Author’s response to reviews

Title: Cumulative solar ultraviolet radiation exposure and basal cell carcinoma in a nationwide US cohort using satellite and ground-based measures

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Version: 1 Date: 09 Oct 2019

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Response to the comments of referee 1 on “Cumulative solar ultraviolet radiation exposure and basal cell carcinoma in a nationwide US cohort using satellite and ground-based measures” by MP Little et al (ENHE-D-19-00280)

This well written manuscript addresses the issue of dose-response of solar UV exposure in skin cancer risk. While it is well established that sun exposure causes skin cancer, we don't have good data on "how much?", which is actually a critical piece of missing information in developing effective interventions. (In contrast to cancer risk factors like obesity and physical activity, where we have data on dose-response).

This analysis goes some way to addressing that question, although still only provides a relative answer, concluding that the highest levels of ambient UV exposure are the ones most consistently linked to skin cancer risk.

Another important contribution of this paper is that we don't have data on non-melanoma skin cancer in our population-based cancer registries (skin cancer not reportable), so large cohorts are the only place we can obtain this kind of information.
While self report of NMSC doesn't sound like it would be particularly accurate, anecdotally it's likely that most people know when they've been diagnosed with NMSC - if the outcome is misclassified, it's likely to over-represent severe disease, and this limitation should be noted. (However, that's unlikely to affect the dose-response strongly, especially because the exposure metric is not self-reported, it's based on residential history, which is in this case relatively objective).

Agreed, up to a point. As we note in the Methods (“BCC case ascertainment and medical validation” section), over 85% of BCC for which we could obtain medical records were medically validated on both second and third questionnaires. As such we regard overascertainment as much less likely than underascertainment in this cohort. However, the medical training that technologists receive and the environment in which they work makes substantial underascertainment unlikely. Nevertheless, we discuss the possibilities for over- and under-ascertainment, and the other points raised by the referee in para 4 of the Discussion.

One limitation not discussed is the representativeness of this population - there should be some discussion of how representative radiation technologists are of the general population (important because the aim is to provide population-based estimates of relative risk). Three main concerns would be (1) their socioeconomic status - strong SES gradients in skin cancer, so if rad techs are relatively well off, they might be at the low end of actual sun exposure and high end of knowledge about avoiding the sun; (2) you'd think that rad techs would be aware of radiation risks, including sun exposure, so are likely to have a different risk of exposure reflected by their residential levels (ie the "ecological" misclassification is likely to be higher in rad techs); (3) access to care likely to be better, and therefore likelihood of being diagnosed with NMSC....

Agreed. We judge that the USRT, like most occupational cohorts, is very unlikely to be representative of the general population, largely because of selection that takes place as a result of being selected for employment. We discuss this further in para 4 of the Discussion. The factors mentioned by the referee undoubtedly also apply, and we have also mentioned them at this point.

The discussion about the two different methods of UV exposure is a bit overdone, especially when they show essentially the same thing - some of that might be replaced with discussion of generalizability (above) and/or the likelihood that residential exposure misclassification will bias results towards the null.

Agreed. We have slightly trimmed the last para of the Discussion (just before the Conclusions), which we assume is the one the referee refers to. As above we have considerably expanded considerations of generalizability in para 4 of the Discussion. We briefly refer to the potential biasing effect of misclassification, which we do not think very likely, in this para also.
Response to the comments of referee 2 on “Cumulative solar ultraviolet radiation exposure and basal cell carcinoma in a nationwide US cohort using satellite and ground-based measures” by MP Little et al (ENHE-D-19-00280)

This paper provides a precise quantitative description of the association between exposure to ambient ultraviolet radiation (UVR) and the incidence rate of Basal Cell Carcinoma (BCC).

The population studied is a large cohort of 63,912 white cancer-free US radiologic technologists from entry (1983-1998) to exit (2003-2005) with known ultraviolet irradiance at up to 5 residential locations; 2,151 cases of BCC were identified. Using generalized-additive models, the association between the incidence rate of BCC and ambient cumulative ultraviolet radiant exposure is described, using either ground-based National Solar Radiation database Average Daily Total Global data (AVGLO) or satellite-based National Aeronautics and Space Administration Total Ozone Mapping Spectrometer data (NASA-TOMS).

The excess absolute risk (EAR) and the excess relative risk (ERR) of BCC observed in this cohort were modeled using a Poisson regression and a linear, or linear-quadratic or log-linear function of the cumulative exposure to UVR, as estimated from the AVGLO and NASA-TOMS obtained from the residential histories.

The main conclusions drawn from these analyses are the existences of:

- a very marked increase of the EAR and ERR of BCC as a function of cumulative exposure to UVR (estimated by AVGLO or by NASA-TOMS);

- a significant upward curvature of the relationship between AER of BCC and cumulative exposure to UVR (AVGLO and NASA-TOMS) and no such significant curvature of the relationship between cumulative UVR exposure and ERR of BCC;

- a substantial variation in ERR with time after exposure (beginning of ? end of ?) and age at (onset of ?) exposure, whereas no such effect was clearly observed for the AER of BCC?

Overall assessment

This work is based on a large cohort, with good quality observation and a wide range of the exposure of interest. It addresses in detail the interesting question of quantifying the association between UVR and BCC, which was not addressed previously with this level of epidemiological information and analytical effort.

On the other hand, the reader who is firstly very impressed by the clear message given by figure 1 may become perplex when he goes deeper into the reading of this manuscript considering:

- the profusion of models and parameters that are used,

- the pending question of how to interpret results when algorithms do not converge,
- the capacity of this large set of data to allow the estimation of risk as a function of several parameters that are all likely to be tightly correlated together,

- the potential role of other BCC risk factors which are not taken into account in the present analysis.

Main comments

1) Is the cumulative exposure x EAR of BCC association linear or quadratic?

The authors underline in the abstract, results, conclusion, that the linear-quadratic model better fits the association between the EAR of BCC and cumulative exposure UVR than a simple linear model. However they also give as a summary statistics the slope of the simple linear models in the results, conclusion, and abstract.

As a matter of fact, looking carefully at Figure 1, it does not appear that there is a clear upward curvature of the exposure x risk observations. This may not be contradictory with the p-values of the quadratic component of the model as the number of person-years at risk and of BCC cases are very large: the p-value for including a quadratic term may be very small while the difference between the linear and linear-quadratic models may also be quantitatively small.

This point should be clarified for instance by giving a table with the estimated EAR and ERR of BCC and their 95% confidence intervals for a range of percentiles of the cumulative exposure distribution in the cohort (P10% P25% P50% P75% P90%).

From these figures, the authors - and the readers - will be able to appreciate if the linear and linear-quadratic models do differ materially in their capacity to estimate adequately the risk observed:

- if yes, it is appropriate to underline the existence of a curvature, but inappropriate to give the slope of the simple linear model in the abstract, results and conclusion. In this case the estimated EAR or ERR should be given for a few values of the cumulative exposure to UVR to illustrate both the order of magnitude of the EAR and the curvature of their variation with cumulative UVR

- if not, it is not appropriate to underline the existence of curvature in the abstract and conclusion, but appropriate to summarize the association between EAR of BCC and cumulative exposure by the slope in a simple linear model.
Agreed, up to a point. The evidence we find for curvature is not clearcut. The evidence is stronger for the additive risk model fitted using either of the UVR exposure measures (Table 2). The evidence is less strong for the relative risk model using the two UVR exposure measures (Table B1), but there are quite significant problems of model convergence with this second set of models which make interpretation of this problematic. It is quite difficult to be sure from Figure 1 if in fact there is curvature. The uncertainties on the higher levels of cumulative exposure are considerable. Given the grouped person year table that is the basis for all the analysis, it would be really quite difficult to perform the analysis by given percentiles of the UVR exposure, but in any case we are not sure how this would really help one to determine curvature, since these categories would certainly not be equally spaced. The most that can be done is to use the given categories of cumulative radiant exposure in the person year table, and plotting absolute and relative risk at each of these, which is what we plot (more or less) for absolute risk in Figure 1 already. To address the reviewer’s point, we have added a presentation of these values in tabular form in a new Appendix Table B3 in the Appendix. We have also somewhat qualified what we say about curvature, for example in the first para and last para (Conclusions) of the Discussion.

Given this not completely clearcut evidence of curvature, we provide the linear excess risk estimates in the abstract and elsewhere. We have slightly toned down the evidence for curvature cited in the abstract (“there was some evidence of upward curvature” replacing “there was significant (p<0.002) upward curvature”), in particular removing the p-value.

2) Clarify notation in the text, not only in Table footnotes or supplementary information The notation used in the text, even though they follow the common notation in the GAM, should be clarified in the text and not only in the Supplementary material. As an example page 6 and 7 when presenting formula (1): $\lambda$, $t$, $\phi_i$, $\beta_i$, $\alpha$, $H$ should be defined in the text and not only in Supplementary Table B1.

Agreed. We provide more details of these parameters in the Statistical Analysis subsection of the Methods. The parameter is defined in para 1 of this section. The function is defined in the same location.

Time after exposure and age at exposure should be defined as all subjects in the cohort had a lifelong exposure to ambient UVR.

Agreed. We say more about these quantities in para 2 (immediately after expression (1)) in the Statistical Analysis subsection of the Methods.

3) Do the AVGLO and NASA-TOM cumulative exposure metrics describe equally well or not the observations?
Figure 1 might suggest that the EAR of BCC increases more steeply over the range of cumulative exposure to UVR when estimated by AVGLO (from 0 to about 3 / 10,000 PY) than when estimated by NASA-TOMS (from 0 to about 2/10,000 PY, that is 1 third less). On the other hand the values of the AIC criteria given in Table 2 suggests that both estimates of cumulative exposure to UVR provides equally acceptable linear-quadratic fits to the observed data as compared to the simple linear models based on these exposure metrics. The authors concluded:

- in the abstract (page 2) that both measures of cumulative exposure gave similar values for the risk,

- in the conclusion (page 11) that AGVGLO appeared to give a better description of the observations than NASA-TOMS Here again a coherent conclusion should be proposed, and for this purpose a tabulation of the estimates of EAR and their 95%CI over a range of percentiles of the distribution of cumulative exposures (P10%, P25%, P50%, P75%, P90%) will help to appreciate if both exposure measurements do or don't fit similarly the data.

A scatter plot of (xi = AVGLO, yi = NASA-TOMS) over the subjects (i=1,n) for which these two metrics are available will also be important to compare the capacity of both metrics to capture the variation of EAR or ERR of BCC.

Agreed, up to a point. As the referee notes, the AIC statistics given in the rightmost column of Table 2 suggest that the linear-quadratic model using the AVGLO-derived UVR measure fits better than the same model fitted using the TOMS-derived UVR measure; although the linear model fits the NASA TOMS data better than the AVGLO data, this model is clearly not preferred overall. That said, there is not much difference in AIC, at least for the linear-quadratic models. We have added a sentence about this to the Results, also to the penultimate para of the Discussion. As above, we have given a tabulation of EAR by cumulative radiant exposure in Appendix B Supplementary Table B3. Our statements in the Conclusions section of the Discussion and in the Abstract were based more on the intrinsic properties of the two measures addressed in Table 5, rather than anything derived from extrinsic statistical considerations. We do not see the need to modify them. We have provided a scatter plot of the two UVR measures, reproduced from Little et al (Photochem Photobiol 2018 94 1297-1307; Ref 20) showing a very high correlation, as we note in para 6 of the Discussion.

4) Final conclusion

The final conclusion of the abstract (page 2) and the text (page 11) states that:
« If confirmed in other datasets, our results suggest that interventions aimed at reducing risk of basal cell carcinoma should concentrate on those with the highest levels of ambient UVR exposure. » While the originality of the work performed relied on the use of cumulative exposure metrics, the large body of observations available and their precise quantitative analysis, this final conclusion could have been drawn by the authors from the literature they cited and which demonstrates, convincingly, that the incidence of BCC do increases with exposure to UVR.

Agreed. We entirely agree with the referee, that it is abundantly clear from the literature we have cited that BCC increases with exposure to UVR. As the referee notes, what has not been demonstrated hitherto, and is the main point of our paper, is that rate of BCC correlates remarkably well with UVR cumulative radiant exposure, albeit with some evidence of upward curvature in the exposure response.

To provide new quantitative information on this question the authors proposed to introduce duration of exposure through the use of cumulative exposure. From this point of view, it would be interesting that the authors put into perspective (in the abstract, text, conclusion) the role of variability of exposure level (variation of ambient UVR between the dwellings of the subjects in the cohort, related to demography and the spatial variability of UVR over continental USA) as compared to the role of the variability of exposure duration (between subjects in the cohort) in the increase in BCC risk.

Agreed, up to a point. We are not quite sure what the referee is expecting us to provide other than what we have already given. However, it is clear from a previous analysis (Little et al Photochem Photobiol 2018 94 1297-1307; Ref 20) that although the technologists moved a substantial distance during the lengthy follow-up period, there is comparatively little movement in latitude during the length of the follow-up. As such the UVR exposure the subjects received is likely to be at a nearly constant level of radiant exposure. Therefore the variation between the UVR exposure of individuals is largely dictated by the latitude differences in which different individuals largely live. Incidentally, this implies that there is likely to be limited information on variation of risk by age at exposure or time since exposure that can be derived from this cohort. We have added a few sentences along these lines to para 4 of the Discussion.

5) Non-convergence of several models

Several of the models adjusted to the data are given while the algorithm for calculating their parameters estimates did not converge. The authors should help us to disentangle:

- the models where this lack of convergence did not matter because the estimations of the EAR or ERR were "algorithmically" stable even though the estimations of the unknown parameters were not (and therefore these parameters could not be estimated meaningfully, and should not be given in results and tables)

- and where this lack of convergence should lead to ignore this model in the paper.
A discussion of the role of considering several variables, which are tightly correlated together, like age, cumulative exposure, age at first exposure, time after exposure, duration of exposure, should also be given by the authors to distinguish when a model can be meaningfully fitted to the data and when it cannot. From this point of view, analyzing the role the cumulative exposure within different age windows appears to be problematic and this part should be either omitted or discussed in detail.

Agreed, up to a point. We do not quite know what the referee means by “algorithmically stable”. The fact is that lack of convergence is a problem for some models, particularly the relative risk models. We judge that great weight should not be attached to results from these models, but it is probably best to provide the information, and give warnings in the text at various points, as we do. All models are adjusted for age, and even adjusting for this there is a clear independent effect of cumulative exposure, so we disagree with the referee that all these variables must be highly correlated. However, as above there is certainly limited information in the dataset on the effects of age at exposure or time since exposure, as we now point out in para 4 of the Discussion. However, we judge that we should present this material, but point out the possible limitations of the present dataset for ascertaining these effects, as we do in para 4 of the Discussion.

6) Confounding

Page 19, lines 49 to 56, the authors indicate that "In addition to exposure to ambient UVR exposure, education, income, cigarette smoking, alcohol consumption, body mass index, hours exercise per week, eye color, skin complexion, ever sunburnt, number of blistering sunburns before age 15, skin reaction strong sunlight and number of dental X rays were all significantly associated with BCC risk”.

Some of these characteristics may either vary with age or vary from place to place within USA. Some of them may therefore have a potential to be associated with cumulative exposure to UVR and therefore to confound the association between cumulative exposure to UVR and BCC.

This should address in the paper

Agreed, up to a point. The possible modifying effect of these variables (and various others relating to hair color, eye color, Gaelic ancestry etc) on BCC risk and the extent to which they may confound the UVR-BCC exposure response association is the subject of another paper, which focuses on other aspects of the study as well, in the course of being prepared for publication. We found that these variables in general do not confound the UVR -BCC relationship. We judge that it would take the paper too far from it’s present form to include this quite extensive material. Nevertheless, we have included a brief sentence about this at the end of the Statistical Methods.
In the footnote of Table two it is stated:

†All analysis used linear-quadratic model (B1’) with adjustment to the baseline BCC rate for baseline questionnaire, ln[age], birth year, [birth year]2, [birth year]3, [birth year]4, [birth year]5.

What is baseline BCC rate? Is it adjusted for the different covariates that were listed as independent risk factors for BCC? If yes this should be clarified, if not this should be investigated.

Agreed, up to a point. We are not quite sure what “different covariates” were meant by the referee, but we assume some of those listed above. As above, the possible modifying effect of these variables on BCC risk and the extent to which they may confound the UVR-BCC exposure response association is the subject of another paper, which is being prepared (see above).

7) Minor comments

- In the tables EAR and ERR should be given with just one digit after the comma

- Table 1, Lines 10 and 11: the mean (SD) of age should be moved in the good column (no BCC or BCC)

Agreed, up to a point. We agree with the referee that giving four significant figures is excessive, so we have truncated all numbers greater than 10 to a single decimal place. However, we judge that numbers with absolute value less than 10 can remain as they are, so that the number of significant digits is approximately constant (generally no more than 3). We have limited all the AIC values to a single decimal place. We disagree with the referee’s proposed move of the mean (SD) of age in Table 1. To put these numbers in either the BCC or no BCC columns would be very misleading, as they relate to the full cohort, and do not relate to BCC status, which is why we placed them where they are.