Reviewer’s report

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

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Reviewer: Vilhjalmur Rafnsson

Reviewer's report:

Comments on the manuscript: "Cancer Diagnoses among Flight Crew Compared to the General Population," ENHE-D-17-00327.

This is a cross sectional cohort study on female and male flight cabin crew. The analyses have two aims: 1) to describe the prevalence of self-reported cancer diagnoses relative to information obtained in similar way from a sample of the general population, and 2) to study the relation of the prevalence of the self-reported cancer diagnoses to parity and employment years as flight cabin crew, the latter a surrogate of some otherwise unspecified occupational exposure. Although using prevalence rates the results are consistent with findings from previous cancer incidence studies on cabin crew. That is the strength of the study, as well as the large size of the cohort and the long average tenure of the members of the cohort.

There are two serious defects with this report, 1) it is not referring correctly to the literature on flight cabin crew, and 2) the authors are not sufficiently on guard against the consequences of the cross sectional design of the study.

Major points:

The first of these faults is easy to deal with. The most important example is the first sentence in 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 Californian 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;131:2886-2897) numbers 8507 females, and 1559 males, both studies report more cancer sites than the present study, however, neither of these important previous studies are cited directly in the report. Please make a correction and reformulate.

The second one, the cross sectional design is more difficult to deal with, and 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 increase the number of outcome, and counting employment years after the diagnosis of cancer falsely increase 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 calculations 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-years 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.
Other points:

The recruitment of the participants, and the participants must be described in more details. 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 passes 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"?

The recruitment of participants not randomly selected from the AFA files or participants recruited through announcement about the study from local union and through social media is a 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.

Cross sectional study on cancer prevalence is a study on those how have survived, which welcome comments and discussion.

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.

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 licenced male and female pilots, engineers, and navigators (dos Santos Silva I. et al. Int J Cancer 2012:132;374-384), however, other researcher 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 through the whole manuscript.

In 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; confer Table 2.

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 Californian 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 of 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 of 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 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 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 in Discussion.

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 analysing cancer risk in relation to ionizing radiation exposure at 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 early age than at 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 Discussion.

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

Please, take more care in the formulation in the first section of Discussion, page 8; confer the first major point of these comments. The second sentence in Discussion is unclear. Have previous studies on flight attendants reported prevalence of cancers? No. Please correct and reword. It is valuable to have information on the low rates of overweight and smoking among a new cohort of US flight attendants, however, only overweight is strongly related to breast cancer not skin cancers, and smoking is not strongly related to breast or skin cancers, consider the third sentence in Discussion. 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 co-variate into your multivariate analyses? Consider rewording the forth and the fifth sentence of Discussion in light of the missing information on date of cancer diagnosis in relation to tenure analyses, confer the second major point of these comments.

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.

In the second section of Discussion, third sentence, page 8, the discussion and comment are a little bit peculiar. A comparison is made between 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 Discussion.
The second-hand smoke exposure diminished in year 1988 and ceased in year 1998, and in 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 assumes 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.

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

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 analysed separately by gender, and on page 6, that gender-stratified associations were analysed 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.

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-up 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.

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