Author’s response to reviews

Title: Cancer Prevalence among Flight Attendants Compared to the General Population

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Author’s response to reviews:

Dear Editors,

Thank you for the opportunity to submit further revisions for our manuscript, “Cancer Prevalence among Flight Attendants Compared to the General Population,” for consideration at Environmental Health. We have addressed the suggested revisions to the best of our ability. Below is a point by point response to the reviewer’s concerns:

1) Comment on response to by point 1. Reference No. 9 is not the one I mentioned in my point; you make reference to the old Pukkala study on the Finnish cabin attendants from year 1995 instead of the study of several Scandinavian cohorts with information on reproductive factors from 2012 (which in the present version of the manuscript is No. 22).
Response: Thank you for noting this. We have changed the references accordingly.

2) Comment on response to my point 4. The last sentence in your response and speculations on the possible effect of volunteer participation may need reconsideration. Your reference No. 37 is to a study on cardiovascular diseases and attempted to evaluate the representation of self-selected participants as compared to a random sample of the US population, however your study is on cancer prevalence. I recommend you to take a look in Rothman’s book, where he is discussing Smoky Atomic Test in Nevada (Caldwell et al. 1980). The reason for volunteering in your study may be associated with the outcomes and if so, information on individual flight attendants without cancer may be lacking (in other words: cancer free flight attendants may not be participating at the same proportion as those with cancer), and thus not available for internal analysis (mind, that you are calculating OR). It is complicated to argue around or adjust for in the analysis the potential missing information. Maybe the last sentence of your response should be omitted.

Response: Thank you for noting this and providing background information. We have omitted the last sentence of this section, as suggested.

3) Some readers will experience the word “relationship” in headings of the Tables rather determined, and in Method you talk about associations, which many would prefer and that is somewhat softer. Some readers think that relationship is a causal association.

Response: We have changed the word “relationship” to “association” in the table headings.

4) It is explained that the figure for cancers in Table 2 (internal analysis) is lower than in Table 1 (SPR calculation) due to missing data regarding tenure and model covariates. The
figures for breast cancer are in the last version of the manuscript lowered from 163 to 108 (195 in Table 1). Thus, the number of breast cancers is approximately 45% lower in Table 2 than in Table 1, proportion which differs substantially compared with other cancer sites. An explanation is still needed.

Response: In the multivariable analysis for breast cancer, there are 108 flight attendants with breast cancer who were able to be analyzed in multivariable modeling. This is because the model only uses data on flight attendants who have no missing data on all covariates in the model. The number reduced from 163 breast cancer cases analyzed to 108 breast cancer cases analyzed because the data used for multivariable modeling necessitates no missing data on all covariates, and we are not including parity or number of live births as a variable.

5) In the foot note of Table 2, it says that the breast cancer model is further adjusted for number of live births, but in the head of Table 3 it says parity. Is this an important difference? I think this is unnecessarily confusing. Are nulliparous women included in the analyses in both tables.

Response: We have changed to wording to parity in both tables. Nulliparous women are included in analyses presented in both tables.

6) I understand the multivariate analyses in Table 2 and 3 so that tenure is introduced in the calculations as a continuous variable and that the ORs are showing the increase per five-year job tenure. If that is correct, one may consider showing the number of non-cases in the individual analyses, there is enough space in these tables.

Response: We have added this information to the tables.
7) In the parentheses of the heading of Table 3 it says that restriction is made to participants age 45 and older. Does that mean all models shown in Table 3, or just in the model of tenure prior to age 45?

Response: Only the models of tenure prior to age 45 restrict to those age 45 and older. We have clarified this by replacing the text in the parentheses with a footnote that reads: “Models for tenure prior to age 45 are restricted to participants age 45 or over.”

8) Your argument for the restriction to participants age 45 and older in Methods – you say you do it in order to standardize exposure opportunity. That may be good intentions; however, is this necessary or needed in these internal analyses with case-cohort design? You do not have information on when the cancer occurred neither in relation to age of the cohort members, or in relation to the commencement of employment, or in relation to the duration of the employment of the cohort members. The restriction may exclude cases and controls with more than 20 years of exposures, however, also those with shorter exposures, who are important in this setting. Indications of this importance is that according to the study of the Scandinavian cohort of flight attendants (Pukkala et al. 2012), the increased cancer risk for all cancer, breast cancer, and skin cancers is obvious less than 20 years since first employment, and your flight attendants start flying at an early age. Maybe nobody knows exactly how to manage this complicated situation. Can you show us these analyses with and without the restriction?

Response: We show the analyses without restriction to those ages 45 or older below. Results were somewhat different, but did not change any interpretations, so we have maintained our original approach.
Table 3. The relationship between five-year job tenure prior to age 45 (NOT restricted to participants age 45 or over), parity and prevalence of breast cancer among female flight attendants.

<table>
<thead>
<tr>
<th></th>
<th>Overall (total job tenure)</th>
<th>Overall (tenure prior to age 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.99 (0.91, 1.10)</td>
<td>1.29 (0.92, 1.80)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parity (total job tenure)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous</td>
<td>1.27 (0.94, 1.71)</td>
<td></td>
</tr>
<tr>
<td>1 to 2</td>
<td>0.95 (0.84, 1.06)</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>1.22 (1.05, 1.42)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parity (tenure prior to age 45)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous</td>
<td>1.62 (1.01, 2.62)</td>
<td></td>
</tr>
<tr>
<td>1 to 2</td>
<td>1.01 (0.82, 1.24)</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>1.16 (0.93, 1.43)</td>
<td></td>
</tr>
</tbody>
</table>

1. All models are adjusted for age, overweight, education, and smoking history.
9) In Table 3, two categories of job tenure analyses are shown, for total tenure and tenure prior to age 45. I assume that the first pair of these analyses were without stratification on parity, the second pair were stratified on nulliparous, para 1 to 2, and para 3 and higher. It is not very descriptive or clear to name the analyses without stratification “overall,” they are simply non-stratified, and the other pair of analyses are stratified on parity, please put the nomenclatures of these categories straight. Whether the first pair of tenure analyses were adjusted for parity is highly probable, however, that needs to be clearly stated in the head of the table, in a foot note, or somewhere in the table, so Table 3 and its content stands independent, without support from what may be happening in Table 2.

Response: We have made the above changes to Table 3. Specifically, we now write “lifetime job tenure” and “job tenure prior to age 45,” and included the fact that we adjusted for parity in the footnote with the other covariates.

10) The number of cases in the first model in Table 3 were 163 but at present the cases are 108, as in Table, please explain this reduction. The number of cases regarding “overall,” tenure prior to age 45 (second model) have changed from 131 to 90, however, in the first version of the manuscript the number in this category was 144, please explain.

Response: In the multivariable analysis for breast cancer, there are 108 flight attendants with breast cancer who were able to be analyzed in multivariable modeling. This is because the model only uses data on flight attendants who have no missing data on all covariates in the model. The number reduced from 163 breast cancer cases analyzed to 108 breast cancer cases analyzed because the data used for multivariable modeling necessitates no missing data on all covariates, and we are not including parity or number of live births as a variable. The reduction in Table 3 (second model) to 90 cases is resulting from this same reason. This is the data for which parity is measured.
11) In the first model with the stratification on parity, and total job tenure the figures for cases, odds ratios, and confidence intervals are exactly the same as in the previous version of Table 3, and the number of cases is higher than in the first model, non-stratified. In the old Table 3 there were 162 cases in this model, and the new Table 3 the number of cases regarding this model was lowered from 162, i.e. quite near 163 which were the number of cases originally reported in the first model of the old Table 3. Please put all these issues straight.

Response: The figures in the current Table 3 are all accurate in this revision.

12) In the last model of Table 3 the sum of cases is 127, somewhat higher than reported in “overall” tenure prior to age 45. In the old Table 3 there were 143 cases in this model, one less than 144, which was the number of cases previously reported in the second model of the old Table 3. Here the OR for strata para 1 to 2 is reported 1.95, is 0.95 correct? That figure is reported in Results. The OR for strata para 3 and higher is exactly the same as in the previous version of Table 3, is that ok? Please take a careful look at these figure, and correct.

Response: We have changed 1.95 to 0.95 in this Table. All figures for effect estimates and sample sizes are now accurate in Table 3.

13) The adjustment or stratification for parity is not mentioned in Methods, please add this and explain the reason why these particular categories of parity were chosen.

Response: We have added the following text to the Methods section, describing the parity stratification and the reason these categories were selected:
“For breast cancer, we evaluated these associations both overall and stratified by parity (nulliparous, 1-2, 3+). Parity categories were chosen based on previous studies of breast cancer among cabin crew [20, 21].”

14) In the last paragraph in Results, unnamed previous study is quoted concerning breast cancer risk and parity, which are better placed in Methods, supported with references; this point is related to the previous one.

Response: Thank you for noting this. We now reference these studies (and cite them), in the methods section, as shown for comment 13.

15) These previous studies are your references number 32 and 33, however they were studying the association of cosmic radiation and circadian rhythm disruption with breast cancer incidence, however, your association analyses concern job tenure and breast cancer prevalence, and this has to be put clear. This point is related to the two previous points.

Response: We have included the following text in the discussion section to acknowledge these differences between our studies:

“Our findings of a stronger association between tenure as a flight attendant and breast cancer among women with three or more children is, interestingly, consistent with two other recent publications on this topic among cabin crew [20, 21]. The authors of the latter studies, which evaluated breast cancer in relation to calculated cosmic radiation exposure and Circadian rhythm disruption, hypothesized that these unexpected results may be due to Circadian rhythm changes…”
16) Did you in your present analyses of nulliparous flight attendants find high OR with confidence intervals not including unity? If the answer is no, you should revise the Results and Discussion section dealing with these issues. Narrow confidence intervals are needed for firm interpretation in subgroup analyses, where the number of cases is lower than in the total cohort.

Response: We have altered the text in the manuscript accordingly:

“Finally, we found evidence of a positive association between job tenure as a flight attendant and breast cancer among those with 3 or more children, and associations were strongest when combining these parity subgroups with the job tenure measure prior to age 45. We also found some evidence of a tenure-breast cancer association among nulliparous flight attendants, though the associated confidence intervals were less precise and included the null. For example…”

“We report associations between duration of employment as a flight attendant and breast cancer risk among women who had three or more children, with some evidence of an association among nulliparous women as well, though the latter association was imprecise. Nulliparity is a risk factor for breast cancer, and women who are parous may be less susceptible to the effects of carcinogenic exposures on the breast due to breast cell differentiation occurring after a first pregnancy [32, 33]. Hence, our findings of a somewhat stronger association between job tenure and breast cancer among nulliparous women…”

17) Did you find higher OR in the analyses with job tenure prior to age 45 than in the analyses of total job tenure, when evaluating breast cancer risk? If that is the case, please comment on the results in Discussion, and tell us whether that is supporting the view that exposure at young age is relevant for the breast cancer risk. Mind that you only have surrogate of the exposures to cosmic radiation and circadian rhythm disruption.
Response: We have added the following text to the Discussion:

“Although we evaluated job tenure prior to age 45 or age 40 in relation to cancer prevalence, in part to isolate the potential effects of ionizing radiation exposure at younger ages, these restrictions generally did not meaningfully alter our results. This may be because ionizing radiation exposure is also important to cancer risk at older ages, and because it is difficult to disentangle the relevant exposure years in our study population, which has a median tenure of 19 years of employment and for which cancer diagnosis date was not recorded. One possible exception is for breast cancer, for which associations were somewhat stronger when evaluating tenure prior age 45 rather than lifetime tenure. These results, while imprecise and requiring replication in a study that estimates cosmic ionizing radiation exposure directly (rather than using tenure as a proxy), may suggest that flight-related exposures are most important to breast cancer risk when occurring at earlier ages.”

18) Furthermore, did you consider studying the job tenure prior to age 45 in association with melanoma, and non-melanoma skin cancers? Do not the breast cancer analyses indicate that exposure at young age is more relevant than the total tenure? Skin cancer cases are numerous and these analyses would be with fewer covariates, unless you have access to information on the interesting confounder sunbathing habits and host factors related to skin cancers.

Response: We already evaluated associations with skin cancer when restricting to tenure prior to age 45, and did not observe meaningful differences in effect estimates, as mentioned in the text. We did not have information on sunbathing habits or other skin-cancer specific covariates.

“With the possible exception of breast cancer, associations with most cancers were not meaningfully changed by restricting the exposure of interest to job tenure prior to age 40 or 45 (Table 3 for breast cancer; other data not shown).”
“Although we evaluated job tenure prior to age 45 or age 40 in relation to cancer prevalence, in part to isolate the potential effects of ionizing radiation exposure at younger ages, these restrictions generally did not meaningfully alter our results.”

Thank you again for your consideration, and please let me know if you have any additional questions or concerns.

Sincerely,

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