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 the additional 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”. 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 2 (JL)

1. **3:1 ratio by sex and 5-year age group (page 3) (statement not clear).**

   The statement has been rephrased for clarity:

   “… and were frequency-matched to cases by sex and 5-year age group in an approximate 3:1 ratio.”

2. **Higher rates of pancreatic cancer occur in industrialized countries and survival differences by race have been observed (vague statement (page 2), add some follow up statement to show the link of this statement).**

   This statement has been clarified:

   “The incidence of pancreatic cancer varies by age, sex, and race - and survival differences by race have been observed.”

3. **Pancreatic cancer usually develops over many decades, with >70% of cases diagnosed after age 60 (This statement is not required to be mentioned when they have taken the range of models from (21 to 85 years old).**

   This statement has been omitted.

4. **A total of 532 cases and 1,701 control participants completed the interview and a total of 516 cases and 1628 controls with smoking data were included in the final analyses.( on what basis only a few out of all were selected? The numbers mentioned in the abstract should be 516 and 1628 instead of 532 and 1701).**

   As stated those participants not included in the final analyses were those case and control participants for whom cigarette smoking data were available. Those participants not included in the analyses of cigarette smoking were those who reported smoking cigars or pipes only (as noted in the footnote of Table 3). To make this clearer to the reader and avoid confusion regarding the total number of participants for whom smoking data were available (cigarettes, pipes and cigars) we have modified this sentence in the results text:

   “A total of 532 cases and 1,701 control participants completed the interview. There were 16 cases and 73 controls who reported smoking cigars or pipes but not cigarettes leaving a total of 516 cases and 1628 controls who were included in the final analyses of cigarette smoking.”
The total numbers in the abstract accurately reflect the number of participants for whom we have smoking data (cigarettes, pipes and cigars) available for analysis. Cigar and pipe smoking were analyzed separately and we state that no association with pancreatic cancer risk was found. Reporting 516 cases and 1628 controls in the abstract is incorrect as it does not include pipe and cigar smokers. The modification to the text as suggested by this reviewer clarifies what appeared to be an inconsistency in the number of participants included in our analyses.

5. **Participants were defined as smokers if they had smoked >100 cigarettes in their lifetime.** Participants were considered cigar and/or pipe smokers if they had ever smoked pipes and/or cigars for >6 months. Body mass index (BMI; weight in kilograms divided by height in meters squared) was based on self-reported height and usual adult weight and was categorized based on quartiles of the distribution among controls by sex as follows: men: <23.1; 23.1-<25.1; 25.1-<27.1; >27.1 kg/m2; and women: <21.5; 21.5-<23.4; 23.4-<25.8; >25.8 kg/m2. Participants were defined as consumers of alcohol if they had ever had at least one alcoholic drink per month (References for the standards mentioned?).

The question regarding smoking >100 cigarettes to identify ever smokers is consistent with smoking screening questions in population-based studies. The additional variables listed have been published as risk factors for pancreatic cancer. References are included.

6. **Primary topics included on the questionnaire were: demographic factors, detailed job and occupational history, use of tobacco products and alcohol consumption, medical history including allergies, diabetes, pancreatitis and gallbladder disease, family medical history, anthropometric data and a detailed assessment of diet including average consumption of specific foods, vitamin supplement use and dietary modifications (references for why these criteria are chosen? What is the relation of the other abnormalities such as gall bladder disease etc with the present study?).**

The list of variables included in the methods is in large part a demonstration of the rigor and thoroughness with which this study was conducted. A large number of publications have been generated from this study (referenced appropriately in the introduction and methods). Since many of these are established risk factors we adjusted for them in our multivariate analyses of smoking (e.g. diabetes, pancreatitis, gallbladder disease, alcohol intake and body mass index) since they are potential confounders.

7. **Data as well as the mention of cigar/pipe smoking not very strong.**

This is a fair comment and we agree. Given the lack of large individual datasets examining this question we believe that these results still provide a valuable contribution to the literature.

8. **Smoking 40 or more years was associated with similar increases in risk for men (OR=1.8, 95%CI=1.2-2.9), women (OR=1.8, 95%CI=1.2-2.7) and non-Hispanic white men and women (OR=1.8, 95%CI=1.3-2.6) (the first men and women belongs to which race/ethnicity?).**

The analyses of men and women included all races/ethnicities. This is indicated in the manuscript.

9. **Participants who smoked for at least 40 years had an OR of 1.8 and those who smoked at least 40 pack-years had an OR of 2.0. But Former smokers who quit <5 years prior to diagnosis or interview had an elevated risk (OR=2.2). (risk for those who had quit is more than the current smokers?????).**

These results are driven by the small sample of participants who quit <5 years (31 cases and 51 controls) and do not support an interpretation that those who recently quit are at increased risk over current smokers. The confidence intervals for the quit <5 years group (1.3 - 3.7) are substantially wider.
than those for current smokers (1.4 - 2.7). To alleviate any confusion we have removed results from tables and text for those who quit <5 years and focus on smoking cessation for <10 years.

10. **Passive smoking**......*The categories are not mutually exclusive, which allowed for the examination of exposure to multiple exposure environments. Analysis of mutually exclusive exposure environments did not yield significant associations with pancreatic cancer risk (statement not very clear).*

The statement has been rephrased for clarity:

“The categories are not mutually exclusive, which allowed for the examination of exposure to multiple exposure environments (e.g. exposure at home and work). Analysis of mutually exclusive exposure environments (e.g. exposure at either home or work) did not yield significant associations with pancreatic cancer risk (data not shown).”

11. **However, sample size limited our examinations to participants who ever smoked pipes and cigars (not considering current or past smoking) and who also smoked cigarettes. (page 8, confusing statement).**

The statement has been rephrased for clarity:

“However, limited sample size restricted our examinations to participants who ever smoked pipes and cigars and who also smoked cigarettes.”

12. **Moreover, childhood household exposure to cigarette smoke was not associated with an increased risk of pancreatic cancer. This is supported by our results which demonstrate no increased risk for direct smoking after ten years of cessation (age range of the cases starts from 21….childhood exposure????).**

Since smoking is among the strongest risk factors for pancreatic cancer we believe it is reasonable to examine risk factors related to passive smoke regardless of age of exposure. This study adds important information to the published literature since previous studies also did not identify a link between passive or secondhand smoke exposure and pancreatic cancer. Both of the previous studies were limited by small sample sizes thus leaving this an open question. By assessing both childhood and adult exposure to passive smoke we more thoroughly examined whether exposure at any particular time may influence risk of pancreatic cancer.

Thank you for your consideration of our manuscript.

Sincerely,

Gregory Tranah, PhD.