Author's response to reviews

Title: Cigarette, cigar and pipe smoking, passive smoke exposure, and risk of pancreatic cancer: a population-based study in the San Francisco Bay Area

Authors:

Gregory J Tranah (gtranah@psg.ucsf.edu)
Elizabeth A Holly (elizabeth.holly@ucsf.edu)
Furong Wang (furong.wang@ucsf.edu)
Paige M Bracci (paige.bracci@ucsf.edu)

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Author's response to reviews: see over
Dear Dr. Norton:

We are pleased to submit responses to reviewer comments for our manuscript, “Cigarette, cigar and pipe smoking, passive smoke exposure, and risk of pancreatic cancer: a population-based study in the San Francisco Bay Area”. We appreciate the reviewers’ comments and suggestions for revisions and believe the manuscript to be stronger with these changes. Each comment is shown in bold italics, followed by our response. In the text of the revised manuscript we indicate the changes by underlining the updated section.

Reviewer 1 (UAW)

1. P7L1. In table 3 the percentage of individuals 5-10 years post smoking seems to be identical in PC as well as in controls. For the statement of a 70% reduction of risk for PC, the sample size of this sub-group seems to be too small especially since then, former smoking 15-20 ago would protect from pancreatic cancer - which is unlikely. Additionally, in an older prospective study by Fuchs CS et al. (Arch Int Med 156(19)) the authors report a rapid reduction in PC risk after smoking cessation of 48% within the first two years. This would further support the data in table 3 that the adverse effects of cigarette smoking on pancreatic cancer development are greatly reduced with the first 5 years after smoking cessation.

As we state in the results section (Page 6), the 70% reduction in risk is relative to current smokers. Our data for smoking cessation ≥ 15 years are not consistent with a ‘protective’ effect since the 95% CIs for these analyses include unity. This was stated in the discussion (page 8). Our conclusion that cigarette smokers who had stopped smoking for ten or more years prior to diagnosis or interview had no increased risk of pancreatic cancer relative to nonsmokers is consistent with other published reports. We are aware of the Fuchs et al. study and our results are consistent with a more recent meta-analysis of 82 published cohort and case-control studies.

2. P15 Table 4. In table 3 the odds ratio for PC development already decreases >5 years after smoking cessation. It is unclear why the authors chose 10 years and not 5 or 15 according to their own data in table 3? Generally the reader needs more and clearer help on the interpretation of table 4. It is hard to believe that for past smokers the risk for developing pancreatic cancer is lower the more they smoked.

We chose to report the data for 10 years in addition to the 5-year data to allow comparisons to previously published data. For the results presented in Table 4, we tested the homogeneity of ORs following the recommendation from reviewer 2. We tested homogeneity with the Breslow-Day test and found no significant differences for the three analyses reported in Table 4. These analyses are reported in the methods (Pages 5-6) and the results on Page 7 and in table 4.

3. P1 L4. Where is the California Pacific Medical Center Research Institute located?

The CPMC Research Institute location is co-located with the UCSF Department of Epidemiology and Biostatistics as many members are also on the UCSF faculty. This information is available on the title page:

California Pacific Medical Center Research Institute
San Francisco Coordinating Center, UCSF
4. P3 L7. “...may relieve pancreatic cancer symptoms but have little impact on course of disease”. This statement is not correct. Even though the survival benefit in months may be small, chemotherapy and surgery significantly increases the median survival with a high level of evidence.

We have omitted this statement from the introduction.

5. P4L16. “A total of 532 cases...”. This is confusing. Does it mean a total 794 eligible cases out of which 67% completed the interview?

Yes, the reviewer is correct. The 67% response rate indicates that among cases who met study eligibility criteria, 67% provided informed consent to participate and completed an in-person interview.

6. P3L8. Pancreatic cancer usually develops over many decades. This statement is speculative. Neither molecular factors nor the timescale of pancreatic cancer development have been identified to date.

We have omitted this statement from the introduction.

7. P4L17. How is the refusal rate explained? Is there also a refusal rate in the control group?

The refusal rate is the percent of those eligible who declined to participate. Reasons for nonparticipation included, too ill, could not locate, and declined to participate. In case populations this is important as it shows the willingness and cooperation of patient populations, despite their illness, to partake in research studies if they are able. We cite previous publications from this case-control study where the response rate was computed. The citations state:

“Ineligible patients included 735 patients who died before contact and 85 who could not complete an interview in English. Among the 718 eligible Bay Area patients, 140 were too ill, 20 had physician-indicated contraindications to contact, 68 refused to participate, 18 could not be located and five did not participate for other reasons “.

We would be happy to include the already published information into the text of the paper if the editors would prefer. The refusal rate among controls was 9% (Page 4).

8. P5L15. “…defined as smokers if they had smoked > 100 cigarettes...”. The definition of smoker is very strict and an influence of the smoking of 100 or 200 cigarettes in a lifetime is very unlikely to increase the risk for pancreatic cancer.

The reviewer is correct that the definition of smoker is clearly defined and that the risk for someone who was considered a smoker, but who had only smoked 100 cigarettes was very low. The question is used for screening ever smokers from never smokers and is consistent with smoking screening questions in population-based studies. The information collected after the participants answer this screening question then allows for a detailed analysis of smoking behavior including frequency, duration, age at which smoking started and cessation began. Because of variability in the number of cigarettes smoked using this strict definition, we divided the smokers into multiple categories, both in quantity and years smoked to better assess the risk of cigarette smoking. Collecting the data in this manner allows one to assess the smoking effect rather than to assume that those who are light smokers are not at risk for pancreatic cancer.

9. P6L3. Why were patients with completed interview excluded from the analyses?

The only patients who were excluded were those who were later found not to have confirmed pancreatic cancer upon final review of the data. No patients with completed interviews who actually had pancreatic cancer were excluded. This is now clarified that in the text of the manuscript (Page 4).
10. P6L15. **Please give the absolute numbers for this sub-analysis since sample size is expected to be very small.**

These three analyses were subset to the largest subgroups in the study: women (241 cases, 818 controls); men (291 cases, 883 controls); and non-Hispanic white participants (417 cases, 1357 controls). The stability of results across all three groups demonstrates the robustness of these sample sizes for examining risk associated with smoking 40+ years. We state that sample sizes were too small to examine associations among other race and ethnicity groups (page 6).

11. **P6L19. Two periods.**

Extra period omitted.

12. **P8L11 The OR of 1.6 in past smokers is first mentioned in the discussion and cannot be found in the result section.**

This result is first detailed on Page 6 of the results section and we have simplified this sentence in the discussion removing the 1.6 OR.

13. **P12 Table1. Is there any p-trend?**

Table 1 provides basic population characteristics. These are meant to be study population descriptors of the frequency-matched factors and other variables to be considered in adjusted analyses of smoking. Reporting p-values would not be appropriate as these numbers are not results from statistical analyses and are not being compared with risk of pancreatic cancer.

14. **P13 Table 2. The definition for former smoking is not given. What is the p-trend for cigar and pipe smoking?**

The definition of former smokers is clarified in the methods (page 5) and in tables 2-4. The number of cigar and/or pipe smokers is modest and does not permit the analysis of dose or duration. We have analyzed cigar/pipe smokers as ever vs. never smokers, therefore no trend analysis can be computed.

Reviewer 2 (JL)

1. **Page 3, para 1, "Pancreatic cancer usually develops over many decades, with >70% of cases diagnosed after age 60.": This is an odd construction with two essentially non-connected elements. The proposition that pancreatic cancer may or may not develop over decades is largely unrelated to most cases being diagnosed at ages over 60 years.**

We have omitted the statement regarding development over many decades from the introduction.

2. **Page 3, para 3, "We quantify the dose-response relationship between cigarette smoking and pancreatic cancer...": Given that the authors simply present ORs by categories of duration, cigs/day and pack-years, this statement seems to overstate their analysis in regards quantifying the "dose-response relationship". There is little analysis focused on characterization of the "dose-response".**

We agree that the term dose-response does not accurately describe the categorical nature of our analyses. Analysis of smoking duration by categorical levels has allowed us to compare our results to those of previous studies and expand upon them in several ways. We have removed the term “dose-response” and clearly describe the categorical nature of the data when referring to our study (pages 6 and 9).

3. **Page 4, para 1, "There were 65 out-of-area pancreatic cancer patients identified through clinical records at the UCSF Medical Center who were eligible to participate because they met all study criteria**
other than their place of residence at the time of diagnosis.": It sound like these 65 patients were included as cases, even though they failed to meet study criteria (since they were not resident of the 6-county area at diagnosis). It seems to me that either design specifications are important and therefore investigators adhere to those specifications or the design specifications are not important. If the latter, then why establish any criteria at all if they may be ignored -- just use any cases. I would guess that controls for these subjects did reside in the study area. Thus, if study area is sufficiently important to include as part of the design and serve to limit study subjects, then these 65 should be omitted.

The controls for the 65 out-of-area cases were from the same communities as were the out-of-area cases and adhered to all of the same study-design requirements as the cases and controls for the rest of the study. Population-based controls for these patients were identified by RDD using the same area code and 3-digit prefix of the patients’ home phone number. Out of area cases did not differ from Bay Area cases, and out-of-area controls did not differ from Bay Area controls on demographic characteristics of age, sex, marital status, education or on smoking history. Analyses excluding these “out of area” cases and their controls do not change the OR values that we have presented.

4. **The authors state that their study was population-based, and list it as a strength in the Discussion.**

The reviewer is correct and we agree and thank the reviewer for pointing this out (page 9).

5. **Page 7, line 8ff and Table 4: First, Table 4 does not clearly specify the referent category for ORs. Also, the authors make various claims for ORs by cessation within categories of duration, cigs/day and pack-years. The authors need to support these claims with p-values for homogeneity of ORs. Based on inspection and on the CIs, it appears that ORs by cessation are homogeneous across the various categories. Given the CIs, the ORs of 1.8 and 1.3 (and 1.8 and 1.4) are very likely statistically homogeneous.**

We state in the title and the footnotes that the analyses are in comparison with nonsmokers. We tested the homogeneity of ORs using the Breslow-Day test and found no significant differences for the three analyses reported in Table 4. These analyses are reported in the methods (Pages 5-6) and the results on Page 7 and in table 4.

Reviewer 3 (SB)

No comments provided.

Thank you for your consideration of our manuscript.

Sincerely,

[Signature]

Gregory Tranah, PhD.