to reviews:

Reply to review

Concerning manuscript number 1764202944633032 entitled "Mortality in cancer patients with a history of squamous cell carcinoma – a nationwide population-based cohort study”.

We are grateful for the careful review of the manuscript. Below we reply to each comment, and we have revised the manuscript accordingly. We believe that the manuscript has improved, and hope you will find it suitable for publication. We are of course willing to make further changes if necessary.

We submit a clean copy of the manuscript.

Should you have questions or concerns regarding the manuscript, please do not hesitate to contact me.

Yours sincerely,

Sigrun Alba Johannesdottir

Department of Clinical Epidemiology, Aarhus University Hospital

Olof Palmes Allé 43-45

DK-8200 Aarhus N, Denmark

E-mail: saj@dce.au.dk
In this paper by Johannesdottir et al from the Clinical Epidemiology Unit in Aarhus, Denmark, the authors report mortality risks in cancer patients who have a prior history of cutaneous SCC. Overall, I congratulate the authors on a very interesting study, which is well-written and thought provoking. I found the hypotheses to be interesting, and the statistical analysis to be appropriate and well done. I agree with the authors’ conclusions, based on their data, and think it is likely that a prior skin SCC is a marker of immune suppression and poorer outcome from subsequent cancers. However I do have a few concerns about methodology that should be addressed before publication.

- Major Compulsory Revisions

1. The authors do not clearly state in the Title, Methods, or elsewhere in the paper, that the prior history was one of CUTANEOUS squamous cancer. The ICD codes for histology provided in the supplementary file do not clearly rule out the possibility of SCC of other sites, such as head and neck, esophagus, lung, etc. I assume the authors only included skin squamous cancers, but I see no discussion of how this was done. I would recommend this be clearly stated in the title of the paper and throughout the text.

   Reply: To avoid such misunderstanding, we have now specified the exposure as cutaneous SCC in the text. Regarding the diagnostic codes, we combined ICD-10 C44 (specific to non-melanoma skin cancer) with morphological code 80513, 80523, 80703, 80713, 80743, 80753, 80763, 80943, or 80953 to accurately identify patients with cutaneous SCC.

2. The authors are correct to adjust for factors such as age, comorbidity, cancer-directed treatment, etc., in adjusting the mortality ratios. The odds ratios and 95% CI for each of these factors should be provided in a table showing the full results of the Cox regression.

   Reply: To address this comment, we have added a table 3 showing the output for the Cox regression model and made a reference to it in the text (page 10 line 7).

3. I think that most readers’ major concern with this paper will be the lack of discussion of adjusted MRRs. The crude MRRs are interesting, but the authors have correctly noted that patients with a prior skin SCC tended to be older, male,
have more comorbid conditions, and to not have received cancer-directed therapy. Readers will be concerned that a history of prior skin SCC could simply be a robust marker for a patient with poor overall physiologic fitness to handle the stress of a new cancer and treatment thereof, and the reason they are more likely to die is simply their older age, higher comorbidity, lower likelihood of receiving treatment, etc. Even if all these covariates (age, gender, comorbidity, treatment, etc) were all controlled for, one would still have significant concern that the difference in crude MRRs could be due to other, unmeasured factors. I think it would be premature to conclude that this is all attributable to immunosuppression – are there any other possible causal pathways? Certainly, the possibility of other contributing factors should be acknowledged. Also, I would recommend the authors address the data presented in Table 2 – after correction, it looks like the elevated mortality risk only remains significantly elevated for lung cancer, not for any other cancer site. Unfortunately, this was not addressed in the text, but it seems quite striking. Can the authors give an explanation for these findings – how do they affect the authors’ conclusions?

Reply: We agree with the reviewer that there may be other causal pathways than the one put forth in the text and we do not conclude that our results are all attributable to immunosuppression although this is our primary hypothesis. Since this study is purely epidemiological, we are unable to test the various hypotheses for our finding. To make this clearer, we have added the following sentence to the discussion (page 12 line 5-6): “Furthermore, alternative explanations such as field cancerization due to an unidentified carcinogen may also explain our findings”.

Regarding significance it is correct that if relying on p-values it may look as if the mortality rate is increased only for lung cancer (and possibly rectal cancer depending on the definition of significance as p-value#0.05 or <0.05). However, we prefer not to do statistical testing for several reasons. The p-value is a function of both the size of the study and the strength of the effect. Because we are examining a rare exposure even large differences in the effect would turn out statistically non-significant. In addition, the p-value does not incorporate e.g. potential bias and hence the p-value is a biased unit as well. The interpretation of p-values alone is therefore complicated and we feel that little information is gained (please see Epidemiology - an introduction. Rothman K.J., Oxford University Press, pp 117-123).

- Discretionary Revisions

4. I am not sure it’s correct to consider autoimmune diseases as proxies for immunosuppression, as these diseases, such as rheumatoid arthritis, Sjögrens, sarcoidosis, etc – do not cause immunosuppression. What was the rationale here? Granted, a small proportion (especially in the modern era) of these patients would have been treated with chronic corticosteroids, causing immunosuppression – if this was the rationale, why not use corticosteroid use
instead of autoimmune disease as the covariate?

Reply: The rationale is that many of the diseases are associated with immunosuppression either due to the disease state itself or the treatment. It would have been ideal to use treatment with these medications as a proxy measure; however, this information was not available to us. To address the comment, we have added the following sentence to the methods section (page 6 line 20-24): “According to our hypothesis cutaneous SCC is associated with poor prognosis in cancer patients due to underlying immune incompetence. We would therefore expect diseases involving the immune system or immunosuppressive therapies to be more frequent in patients with a history of SCC. To examine this, we also included a list of autoimmune diseases, as a proxy measure of immune function.” Furthermore, the following has been added to the discussion (page 12 line 7-13): “The low number of observations limited the analysis of associations for subtypes of autoimmune diseases, and since the degree of immunosuppression varies with severity and type of autoimmune disease “a history of any autoimmune disease” may be an imperfect reflection of immunosuppression. Furthermore, information on a history of autoimmune disease may be underreported, especially in the mild cases. These limitations prevent us from ruling out a differential effect in people with autoimmune disease.”

5. Might the authors want to include other second cancers that are known to be related to immune status, such as renal cell cancer or melanoma?

Reply: We did consider including other cancers, but because of the rarity of a history of SCC of the skin among cancer patients, we chose to focus on the most common types of cancer (cancer of the lung, colon, rectum, breast, or prostate). In addition, we included NHL because of its link to immune function and for comparison with previous studies on the topic. To make this clearer, we have added this explanation to page 5, line 3-7.

Reviewer by Dr. Nabil Saba

1. In this report, Johannesdottir et al perform a nationwide population-based study looking at associations between having a history of SCC and the prognosis from having a second index malignancy namely NHL, lung, colorectal, breast or prostate cancer. Even though the analysis and results do indicate that patients with a known diagnosis of SCC appear to have a worse prognosis it is rather difficult to attribute these findings to a particular factor such as an immune suppressed state. There is also little information provided to the reader about the primary sites and stages of the SCC and the status of these tumors at the time of diagnosis of the index malignancy, which makes the results difficult to interpret.

Reply: There seems be a misunderstanding regarding the primary cancer. We
only included squamous cell carcinomas of the skin and not other types of squamous cell carcinomas. To make this clearer, we have described this more clearly in the introduction and the methods section (see reply to comment 1 by Dr. Luc Morris).

2. Even though there has been links between immunosuppression and the occurrence and prognosis of patients with SCC of the skin there is no clear evidence that patients with SCC in general are more likely to have an overall immune suppressed state. Rather such a state increases the risk of SCC notably of certain types such as skin SCC.

Reply: Please see our reply to the previous comment.

3. In addition, the risk of developing these index cancers is influenced by a host of factors including genetic environmental and others such as field cancerization at least in the case of lung cancer. We agree with the author’s statement on page 4 that focusing on patients with known immunosuppression state such as HIV and organ transplant would be more helpful in answering questions specific to immune suppression as a key factor in affecting outcome. How do the authors account for the fact that field cancerization in patients with known SCC increases the risk of having other aero digestive malignancies namely SCC of the lung? The occurrence of lung cancer in these patients is probably linked to exposure to known carcinogens and probably has little to do with an immune compromised state.

Reply: Please see reply to comment 3 by Dr. Luc Morris. We agree that the subject of field cancerization is interesting and it is possible that a known carcinogen may increase the risk of both cutaneous SCC and a second primary. However, it is important to keep in mind that it is not the occurrence of a second cancer, but the mortality of a second cancer, that we are examining. Although unknown to us, such factors may exist and it is indeed an interesting hypothesis. Unfortunately, we lacked the data to examine it further.

4. Finally, it would be helpful if the authors elaborated on the reasoning behind their choice of index cancers as there is no clear evidence that these particular types of cancers with the exception of lymphoma and lung cancer are more likely to occur in patients with an immune suppressed state compared to other cancers.

Reply: Please see reply to comment 5 by Dr. Luc Morris.