Reviewer's report

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

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Reviewer: Luc Morris

Reviewer's report:

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.

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.

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?

- 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, Sjogrens, 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?

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?

Level of interest: An article of importance in its field

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.