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 revisions for our manuscript, “Cancer Diagnoses among Flight Crew 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 reviewers' concerns:

EDITOR COMMENTS:

1) Please describe the degree of overlap between the results presented in this manuscript and your other manuscript (under review): “Describing general flight crew health relative to NHANES.”
Response: The other manuscript, which had been under review but has been rejected from Environmental Health (and is in press at a different journal), was an overview of a wide range of health conditions (cardiovascular, respiratory, allergic, mental health, musculoskeletal, etc.) among flight attendants relative to the general population, using the same subset of the FAHS and NHANES study populations as the cancer study currently under review. I am including the abstract below. This first paper reports on “all cancers” and “reproductive cancers,” as shown in the abstract, in order to make it directly comparable to our initial NHANES comparison study published in 2014. The goal of our research was always to publish both a general health profile and a study evaluating individual cancers.

We do not aggregate any of the cancers we are evaluating in the current study into broader categories.

We now cite the above FAHS-NHANES study in the current manuscript, as follows:

“We have since completed the second wave of the FAHS in 2014-2015, in which we also report associations between flight attendant work and the prevalence of cancer at all sites and aggregated reproductive cancers [11].”

BACKGROUND: Flight attendants are an understudied occupational group, despite undergoing a wide and unique range of adverse job-related exposures. In our study, we aimed to characterize the health profile of cabin crew relative to the U.S. general population. METHODS: In 2014-2015, we surveyed participants of the Harvard Flight Attendant Health Study. We compared the prevalence of their health conditions to a contemporaneous cohort in the National Health and Nutrition Examination Survey (NHANES 2013-2014) using age-weighted standardized prevalence ratios (SPRs). We also analyzed associations between job tenure and selected health outcomes, using logistic regression and adjusting for potential confounders. RESULTS: Compared to the NHANES population (n=2,729), flight attendants (n=5,366) had a higher prevalence of female reproductive cancers (SPR=1.66, 95% CI: 1.18-2.33), cancers at all sites (SPR=2.15, 95% CI: 1.73-2.67 among females), as well as sleep disorders, fatigue, and
depression, with SPRs ranging between 1.98 and 5.57 depending on gender and the specific condition examined. In contrast, we observed a decreased prevalence of cardiac and respiratory outcomes among flight crew relative to NHANES. Health conditions that increased with longer job tenure were sleep disorders, anxiety/depression, alcohol abuse, any cancer, peripheral artery disease, sinusitis, foot surgery, infertility, and several perinatal outcomes. CONCLUSIONS: We observed higher rates of specific adverse health outcomes in U.S. flight attendants compared the general population, as well as associations between longer tenure and health conditions, which should be interpreted in light of recall bias and a cross-sectional design. Future longitudinal studies should evaluate specific exposure-disease associations among flight crew.

REVIEWER 1:

1) [This report] is not referring correctly to the literature on flight cabin crew....The most important example is the first sentence in the Discussion, page 8, which says: “To our knowledge, we have conducted the largest study characterizing cancer rates among flight crew relative to the general population, which has included profiling a wide range of cancers.” This statement is not correct. The cohort in the study of California flight attendants (Reynolds P. et al, Cancer Causes Control 2002;13:317-324) numbers 6895 females and 1216 males, and the cohort in the Nordic airline cabin crew study (Pukkala E et al. Int J Cancer 2012;13 1:2886-2896) numbers 8507 females and 1559 males. Both studies report more cancer sites than the present study. However, neither or these previous studies are cited directly in the report. Please make a correction and reformulate.

Response: Thank you for noting this omission on our part. We now include these important citations in our introduction ("Results have been mixed, but overall point towards associations between in-flight exposures or job tenure and increased rates of breast and skin cancers, as well as cancers at all sites [6-9].") and discussion sections ("Our finding of a greater prevalence of breast and skin cancers among flight crew is consistent with most of the epidemiologic literature on this topic to date [6-9]."). We have formulated the first sentence of the discussion to read:
“We have conducted a large and comprehensive study characterizing cancer rates among U.S. cabin crew relative to the general population, which adds to the relatively sparse literature on this topic and has included profiling a wide range of cancers.”

2) The authors are not sufficiently on guard against the consequences of the cross-sectional design of the study...It is not sufficient to admit it as a handicap without explanation and further reflections. The cross-sectional design means the researcher is obtaining simultaneously information on outcome and exposure so there is a risk that exposure is influencing outcome measures and vice versa, and structured questionnaires and interviews are used to counteract this possible source of bias, and that is the case in the present study, but need to be pointed out clearly by the authors. On the other hand, the occurrence of the cancers is not dated in the questionnaire so the cancers may have occurred before the employment as cabin attendants, sometime during their career as cabin attendants, or after termination of the employment. The timing of possible outcome events was carefully noticed in the Reynolds et al. study, and in the Pukkala et al. study. So the flight cabin crew in the present study may continue their employment after the diagnosis of cancers, for example melanoma, other skin cancers, thyroid cancer, and even breast cancer (all with good prognosis), putting the tenure calculations in a whirlpool. It is difficult to predict in what direction this shortcoming is leading, whether it results in under- or overestimation of the OR in the five-year job tenure analyses, as cancer diagnosis before employment falsely increases the number of outcomes, and counting the employment years after the diagnosis of cancer falsely increases the amount of exposure. The analyses with job tenure prior to age 45 (see later comments on tenure prior to age 45) is an improvement because that calculation focuses on exposures at early age, and most of the cancers of interest peak late in the population, for example at 85 years (melanoma, and non-melanoma skin cancer), or at 60 to 65 years (breast cancer), so the possibility that the exposure occurred before the outcome is increased. Thus, analyses of the association between five-year job tenure prior to 45 years and prevalence of all cancer sites, confer Table 2, should be conducted. The shortcoming related to lack of knowledge of the date of cancer diagnosis should also be mentioned and explained in Methods and discussed in Discussion.
Response: We have added the following text to the limitations section to address this issue:

“Limitations of our study include its cross-sectional design, which precludes inferences about causality, as an observed association may reflect the effect of flight attendant work on a given condition, or the effect of an outcome on a factor related to employment as a flight attendant. Use of structured questionnaires, as in our study, aims to minimize this bias. However, we also note a further limitation that the date of cancer diagnosis was not recorded in the FAHS questionnaire; hence, some cancers may have been diagnosed prior to employment as a flight attendant, and some flight attendant work (i.e. exposure) may have occurred following a cancer diagnosis, making the direction of the potential bias unclear. These limitations are counteracted in part by our analyses evaluating job tenure prior to age 40 and 45 years in relation to cancer prevalences, as many cancers, including of the skin and breast, occur later in life. Therefore, this restriction increases the probability that the exposure of interest occurred prior to the reported cancer outcome.

We also note the issue regarding dates of diagnosis in the methods section, using the following text: “We note that dates of cancer diagnoses were not recorded in the FAHS questionnaire.”

3) The recruitment of the participants, and the participants must be described in more detail. In the previous publication, the authors say that the surveyed flight attendants were employed by two domestic carriers. Does that mean that the flight attendants were only flying domestic flights or were they also flying international flights? This is of interest because if they were only flying domestically, their possible disturbance of circadian rhythm is less likely than if they are also flying international flights, which are longer and often pass more time zones. Further, do the words “employed by” mean that the flight attendants were current workers, or were there some former workers included? Could some of these confusions be solved by changing “domestic” for US?
Response: Thank you for noting these clarifications. We have included the following text in the methods section to elucidate these points:

“All current or former U.S. flight attendant was eligible to participate in the FAHS (91% of the participants in the current study were currently employed as flight attendants, and 9% were former flight attendants). While Wave 1 of the FAHS restricted participants to flight attendants employed by two U.S. airlines, Wave 2 was open to any U.S. flight attendant. Hence, participants in the current study worked for a wide range of airlines, flying both domestically and internationally.”

We also include a more comprehensive set of variables in Supplemental Table 1 (showing descriptive statistics for the FAHS and NHANES), in order to better describe our study population.

4) The recruitment of participants not randomly selected from the AFA files or participants recruited through announcement about the study from local unions and through social media is subject to bias, which the authors have failed to discuss. Discussion on this issue should include references to studies dealing with the possible selection bias due to volunteer participants. The flight attendants are well educated and of high social class, and possible cancer risk among the occupations of pilots and cabin crew have often been the issue in social media, and elsewhere, and that may have attracted those with cancer and bad health to participate; please discuss.

Response: Thank you for noting this. We have included the following text in the discussion section to address this issue:
“A further limitation of our study is that we recruited flight attendants from a mix of company rosters, on-site airport recruitment, and an online/social media presence. Volunteer participants not recruited from employee files may have contributed to selection bias. For example, volunteer participants may differ from those recruited using a more randomized approach in terms of various factors, including their socioeconomic status, attitude toward health research, and factors related to time and ability to complete online surveys, as discussed in a recent analysis with regard to online recruitment in the Heart eHealth Study relative to NHANES [37]. However, the above analysis reported that, while selection bias was likely on a variety of factors, such as gender and marital status, it was much less likely to affect internal (rather than external) validity of exposure-outcome associations [37]. This is likely to be especially true in a relatively homogenous workforce than in a general population study recruited online. It is also important to note that an online recruitment strategy has many advantages in terms of efficiency, reliability of data collection and coding, and the ability to reach a wider range of potential study participants [37]. Another source of selection bias is that our study may have attracted a disproportionate number of flight attendants with cancer, as flight attendants with worse health are likely to be more motivated to participate in an epidemiological study of flight attendant health, and the question of cancer risk in relation to flight exposures is well known within the aviation community. However, it is reassuring that our results are consistent with previous studies that recruited participants from employee rosters [7-9]. Further, while affecting generalizability of our findings (external validity), it is less likely an increase in recruited participants with cancer would affect associations with job tenure (internal validity) [37].”

5) A cross-sectional study on cancer prevalence is a study on those who have survived, which welcomes comments and discussion.

Response: We have included the following text in the discussion to address this issue:
“Finally, we note that our reliance on prevalence rather than incidence of cancer confuses the issues of cancer risk and survivorship in interpreting our results. This is in part ameliorated by the fact that breast and skin cancers have relatively low mortality rates (especially for basal cell carcinoma, which is not considered fatal or disabling), and that we are comparing to prevalence rates in NHANES as well. Nevertheless, the limitation remains, and it is also important to note that flight attendants may differ from the general population of U.S. workers with regard to health insurance access, paid leave policies, and other benefits that could affect survivorship, and may be more likely to have access to an urban center with better quality health care for cancer treatment. It is reassuring that our results are consistent with previous studies that relied on cancer incidence [8,9].”

6) Any current and former flight attendants were eligible to participate (Methods, page 4). However, no figures or proportions of these are shown. Those recruited at the air terminals must have been actively employed at that point in time. Were not the majority of the flight attendants in the study currently working as flight attendants? The reader needs information here.

Response: We have included this information in the methods section, using the following text:

“Any current or former U.S. flight attendant was eligible to participate in the FAHS (91% of the participants in the current study were currently employed as flight attendants, and 9% were former flight attendants).”

We also conducted a sensitivity analysis among currently employed flight attendants, described as follows:
“Finally, we conducted a sensitivity analysis restricting SPRs and tenure analyses to the 91% of our cohort who were currently employed as flight attendants, in order to better match the NHANES comparison population.”

“Similarly, restricting both the tenure analyses and the SPR calculations above to currently employed flight attendants (91% of the cohort) did not meaningfully alter the results, nor did restricting tenure analyses to participants over the age of 40 or 45 (data not shown).”

7) Consider changing the title. a) The study is about prevalence of self-reported cancer. b) Flight crew is not accurate, and can easily be misunderstood. In the literature “professional flight crew” take place where the authors meant licensed male and female pilots, engineers, and navigators (dos Santos Silva I. Et al. Int J Cancer 2012;132;374-384). However, other researchers understood it as flight attendants (Liu T et al. J travel Med 2016;23:1-7). Deck crew is sometimes used on pilots, flight engineers and navigators. I suggest a change from flight crew to flight attendants, cabin attendants, or cabin crew, with consequences for the text throughout the whole manuscript.

Response: We have changed the titled to “Cancer Prevalence among Flight Attendants Compared to the General Population,” and have changed “flight crew” to “flight attendants” or “cabin crew” throughout the manuscript.

8) In the Abstract, Results (page 2), there is a sentence starting “Job tenure was positively related...”, which should be corrected to “Job tenure was positively related to non-melanoma skin cancer among females, with a borderline association for non-melanoma skin cancer among males.”
Response: We have made the requested change.

9) The non-melanoma skin cancer is central in this study, and also a bit problematic, or rather the self-reported diagnosis of this entity. While self-reported breast cancer and melanoma were with high sensitivity in the evaluation of the Teachers study (your ref. Number 26), other skin cancers were not. These differences must be reported and discussed. Further, other skin cancers may be underreported to the California Cancer Registry (used to make the evaluation in your ref. 26); it did not show up in Reynolds P. et al. study, but other skin cancers have been found in excess in many previous incidence studies on cabin crew. The present study has the strength that it is the first to report US cohort of cabin crew with excess for non-melanoma skin cancer, which was lacking in the literature, and this finding is consistent with reports from European incidence studies. Other skin cancers (or non-melanoma skin cancers) are a mixture from two main histological types, squamous cell and basal cell carcinomas, and these are differently reported to different cancer registries, and it is not possible for lay people to recognize these, only the pathologist is able to do that. The basal cell carcinoma of the skin is not a deadly cancer. However, it is the only type of skin cancer on which there is a consensus that it is related to ionizing radiation exposure according to IARC (your ref. Number 16). So correction is needed in Discussion, page 8; ionizing radiation is a causal factor (not only risk factor) for basal cell carcinoma of the skin and breast cancer, according to your ref. Number 16. In the present report, it is a necessity to show understanding of the above-mentioned complexity, preferably both in Methods and Discussion.

Response: Thank you for this feedback. We have made the suggested changes and incorporated the aforementioned information throughout the text, as follows:

“Consistent with previous studies reporting on cancer incidence and mortality among flight attendants, we report a higher prevalence of breast, melanoma and non-melanoma skin cancers (comprising basal cell and squamous cell carcinoma) among this occupational group.”
“We note that our study is the first to show an increase in non-melanoma skin cancer among U.S. cabin crew relative to the general population, which replicates findings among European flight attendants and pilots [21, 22].”

“Ionizing radiation is a known causal factor for non-melanoma skin cancer and breast cancer [25], whereas the studies regarding melanoma in relation to ionizing radiation are more conflicted [28].”

“Sensitivity and specificity of self-reported outcomes relative to medical records or linkage to disease registries were found to be moderate to high for common cancers (including breast cancer and melanoma), particularly among those with higher socioeconomic status, such as in our well-educated cohort [35]. However, this has not been the case for non-melanoma skin cancer. We should note that non-melanoma skin cancers are excluded from most U.S. cancer registries, and may be under-reported by those that do include it [36]. This may explain why non-melanoma skin cancer assessed through the California Cancer Registry was not related to flight attendant work [8], in contrast to many studies conducted among cabin crew and pilots, including our own study presented here [21, 22].”

“Finally, we note that our reliance on prevalence rather than incidence of cancer confuses the issues of cancer risk and survivorship in interpreting our results. This is in part ameliorated by the fact that breast and skin cancers have relatively low mortality rates (especially for basal cell carcinoma, which is not considered fatal or disabiling)...”

10) Why was job tenure prior to age 45 chosen in the tenure association analyses (Table 3)? The decision to examine breast cancer in relation to tenure prior to age 45 (or prior to age 40) may be justified with references to studies analyzing cancer risk in relation to ionizing radiation
exposure at an early age. The risk for cancer (breast cancer, and basal cell carcinoma of the skin) is greater when the exposure to ionizing radiation occurs at an early age than at an older age. For this reason, other cancers than breast cancer should also be examined in relation to tenure prior to age 45, and prior to age 40 years (prior to age 40 will be better supported in the literature). Results from these analyses with confidence intervals should be reported and discussed in the Discussion.

Response:

We included the following text to support our choice of a cut-off at age 45, and have also included analyses for the other cancers given job tenure prior to age 45, and prior to age 40:

“We examined cancer prevalence in relation to total net tenure as well as tenure prior to age 40 and prior to age 45 (restricted to participants aged over 40 and 45, respectively, in order to standardize exposure opportunity). For breast cancer, we evaluated this association both overall and stratified by parity. We chose to examine tenure at younger ages in order to approximate exposures during the reproductive years for hormone responsive cancers, and because of evidence that ionizing radiation exposure is most relevant to cancer risk at earlier ages [19, 20].”

These restrictions did not meaningfully alter our results, as we state in the results section:

“Associations for breast and other cancers were not meaningfully changed by restricting to job tenure prior to age 40 or 45 (Table 3 for breast cancer; other data not shown).”

Finally, we discuss these findings in the discussion section, as follows:
“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 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.”

11) Consider rewording the first sentence in Results and omit the words “manuscript” and “under review,” please do not refer to unpublished sources.

Response: We have made the requested change, and now also profile the NHANES population in this table. The text now reads as follows:

“We report characteristics of both FAHS and NHANES participants in Supplemental Table 1.”

12) The second sentence in the Discussion is unclear. Have previous studies on flight attendants reported prevalence of cancers? No. Please correct and reword.

Response: We have corrected the wording of the second sentence of the discussion. It now reads as follows:

“Consistent with previous studies reporting on cancer incidence and mortality among flight attendants, we report a higher prevalence of breast, melanoma and non-melanoma skin cancers
(comprising basal cell and squamous cell carcinoma) among this occupational group relative to the general population.”

13) It is valuable to have information on the low rates of overweight and smoking among a new cohort of U.S. flight attendants. However, only overweight is strongly related to breast cancer (not skin cancer), and smoking is not strongly related to breast or skin cancers. Consider the third sentence in the Discussion.

Response: Thank you for noting this. We have clarified this sentence, as follows:

“This is striking given the low rates of overweight and smoking among flight attendants in our study population, which we take to be indicators of general health and healthy behaviors, as well as being risk factors for some cancers [10, 11].”

14) An important risk factor for breast cancer is alcohol consumption. Do you have information on use of alcohol among the flight attendants to be introduced as a covariate into your multivariate analyses?

Response: We do have information on alcohol consumption, and have included the following text in the methods and results section of the manuscript:

“We also conducted sensitivity analyses further adjusting multivariate job tenure-cancer models for alcohol intake (none, 1-3 servings per month, 1-6 servings per week, 1 or more servings per day), as alcohol consumption is a risk factor for breast cancer [17], and may be for melanoma and non-melanoma skin cancers as well [18].”
“Adjusting for alcohol intake as a sensitivity analysis in our job tenure-cancer prevalence models attenuated associations somewhat for non-melanoma skin cancer among men (OR=1.10 vs. 1.17) and for breast cancer (OR=0.99 vs. 1.05), but not in relation to a 10% change in estimate criterion for determining confounding; adjusting for alcohol intake did not affect results for melanoma or non-melanoma skin cancer among women (data not shown).”

15) Consider rewording the fourth and fifth sentence of the Discussion in light of the missing information on date of cancer diagnosis in relation to tenure analyses.

Response: We have changed this part of the discussion with the following qualifying text:

“We also report associations between job tenure and several cancer outcomes, consistent with previous U.S. and European studies [6-9], though we note that our reliance on cancer prevalence rather than incidence complicates the interpretation of our findings with regard to the timing of work exposures and cancer outcomes, and the conflation of cancer incidence and survivorship. Nevertheless, our study extends the sparse literature on this important topic, confirms previous findings, and is the first study to note an increase in non-melanoma skin cancer among U.S. cabin crew (consistent with studies of European cabin crew). Our work informs future research directions regarding the health of this understudied group of workers, and highlights the question of what can be done to minimize the adverse exposures and cancers common among cabin crew.”

16) In the second section of Discussion, second sentence, page 8, please omit males. The SPR and OR for male cancers are with wide confidence intervals, which all included unity. You may later obtain more precise results after introducing tenure prior to age 40 and 45 in the association analyses for breast cancer and skin cancers.
Response: We changed the wording on this sentence as follows:

“We also observed that job tenure as a flight attendant was associated with the prevalence of non-melanoma skin cancer, as well as breast cancer (within parity subgroups), among females.”

17) In the second section of the Discussion, third sentence, page 8, the discussion and comment are a little bit peculiar. A comparison is made between a mortality study and cancer incidence studies concerning breast cancer and melanoma. The present study is neither about mortality nor cancer incidence. To evaluate possible cancer risk of cancers with good prognosis, incidence studies are better suited than mortality studies, and mortality studies are only able to evaluate the risk of fatal cancers; however, that does not concern the present study. In the present study with cross-sectional design and the recruitment as described, one is only able to evaluate the risk of cancer among those who are surviving, and those who are prepared or willing to participate, and that limitation should be mentioned and discussed in the Discussion.

Response: Thank you for noting this. We have deleted this text from the Discussion (marked using track changes). We also include information about the limitations mentioned here, using the following text:

“We also report associations between job tenure and several cancer outcomes, consistent with previous U.S. and European studies [6-9], though we note that our reliance on cancer prevalence rather than incidence complicates the interpretation of our findings with regard to the timing of work exposures and cancer outcomes, and the conflation of cancer incidence and survivorship.”
“Limitations of our study include its cross-sectional design, which precludes inferences about causality, as an observed association may reflect the effect of flight attendant work on a given condition, or the effect of an outcome on a factor related to employment as a flight attendant. Use of structured questionnaires, as in our study, aims to minimize this bias. However, we also note a further limitation that the date of cancer diagnosis was not recorded in the FAHS questionnaire; hence, some cancers may have been diagnosed prior to employment as a flight attendant, and some flight attendant work (i.e. exposure) may have occurred following a cancer diagnosis, making the direction of the potential bias unclear. These limitations are counteracted in part by our analyses evaluating job tenure prior to age 40 and 45 years in relation to cancer prevalences, as many cancers, including of the skin and breast, occur later in life. Therefore, this restriction increases the probability that the exposure of interest occurred prior to the reported cancer outcome.”

“A source of detection bias is that our study have may attracted a disproportionate number of flight attendants with cancer, as flight attendants with worse health are likely to be more motivated to participate in an epidemiological study of flight attendant health, and the question of cancer risk in relation to flight exposures is well known within the aviation community. However, it is reassuring that our results are consistent with previous studies that recruited participants from employee rosters [7-9]. Further, while affecting generalizability of our findings (external validity), it is less likely an increase in recruited participants with cancer would affect associations with job tenure (internal validity) [37].”

18) The second-hand smoke exposure diminished in year 1988 and ceased in year 1998, and in an attempt to evaluate related cancer risk (measured by self-reported prevalence of cancer and SPR), restriction was made to those in the cohort who had been flying before the year 1988. These analyses are handicapped in a similar way as the other tenure analyses because it is not known whether the cancers have been diagnosed before or after the year 1988. Further, in Supplemental Table 2, the prevalence rates for the cancer sites in NHANES are the same as the corresponding prevalence rates for the cancer sites in NHANES in Table 1. One assume that this
must be incorrect in the Supplemental Table, the indirect age-adjustment (and consequently the expected rates) needs to be done separately for the restricted cohort, which is older and with different age distribution than the unrestricted cohort in Table 1. Beside the above mentioned, consider that the second-hand smoke exposure diminished more than 25 years before 2014, the year up to which the prevalence figures were obtained in the study, and the cancers in question (breast cancer and skin cancers) are not particularly smoking related; these issues need to be corrected and discussed.

Response: We have corrected the issues identified with the second-hand smoking analyses, by standardizing to a restricted NHANES cohort (those age 45 years or greater), and continuing to restrict the FA population to those born in 1971 or earlier (and are thus eligible to have been working as a flight attendant by 1988); this restriction should limit the number of people who were diagnosed before 1988. We have included the following text throughout the manuscript to clarify this issue:

“We also conducted a secondary analysis evaluating the age-adjusted comparative prevalence of cancers for flight attendants exposed to high levels of historical occupational secondhand smoke prior to 1988, standardized to the subset of NHANES participants ages 45 or older.”

“The SPR for melanoma and non-melanoma skin cancers were modestly elevated among males overall (SPR=1.47, 95% CI: 0.72-3.01, and SPR=1.11, 95% CI:0.78-1.59, respectively), and were considerably higher (though less precise) among men exposed to high levels of occupational secondhand smoke (SPR=3.80, 95% CI: 1.67-8.65 and SPR=2.43, 95% CI: 1.53-3.87) (Supplemental Table 2).”

We have also included the following discussion in the manuscript:
“We were also able to conduct analyses among crew with in-flight secondhand smoke exposure prior to 1988, and found that some associations were strengthened among this subset of participants. Interpretation of these results is somewhat hampered by the fact that participants' occupational secondhand exposures ended by 1998 at the latest, and studies regarding smoking or secondhand smoking and breast and skin cancers have had mixed results [23, 24]. However, secondhand smoke has been linked to breast and skin cancers in some studies, and unlike for cardiovascular disease, smoking-related risk of cancer never falls to baseline, even years after cessation of the exposure [23, 24].”

19) Lower number of cases in Table 2 and in Table 1 needs to be clarified. Is the lower number due to missing data on tenure? Please explain.

Response: The lower number of cases in Table 2 is due to missing data on tenure (tenure was calculated based on a complete work history, including duration of employment and months of leave – not every participant provided this information), and missing data on other variables included in multivariate models. We have clarified this in the results section using the following text:

“Sample size is lower for the tenure analysis than for the SPR calculations because of missing data regarding tenure and model covariates; missingness for these variables is reported in Supplemental Table 1.”

20) In Table 2 there seems to be an analysis with the gender combined for thyroid cancer. That is unexpected as in Methods, page 5, under Statistical analyses it says that SPR were analyzed separately by gender, and on page 6, that gender-stratified associations were analyzed between job tenure and diagnosed cancers. The analysis of “all” for thyroid cancers is not very informative, and is not commented on in the main text of the report, and may best be omitted.
Response: Thank you for noting this. We have altered Table 2 to include only females for thyroid cancer (there were not enough males to conduct a separate analysis for the male participants).

21) The possibility of detection bias deserves discussion in this report on flight attendants, who are of high social class, and who may be subject to frequent medical check-ups due to their profession, and who may be aware of the discussion on cancer risk mentioned in social media and elsewhere among pilots and flight attendants.

Response: Thank you for noting this. We have included the following discussion in our limitations section to address this issue:

“Our study have may attracted a disproportionate number of flight attendants with cancer, leading to detection bias, as flight attendants with worse health are likely to be more motivated to participate in an epidemiological study of flight attendant health, are likely to attend regular medical check-ups, and the question of cancer risk in relation to flight exposures is well known within the aviation community. However, it is reassuring that our results are consistent with previous studies that recruited participants from employee rosters [7-9]. Further, while affecting generalizability of our findings (external validity), it is less likely an increase in recruited participants with cancer would affect associations with job tenure (internal validity) [37].”

REVIEWER 2

1) Add the NHANES population to Supplemental Table 1 so we can see how the two populations compare in terms of sociodemographic variables and cancer risk factors. It should also be included in the main manuscript (not as a supplement) because this table will help us understand the potential for residual confounding. This table also needs to be expanded to include risk
factors for the cancers investigated, such as parity, age at first birth, age at menarche, family history of cancer, or any other important risk factor available.

Response: As suggested, we have added information on NHANES to Supplemental Table 1. Unfortunately, we are not able to include it as a main table because of size/formatting restrictions for main tables vs. supplemental tables. We have added the following cancer risk factors to this table (in addition to smoking history and overweight status, which were included previously): alcohol intake (a binary yes/no variable reflecting usual intake patterns), usual alcohol intake category (none, 1-3 times per month, 1-6 times per week, at least 1 time per day), and number of live births (the variable in our dataset that most closely approximates parity).

2) The comparison population was restricted based on educational attainment, household income, and current employment status, and the same needs to be done to the flight attendant cohort. Currently, flight attendants who have left work because of a cancer diagnosis are still eligible for the study but NHANES participants in the same situation are excluded. This would artificially increase the SPR.

Response: We have conducted a sensitivity analysis restricting to currently employed flight attendants, and describe it in the following methods and results text:

“Finally, we conducted a sensitivity analysis restricting SPRs and tenure analyses to the 91% of our cohort who were currently employed as flight attendants, in order to better match the NHANES comparison population.”

“Similarly, restricting both the tenure analyses and the SPR calculations above to currently employed flight attendants (91% of the cohort) did not meaningfully alter the results (data not shown).”
3) The study design implicitly includes cancer survivors and excludes people who died from cancer. Because of this, an increased SPR could just mean that flight attendants have a better chance of surviving cancer than the general population, not that they have a higher incidence of cancer. This could be due to health insurance access, paid leave policies, or other benefits that this workforce might enjoy compared to the majority of U.S. workers, or to sociodemographic differences that lead to better survivorship, such as living in or near an urban center (a large proportion of the study population likely lives near a hub). This needs to be added to the discussion.

Response: We have included a write-up of this limitation in the discussion, as follows:

“We also report associations between job tenure and several cancer outcomes, consistent with previous U.S. and European studies [6-9], though we note that our reliance on cancer prevalence rather than incidence complicates the interpretation of our findings with regard to timing of work exposures and cancer outcomes, and the conflation of cancer incidence and survivorship.”

“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 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.”

“Finally, we note that our reliance on prevalence rather than incidence of cancer confuses the issues of cancer risk and survivorship in interpreting our results. This is in part ameliorated by the fact that breast and skin cancers have relatively low mortality rates (especially for basal cell carcinoma, which is not considered fatal or disabling), and that we are comparing to prevalence rates in NHANES as well. Nevertheless, the limitation remains, and it is also important to note that flight attendants may differ from the general population of U.S. workers with regard to
health insurance access, paid leave policies, and other benefits that could affect survivorship, and may be more likely to have access to an urban center with better quality health care for cancer treatment. It is reassuring that our results are consistent with previous studies that relied on cancer incidence [8,9].”

4) The general U.S. population is likely not a good comparison group for a cohort of flight attendants, and confounding could be a problem. Although no details on the NHANES population are provided in the manuscript, there is a mention that the racial/ethnic compositions are strikingly different (75% vs. 43% non-Hispanic white), which suggests there could be large differences in cancer incidence and survival between the groups if other variables differ as well. There is evidence that BMI and parity (for example) differ substantially between flight attendants and the general population. The sensitivity analysis restricting to non-Hispanic whites and the exclusion of NHANES participants without high school degrees and below a certain income/poverty ratio certainly help (particularly if the same exclusions are applied to the FAHS cohort), but there is still potential for residual confounding that should be acknowledged. Providing data on the NHANES population (see comment above) would also help to determine how different the two populations are. This problem needs to be acknowledged in the discussion.

Response: Thank you for noting this. First, we have added information on the NHANES population, including regarding number of live births (to approximate parity), alcohol intake, overweight status, and smoking status, to Supplemental Table 1.

We have also included the following write-up in the discussion to acknowledge this limitation:

“Another potential limitation of our study involves the question of whether a population of flight attendants is sufficiently comparable to the general U.S. population with regard to cancer risk factors, and whether differences in risk factors may introduce bias to the SPRs. For example, we report substantial differences in racial profile, smoking status, overweight, and number of live
births between the FAHS and NHANES cohorts, all of which are related to the risk of various cancers. We have counteracted this issue in part by restricting the NHANES comparison group to currently employed adults with at least a high school degree and above a certain income to poverty ratio, and by conducting sensitivity analyses restricting to non-Hispanic white participants that showed no meaningful differences in results. We also note that the FAHS includes a substantially smaller percentage of current smokers and overweight participants than the NHANES population, which would be expected to decrease the risk of several cancers, whereas we observed increased SPRs. At the same time, we should note that FAHS participants had fewer children than NHANES participants (which is a risk factor for breast cancer), though this is in part ameliorated by the fact that we observed associations between tenure and breast cancer within parity subgroups. Finally, even with the above reported sensitivity analyses, we acknowledge that the potential for residual confounding by cancer risk factor profiles differences between the populations (such as for race and parity) still exists.”

5) A previous study (reference 24) found that differences between parity and age at first birth between flight attendants and the general population could explain the increased risk for breast cancer seen for flight attendants. At the very least, adjustment for parity (and age at first birth if available) seems warranted in the models, along with reporting the distributions of these variables in the FAHS and NHANES populations.

Response: Thank you for noting this. First, we now include information on parity (approximated by number of live births) within the FAHS and NHANES in Supplemental Table 1. We do find that mean parity is lower in the FAHS cohort than in NHANES – 0.8 vs. 2.1. We report this in the results section of the text, as follows. Unfortunately, we do not have information on age at first birth in the FAHS.

“Mean number of live births also differed between females in the two study populations (0.8 for FAHS vs. 2.1 for NHANES), despite NHANES having a higher percentage of women still in their childbearing years than the FAHS.”
We also now adjust our tenure-breast cancer analyses for parity, as indicated in the methods text and Tables 2 and 3. Adjusting for parity did not meaningfully alter the findings for breast cancer in relation job tenure, overall and prior to age 45.

6) Discussion (line 204): the limitation that the same set of covariates was used for every model can be easily addressed by re-running the models with the appropriate covariates instead of waiting for the next paper in the series to do the adjustment. Is there a reason this cannot be done now?

Response: Thank you for noting this. We have added adjustment for alcohol intake in sensitivity analyses for all cancers, based on a further literature search, and have described this in the text and associated tables, as follows:

“We also conducted sensitivity analyses further adjusting multivariate job tenure-cancer models for alcohol intake (none, 1-3 servings per month, 1-6 servings per week, 1 or more servings per day), as alcohol consumption is a risk factor for breast cancer [17], and may be for melanoma and non-melanoma skin cancers as well [18].”

“Adjusting for alcohol intake as a sensitivity analysis in our tenure-cancer models attenuated associations somewhat for non-melanoma skin cancer among men (OR=1.10 vs. 1.17) and for breast cancer (OR=0.99 vs. 1.05), but not in relation to a 10% change in estimate criterion for determining confounding; adjusting for alcohol intake did not affect results for melanoma or non-melanoma skin cancer among women (data not shown).”

We have also adjusted breast cancer models for parity, as indicated in the text and tables. This adjustment also did not meaningfully alter results.
7) Table 2: there are fewer cancer cases in Table 2 than in Table 1. The exclusions that have been made need to be described in the manuscript (number of participants and reasons for exclusion). If these exclusions were for missing data, include the counts of individuals with missing data for each variable in Supplemental Table 1.

Response: We have included counts for missing data in Supplemental Table 1, and have included the following text in the manuscript to describe the exclusions:

“Sample size is lower for the tenure analysis than for the SPR calculations, because of missing data regarding tenure and covariates; missingness for these variables is reported in Supplemental Table 1.”

8) Supplemental Table 2: based on the participants counts, the NHANES population was not age-restricted for this analysis. For a flight attendant to be working in 1988, they would have to be, at the latest, born in 1970 (18 years old). Thus, the FAHS population in this analysis would have been 45+ years old in 2015. The NHANES population must therefore also be restricted to participants 45+ years old for this analysis, to avoid artificially decreasing the prevalence of cancer in the comparison population by including younger (18-44) people who have a lower prevalence of cancer.

Response: Thank you for noting this. We have implemented this change for Supplemental Table 2, and have clarified this in the text, as follows:

“We also conducted a secondary analysis evaluating the age-adjusted comparative prevalence of cancers for flight attendants exposed to high levels of historical occupational secondhand smoke prior to 1988, standardized to the subset of NHANES participants ages 45 or older.”
9) Was there information on the age at which the cancer was diagnosed in FAHS and NHANES, and could cancers diagnosed before age 20 (for example), which are unlikely to be occupationally related, be excluded?

Response: Unfortunately, we do not have a way of knowing at what age cancer was diagnosed. We now note this at length in the limitations section of the discussion, as follows:

“We also note a further limitation that the date of cancer diagnosis was not recorded in the FAHS questionnaire. Hence, some cancers may have been diagnosed prior to employment as a flight attendant, and some flight attendant work (i.e. exposure) may have occurred following a cancer diagnosis, making the direction of the potential bias unclear. These limitations are counteracted in part by our analyses evaluating job tenure prior to age 40 and 45 years in relation to cancer prevalences, as many cancers, including of the skin and breast, occur later in life. Therefore, this restriction increases the probability that the exposure of interest occurred prior to the reported cancer outcome.”

10) Methods (line 111): define “high levels of historical occupational secondhand smoke.” Is this based solely on working in 1988 or earlier, or was this based on a question about exposure?

Response: Thank you for noting that this was unclear. We have altered the text as follows:

“We also conducted a secondary analysis evaluating the age-adjusted comparative prevalence of cancers for flight attendants exposed to high levels of historical occupational secondhand smoke prior to 1988, standardized to the subset of NHANES participants ages 45 or older. Occupational smoking exposure was based on reported work histories – those working as flight attendants prior to 1988 were considered to be in the highly exposed subgroup.”
11) Add additional waves of NHANES data. Doing so would be unlikely to cause substantial time effects but would increase the sample size in the comparison group, producing more precise estimates. The NHANES sample sizes are very small (<10 cases for 4 types of cancer), making interpretation of results difficult.

Response: Unfortunately, we were not able to find a way to merge the multiple waves of NHANES data. However, after viewing data for other waves, it seems that even if it were possible, adding more waves of NHANES data would not resolve the issue that these cancer outcomes are rare in general, and therefore will lead to small prevalences regardless of using more NHANES data. In addition, our cohort design means that we are following a generation that is matched to the NHANES in a particular time period as a way to try to standardize common environmental exposures not related to occupation; hence, matching time periods as closely as possible is relevant to our optimal study design.

12) The analysis of “job tenure to age 45” should be restricted to participants in FAHS and NHANES who are 45+ years old to avoid mixing in participants who are less than 45 years old and have not yet had the opportunity to accrue as much exposure as those who are above 45 years old. Ideally the whole job tenure analysis would have some sort of similar restriction to avoid all the low risk (young) participants clustering in the low exposure (low job tenure) part of the distribution – in the model, it is impossible for the low risk flight attendants to have high exposure. Adjusting for age likely does not fix this, as it seems to be a problem of non-positivity, not a problem of confounding. This should either be addressed analytically, or if this is not possible, in the discussion.

Response: We have restricted all “job tenure to age 45” (or 40) analyses to participants in the FAHS and NHANES who were above 45 (or 40, respectively). Overall, this did not alter results very much, though it did attenuate the association between tenure and breast cancer among nulliparous women from OR=1.6 to OR=1.4, with an accompanying lack of precision. We have indicated this change in the text, as follows:
“We also examined cancer prevalence in relation to total net tenure as well as tenure prior to age 40 and prior to age 45 (restricted to participants aged over 40 and 45, respectively, in order to standardize exposure opportunity); for breast cancer, we evaluated this association overall and stratified by parity.”

We have also performed a similar restriction for the secondary analysis examining cancer SPRs among people occupationally exposed to secondhand tobacco smoke prior to 1988.

Finally, we conducted sensitivity analyses restricting all tenure-cancer analyses to participants over age 40 and 45, as indicated in the text. This analysis did not meaningfully alter the results:

“We examined cancer prevalence in relation to total net tenure as well as tenure prior to age 40 and prior to age 45 (restricted to participants aged over 40 and 45, respectively, in order to standardize exposure opportunity); for breast cancer, we evaluated this association both overall and stratified by parity.”

“Similarly, restricting both the tenure analyses and the SPR calculations above to currently employed flight attendants (91% of the cohort) did not meaningfully alter the results, nor did restricting tenure analyses to participants over the age of 40 or 45 (data not shown).”

13) Discussion (line 218): why is it stated that these findings are applicable to pregnant women? These results do not seem to be related to pregnancy.

Response: We have modified this sentence as follows (i.e. we deleted the reference to pregnant women):
“Our study findings contribute to the sparse literature on flight attendant health, which may also be applicable to passengers, especially frequent flyers.”

14) Discussion (line 153) and Conclusion (line 224): this is not the largest study of cancer rates among flight crew relative to the general population, nor is it the largest study of cancer rates among flight crew. At least two of the studies cited (references 23 and 24) have included over 6,000 flight crew.

Response: We have modified the text as follows:

Discussion: “We have conducted a large and comprehensive study characterizing cancer rates among U.S. cabin crew relative to the general population, which adds to the relatively sparse literature on this topic and has included profiling a wide range of cancers.”

Conclusion: “We have conducted a large and comprehensive study characterizing cancer prevalence rates among flight attendants relative to the general population. Despite low smoking and obesity levels, we report that flight attendants have elevated rates of several cancers, especially breast, melanoma, and non-melanoma skin cancers. Ours is the first study to report an elevated rate of non-melanoma skin cancer in a U.S. flight attendant cohort (consistent with European studies).”

15) Table 1: the column header “NHANES count, weighted,” should be “unweighted.” If the number of cancer cases had been weighted to the U.S. population, this number would have been in the thousands.

Response: Thank you for noting this! We have made this change in the table and in Supplemental Table 2.
16) Table 2: where are the results for uterine, cervical, and gastrointestinal cancers?

Response: We decided to focus on a smaller subset of cancers for the tenure analyses, to try to minimize multiple testing and because the number of cases for these cancers were relatively low.

Thank you again for your consideration of our work! Your comments and suggestions have greatly improved our manuscript.

Please let me know of any and all further questions and clarifications that you may have!

Sincerely,

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