Author's response to reviews

Title: Incidence of cancer among licenced commercial pilots flying North Atlantic routes

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Author’s response to reviews:

Dear Editor.

We are thankful for your suggestion to revise our manuscript.

We thank the reviewers for their valuable feedback and comments.

We have carefully reviewed the comments and amended accordingly.

Here are our point-to-point responses to every comment.

Reviewer reports:

Reviewer #1

1. There isn't enough literature in the introduction section to back up the relationship between frequent travels by pilots at aviation altitudes and exposure to cosmic ionizing radiation which in turn could cause cancer. Kindly include about 7 or more literature in your introduction to buttress the link between frequent air travel, cosmic radiation and cancer.

Response: We have included a few studies on cancer incidence among flight attendants (paragraph 2, page 3).

2. On page 4, line 58, explain the briefly the meaning of effective dose of radiation.

Response: We have included an explanation of effective dose (para 1, p. 5).

3. Present the mathematical formula based on which the CARI-6 software was used to compute the effective dose rate of radiation (line 1, page 5)
Response: We have included further explanations and reference where the mathematics in CARI-6 is explained (para 1, p. 5).

4. Explain the meaning of CARI-6 software and reference the author.

Response: We have included explanation of the purpose of the software as well as a reference for details of the model the software relies on (para 1, p. 5).

5. Line 16, page 5: Under statistical analyses, state the mathematical formulae used for all the statistical packages. These statistical packages are based on mathematical formulations which you need to state as equations.

Response: We rephrased and clarified SIR calculations and Poisson regression with additional references (para 3 and 4, p. 5).

6. Page 6, line 17: UVA radiation is the most subtle form of UVR and its impact may never be carcinogenic, especially based on the small quantity that penetrates the aircraft's windscreen. If you think otherwise, include the estimate of the intensity of UVR that can permeate the aircraft's windscreen vis-a-vis the standard regulatory limit.

Response: We have included a sentence emphasizing this point (para 3, p. 10).

Reviewer #2

This is a very weak paper and it provides no new insight into the carcinogenicity of cosmic radiation. The associations that it reports are most likely attributable to statistical randomness, confounding, or biases. Furthermore, its conclusions contradict much of what we know about radiation carcinogenesis.

Major weaknesses:

1. Lack of power. The median cumulative ionizing radiation dose for the pilots in this study was 22.55 mSv, with a maximum dose of 83.2 mSv (Table 1). Years of cohort studies with large groups of medical patients and atomic bomb survivors tells us that the relative risks for such doses should be about 1.001 and 1.004, respectively (i.e. ERR= 0.00005/mSv). This is way too small an increase in risk to be seen in a cohort this small (n=551) or for that matter in a cohort of any size. At these dose levels, radiation risks are purely theoretical because they are too small to be measured.

   In fact, we can see that the pilot doses are barely above background doses at ground level. If we take the total person-years (8,514) and divide them by the number of exposed pilots (286), we can see that the average number of years of exposure per pilot were 30 years. Given that background doses at sea level are typically 3 mSv per year, subjects who never flew would have received 90 mSv over this 30-year period. So even the pilots with the highest doses are but
two-fold above background radiation doses. So it seems incredulous that significant increases in any cancers could be seen at these extremely low ionizing radiation doses.

Response: The small study size, resulting in wide confidence intervals, is mentioned as limitations in Discussion, (para 3 p. 11). In response to this comment we have made an addition after the first sentence.

2. Potential Confounding. So how do we explain the statistically significant increases skin cancers that were found among the pilots? The most likely explanation is that they were caused by increased exposure to ultraviolet (UV) radiation. UV exposure is the most important risk factor for skin cancers. The UV doses of the pilots would have been collinear with their ionizing radiation exposure. So their UV exposure is likely a confounder in the study. (A confounder is a variable that is associated with both the exposure and the disease, and results in a false apparent association between the two.) If UV doses had been measured, the potential for UV confounding could have been assessed. But UV doses were not determined. So we cannot be sure that confounding is the explanation, and we cannot discount them (notwithstanding the face versus trunk incidence comparison).

Response: The exposure of the pilots to UVR radiation was not known on individual level and thus not controlled for in the multivariate analyses. This is an uncontrolled confounding factor for skin cancer in the study and is one of its limitations, mentioned several times in Discussion, pages 8 to 10. The possibility of leisure sun exposure of pilots was discussed in lights of results from survey on risk factors for skin cancers among the pilots in Discussion, (para 1, p. 9). The possibility of UVR exposure in the cockpit, thus occupational exposure, was thoroughly discussed in Discussion, (para 3, p. 10). To meet this comment of the reviewer we have added a sentence in Discussion (para 2, p. 11).

3. Potential Biases. But UV doses don't explain the prostate cancer association that was found. How can that be explained? Prostate cancer is the most prevalent cancer among men. Virtually all men eventually get prostate cancer if they live long enough, since age is the most important risk factor. But there are other risk factors for prostate cancer (e.g., obesity and being sedentary). But the prevalences of obesity and a sedentary lifestyle also increase with age. So it is very important that all of these known risk factors be adjusted for when assessing radiation's prostate cancer risk. In this study, only age was adjusted for. Further complicating the analysis is that the cumulative radiation dose is also primarily driven by age (i.e., the more years if flying you experience, the older you'll be, and the higher your cumulative dose will be). Thus, all the age-related risk factors must be carefully adjusted for, otherwise residual age-related confounding could result in false association.

In addition, prostate cancer is highly susceptible to surveillance bias, particularly if it is detected by PSA testing. The Icelandair pilots' annual physicals are probably not exactly the same as other pilots. If there is any difference between the two groups in how they are screened for prostate cancer, the study will be prone to surveillance bias. There is no discussion or assessment of the potential for surveillance bias in this study.
Response: We discussed the possibility of detection bias in the present study in Discussion, (para 4, p. 11). The Icelandair pilots and other pilots, who may have flown domestic flights, underwent frequent medical check-ups, demanded by the Icelandic Aviation Authority, which aimed to evaluate health and fitness to fly. To meet this point raised by the Reviewer we have adapted the last sentence in Discussion, (para 4, p. 11).

Other problems:

4. SIR analysis. It is not clear what group the SIR is being standardized too. SIR is usually used to account for differences in incidence rates between populations that can be explained by differences in demographics such as age, gender and race. These pilots are a very homogeneous group. They are men within a very narrow age range, who are presumably all Caucasians. It is not clear what the SIR is supposed to achieve, and whether the standard population is relevant.

Response: We have now clarified in Methods, that it is the incidence of the general male population in Iceland according to the Icelandic Cancer Registry (para 3, p. 5).

5. Cox Regression analysis. Cox regression would seem like the most appropriate tool for analyzing these data, but we are told that "the data did not meet the criteria for Cox analysis." We are not told, however, in what way the data did not fit the criteria. This is a red flag.

Response: We have included both the criteria for Cox-regression-analysis, and the conditions that our study did not meet, in the manuscript (para 4, p. 5).

6. Unexposed. The non-Icelandair pilots were defined as the "unexposed group." Why would non-Icelandair pilots not have radiation exposure?

Response: The other pilots had never been employed as pilots at Icelandair as stated in Methods, (para 1, p. 4). Thus the files at Icelandair did not include information on whether they had flown as commercial pilots or not, and we do not have information of their possible flight career. It is not stated that other pilots do not have radiation exposure. We have now added clarification on this point in Methods, (para 1, p. 4).

7. Age 40 cut-off. Cumulative dose was calculated up to age 40 because "exposure after this age did not induce BCC among atomic bomb survivors." How is that relevant to this study?

Response: The cumulative effective dose of radiation in mSv up until the individual pilot reached the age of 40 years were estimated and analyzed in relation to incidence of all cancers, and selected cancer sites in the present study. The reason for testing the relation between radiation dose sustained before 40 years of age is explained in Methods, (para 2, p. 5), and maybe the reviewer has missed this. The exposure to radiation is most crucial in early life, and the importance of radiation exposure before 20 or 40 years of age for the subsequent risk of BCC was discussed in Discussion with two references, (para 2, p. 8). In order to clarify this we have improved the explanations of this issue in Methods, (para 2, p. 5).
Additional points from the authors:

We would like to point out changes to the number of events for brain neoplasm of the SIR analysis. We added one D33 diagnosis to the incidence of brain neoplasm (in tables 2 and 3), according to the definition from the Icelandic Cancer Registry. With these changes we gain more accuracy, however it does not change our conclusions.

We believe that the manuscript has improved as a result of the revision and we sincerely hope that it is to your liking.

Best regards, Eva Maria Gudmundsdottir.