Author's response to reviews

Title: Polycyclic aromatic hydrocarbons: Determinants of urinary 1-hydroxypyrene glucuronide concentration and risk of colorectal cancer in the Shanghai Women's Health Study

Authors:

Jonathan N Hofmann (hofmannjn@mail.nih.gov)
Linda M Liao (Linda.Liao@nih.gov)
Paul T Strickland (pstrickl@jhsph.edu)
Xiao-Ou Shu (Xiao-Ou.Shu@vanderbilt.edu)
Gong Yang (Gong.Yang@vanderbilt.edu)
Bu-Tian Ji (jib@mail.nih.gov)
Hong-Lan Li (hlli1974@163.com)
Nathaniel Rothman (rothmann@mail.nih.gov)
Farin Kamangar (kamangaf@mail.nih.gov)
Yu-Tang Gao (ytgao@vip.sina.com)
Wei Zheng (Wei.Zheng@vanderbilt.edu)
Wong-Ho Chow (wchow@mdanderson.org)

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Author's response to reviews: see over
March 19, 2013

Dr. Christina Chap
Senior Executive Editor
BMC Cancer
c/o BioMed Central 236
Gray's Inn Road London
WC1X 8HB
United Kingdom

Dear Dr. Chap:

We would like to thank the reviewers for their thoughtful comments on the manuscript entitled "Polycyclic aromatic hydrocarbons: Determinants of urinary 1-hydroxypyrene glucuronide concentration and risk of colorectal cancer in the Shanghai Women's Health Study" (MS: 2015252335793017). Please see below for a point-by-point response to the editor and reviewer comments. A revised version of the manuscript incorporating the recommendations of the editor and the reviewers is attached; revisions to the manuscript have been highlighted.

This manuscript has not been submitted elsewhere nor is it under consideration for publication by another journal. The authors declare that they do not have any competing financial interests with respect to this work. If you have any questions or concerns regarding this manuscript submission, please do not hesitate to contact me.

Regards,

Jonathan N. Hofmann, PhD, MPH
**Title:** Polycyclic aromatic hydrocarbons: Determinants of urinary 1-hydroxypyrene glucuronide concentration and risk of colorectal cancer in the Shanghai Women's Health Study (MS: 2015252335793017)

**Editorial request:**

-Ethics approval

Ethics - Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration ([http://www.wma.net/en/30publications/10policies/b3/index.html](http://www.wma.net/en/30publications/10policies/b3/index.html)), and any experimental research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

**Response:** The following statement regarding ethics committee review was added to the Methods section on p. 6: "All subjects provided written informed consent, and the study protocols were approved by the Institutional Review Boards of the National Cancer Institute, Vanderbilt University, and the Shanghai Cancer Institute."

**Reviewer #2 comments:**

Version: 1
Date: 18 December 2012
Reviewer: Leah Ferrucci

Reviewer's report:

With limited studies of biomarkers of PAH exposure, this nested case-control study provides additional information to understand the relationship between this exposure and colorectal cancer. While the analysis methods are generally strong, the article could benefit from some additional discussion of the existing literature as well as some minor additions to aid in interpreting the results.

- **Major Compulsory Revisions**

1. Background 3rd paragraph, 1st sentence - Cite the existing studies of PAH exposure biomarkers and colorectal adenoma and cancer. Gunter et al. is only cited in the discussion and Agudo et al. is not currently included.


**Response:** We thank the reviewer for bringing the article by Agudo et al. to our attention. Per the reviewer's suggestion, we have added these citations to the Introduction section on p. 4.

2. Statistical analysis - Please provide additional information on creatinine adjustment in this section. Is there a citation explaining the advantages/disadvantages of this?

**Response:** A study by Han et al. (2008) found that intra-individual variability in 1-hydroxypyrene levels was modestly reduced in first morning void urine samples compared to 24-hour urine samples after adjustment for creatinine. To address potential intra-individual variability related to the use of spot urine samples in this analysis, we performed our main analyses using creatinine-adjusted 1-OHPG concentrations. However, sensitivity analyses were also performed using 1-OHPG concentrations without correction for creatinine, and with creatinine concentration included as an independent variable in the statistical model, as recommended by Barr et al. (2005). Some additional text describing our rationale for performing the analyses with and without creatinine adjustment was added to the Methods section on pp. 7-8.

3. Result (or Tables) - Did the authors evaluate the association between those dietary and environmental exposures associated with the 1-OHPG and colorectal cancer? Mention of these results in the text or tables would be helpful, e.g. was exposure to cigarette smoke (from self or husband) associated with risk in this population? Depending on these findings some mention of the self-reported exposure and disease associations should also be noted in the discussion.

**Response:** We evaluated colorectal cancer risk in relation to those exposures associated with elevated 1-OHPG levels (e.g., personal smoking status, husband smoking status, consumption of fried dough products, cooking with a coal stove). None of these exposures were associated with colorectal cancer risk (P>0.05), though there were few exposed cases for some analyses (e.g. cooking with a coal stove). We added a statement summarizing these findings in the Results section on p. 11, and commented on the consistency with our findings for 1-OHPG levels in the Discussion section on pp. 15-16.

4. Discussion, 2nd paragraph - Please include Agudo et al. in the discussion of existing studies of biomarkers of PAH exposure.

**Response:** The following text summarizing findings from the study by Agudo et al. was added to the Discussion section on p. 13: "More recently, Agudo et al (2012) conducted a case-cohort study evaluating the relationship between aromatic DNA adduct levels in pre-diagnostic leukocytes and risk of colorectal cancer (154 cases). The investigators reported a statistically significant increased risk of colorectal cancer with increasing levels of aromatic DNA adducts, and observed a stronger association for colon cancer than for rectal cancer."
5. Can the authors elaborate on the finding that levels of OHPG were higher in this population than in other non-smoking populations? Are there other important environmental PAH sources that were not assessed that could explain this? Could the spot urine collection method have influenced this?

**Response:** Ambient exposure to particulate PAHs has been associated with elevated urinary 1-OHPG levels among traffic conductors in Taiwan (Huang et al., 2012). We were unable to assess the relationship between exposure to PAHs in the ambient environment and urinary 1-OHPG levels in this investigation. However, given the potential for high ambient exposure to particulate PAHs among study participants living in urban communities in Shanghai, it is likely that this may explain the higher urinary levels of 1-OHPG in this population of non-smoking women relative to other non-smoking populations. We added a statement about ambient exposure to PAHs and cited the study by Huang et al. in the Discussion section on p. 16. Although the use of spot urine samples may have contributed to the intra-individual variability in our data, it is unlikely to account for the overall higher urinary 1-OHPG levels that we observed in this population.

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- **Minor Essential Revisions**

1. **Abstract** - Mention that urine collection was spot samples in the Methods.

   **Response:** Per the reviewer's suggestion, we clarified that spot urine samples were used in the Methods section of the Abstract.

2. **Background, 2nd Paragraph.** Several other studies (listed below) have found dietary BAP to be associated with colorectal adenoma - either for all sites or just rectal adenoma.


   **Response:** We thank the reviewer for bringing these articles to our attention. We have added these citations to the Background section on p. 4.
3. Background, 2nd paragraph last sentence. The review cited (Reference 7) here is old. Please update this reference - several more recent meta-analyses exist, such as:


**Response:** Per the reviewer's suggestion, we have updated this citation to the more recent meta-analysis by Botteri et al.

**References:**

