Author's response to reviews

Title: Indoor Air Pollution Exposure from Use of Indoor Stoves and Fireplaces in Association with Breast Cancer: A Case-Control Study

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Author's response to reviews: see over
White AJ, et al. Indoor Air Pollution Exposure from Use of Indoor Stoves and Fireplaces in Association with Breast Cancer: A Case-Control Study

Environmental Health Review

REVIEWER 1: Jennifer Peel
Reviewer's report:
This is an interesting manuscript examining the association of fireplace use and breast cancer in the U.S. leveraging the Long Island Breast Cancer Study Project (LIBCSP). However, there are some deficiencies in the manuscript (described below) that currently limit the interpretation.

RESPONSE: We are glad to hear the reviewer found the manuscript interesting and have addressed their concerns below.

REVIEWER 1: Specific Comments:
REVIEWER 1, COMMENT 1. The manuscript uses fireplace use / indoor air pollution / PAH interchangeably at different points. The manuscript text (and title) should be very clear that the variable available was self-reported fireplace use (not indoor air pollution or PAHs).

RESPONSE: Thank you for pointing this out. While we agree that other factors contribute to indoor air pollution, we used this terminology in an effort to be consistent with previous research. In particular, a recent and important review article that referred to the burning of solid fuels for heating and cooking as 'indoor air pollution' (Reid et al. 2012). In the title, we clearly state that the indoor air pollution considered here is from use of indoor stoves/fireplaces. Anywhere else in the manuscript that we refer to ‘indoor air pollution’ was clarified to be clear that we are only considering stove/fireplace use (see pages 4, 6, 7, and 17, of the revised manuscript).

REVIEWER 1, COMMENT 2. Furthermore, the manuscript does not adequately justify the focus on PAHs given the multitude of other pollutants produced from fireplaces and synthetic logs.

RESPONSE: We agree that there are many pollutants produced by burning of organic material in fireplaces/stoves. The focus on PAHs is due to the known previously published, consistent associations between PAHs and breast cancer risk in laboratory experiments and epidemiologic studies focused on women (Gammon and Santella 2008), as well as possibly higher levels in synthetic logs (Gullett et al. 2003); which together suggests that PAHs may at least be a part of the biologic mechanism (discussed on Page 16 of the revised manuscript). This comment is now acknowledged in the revised manuscript (page 17), with the statement that:

“Stove/fireplaces may release pollutants in addition to PAHs that may be relevant to breast cancer risk (Reid et al. 2012).”

REVIEWER 1, COMMENT 3. At several points the manuscript references the global public health problem of indoor solid fuel combustion. It is important to acknowledge, and indeed provide information about, the differences between the experience in this Long Island population and indoor solid fuel use in developing countries. What are typical air pollution concentrations in these homes? What is known about PAHs and other pollutants from fireplaces in the U.S. compared to developing countries?
**RESPONSE:** Thank you for giving us the opportunity to expand on this important point. This section has now been added to the discussion of the revised manuscript (Page 14):

“Use of solid fuels for indoor heating and cooking is most common in Africa and Southeast Asia, with a prevalence of use at approximately 60%, and thus, most research on health impacts have been conducted in countries in these geographic areas (Bonjour et al. 2013; Reid et al. 2012). However, solid fuel remains as the primary heating source for approximately 6.5 million U.S. citizens, predominately those of low socioeconomic status (Rogalsky et al. 2014), but may be used recreationally or as a supplemental heating source among non-low income homes (Nahe et al. 2007). Most stoves in the U.S. tend to only be used seasonally and have a flue which removes smoke from the home (Rogalsky et al. 2014). While we do not have measurements of indoor air concentrations from the LIBCSP, one study conducted in a Swedish residential area found wood burning homes had a median benzo[a]pyrene (BaP) level of 0.52ng/m³ (Gustafson et al. 2008); orders of magnitude lower than the mean BaP in wood burning homes in India, 0.70ug/m³ (equivalent to 700ng/m³) (Bhargava et al. 2004). This large discrepancy is likely due to the stove/fireplace type, limited ventilation and increased year-round duration of use. Overall, these differences suggest that exposure levels to PAHs from stoves/fireplaces would be likely lower in countries like the U.S. The association observed with breast cancer risk in this study with lower exposure levels to stove/fireplace use, suggest that if confirmed, this association may be even stronger in low or middle income countries where exposures are much higher. However, to be best of our knowledge, no other study has investigated this research question either in the U.S. or elsewhere.”

**REVIEWER 1, COMMENT 4.** You hypothesized variation by materials burned and by other factors. Did the hypotheses have a direction? The study would be strengthened by this.

**RESPONSE:** We expected the magnitude of the association with stove/fireplace use to be modest, given that in our investigations in the LIBCSP study population in association with other long-term sources of PAHs (including grilled/smoked meat (Steck et al. 2007) and cigarette smoke (Gammon et al. 2004)) we observed modest effect estimates of 1.5-2.0; however, these other PAH-source exposures were long in duration, more direct and more common, and thus we expected odds ratios slightly lower than what we observed with these other exposures – which is exactly what we found for synthetic logs. However, we did not expect magnitude of estimates to vary strongly by the specific material burned (which we already acknowledge in the discussion (Page 13 of the revised manuscript), given all are sources of some types of PAHs. We did hypothesize *a priori* that there would be an increase in risk prior to age 20 years. The last sentence of the introduction (Page 5 of the revised manuscript) was revised to be more specific to our a priori hypotheses as follows:

“We hypothesized that this association would be modestly elevated for all types of material burned, stronger with increasing years of exposure and for early life exposure and that it may vary by susceptible subgroups defined by *GST* gene variants, hormone receptor subtype and *p53* tumor mutations.”

**REVIEWER 1, COMMENT 5.** At some point – describe/discuss the variation that is encompassed by the term “indoor stoves and/or fireplace” (and implications for the results).
RESPONSE: This is a great point. As we originally wrote (in the previous draft of the manuscript on Page 14), we noted that open fireplace use may result in higher exposure and may be why the association reported here is strongest for synthetic logs, which are designed to be burned in open fireplaces. Therefore, collapsing exposure assessment to include both stove/fireplace within one question may have resulted in an attenuation of the association for wood and without this exposure misclassification we may have seen a stronger association with only open fireplace use. We have included this as a limitation of the study in the revised manuscript (Page 16), as follows.

“Collapsing indoor stove and fireplace use into one question is a limitation of this study questionnaire, and may have resulted in an attenuation of the result observed for wood use in the home, which would have been more likely to be used in indoor stoves.”

REVIEWER 1, COMMENT 6. Page 5, last paragraph of Background section: receptor status is not mentioned here, but it is in the Abstract.

RESPONSE: Thank you for noting this omission. In the revised manuscript, we have included the variation by receptor status in the last paragraph of the introduction (Page 5); this is also addressed above in Reviewer 1, Comment 4.

REVIEWER 1, COMMENT 7. Methods: Provide participation rate by method of control selection (<65 years, older).

RESPONSE: We have added in the participation rates for control selection (Page 6 of the revised manuscript as follows:

“The response rate for women <65 years was 76.1% and for women >65 years was 43.3%(Gammon et al. 2002).”

REVIEWER 1, COMMENT 8. Would be helpful and informative to have a table describing population by case and control status (particularly for potential confounders).

RESPONSE: Our revised manuscript now includes a table (Table 1) that presents case-control characteristics stratified by use of indoor stove/fireplaces. (To accommodate this addition, all subsequent tables are now renumbered.) Also, the text of the results of the revised manuscript (Page 11) includes a description of the data presented in Table 1, as follows:

“Case-control participant characteristics, stratified by any stove/fireplace use are displayed in Table I. Distributions of stove/fireplace users and non-users were similar across demographic and breast cancer risk factors.”

REVIEWER 1, COMMENT 9. Methods: why was fireplace use question limited to only Long Island residence? What about other residences?

RESPONSE: The stove/fireplace use question was tied to the residential part of the LIBCSP case-control questionnaire and thus, this limitation is due to the original study design (as mentioned on Page 17 of the revised manuscript), which has now been clarified as follows:

“We are unable to take into account any stove/fireplace exposures from participant’s former residences that were not on Long Island due to the design of the original study questionnaire.”
REVIEWER 1, COMMENT 10. On Page 9 it states that the study population was limited to women who lived on Long Island prior to age 20. It’s not clear if this is for a sensitivity analysis or the main analysis. If the primary analysis – this should be stated earlier.

RESPONSE: As described in the original manuscript (page 7 in the revised manuscript), assessment of residential history (including the query regarding use of indoor stove/fireplace use) was obtained from all women over their entire lifetime, but was restricted to assessing Long Island addresses only. Because study eligibility depended upon Long Island residency at the time of diagnosis (or date of identification for controls), when we examined indoor stove/fireplace use, our analyses include all LIBCSP participants. However, when we considered early life exposures, we could only include women who had resided on Long Island from an early age. We have clarified this issue in the methods section by revising our explanation on Page 9 of the revised manuscript:

“When examining associations for exposures <20 vs. ≥20 years of age, analyses were restricted to women who lived on Long Island prior to age 20 years, given LIBCSP participants were only queried about their residences on Long Island. We considered whether an indoor stove/fireplace was used during a possibly biologically susceptible period, <20 years of age (exposed participants could be classified as exposed for <20 years of age, ≥20 years of age or both); timing was further assessed by whether the participant specifically burned wood or synthetic logs.”

REVIEWER 1, COMMENT 11. Methods, page 8: Point #2 in Statistical Analysis is not clear given that “exposure” was not measured in this study (I assume this statement is referring to material burned, so it should state that).

RESPONSE: This statement was clarified on page 8 of the revised manuscript as follows:

“explored associations with more detailed exposure information, including material burned and timing of exposure.”

REVIEWER 1, COMMENT 12. Methods: How were potential confounders identified? How was the final model decided?

RESPONSE: The confounders were identified using a directed acyclic graph (DAG), which was used to determine the final adjusted model. This information has been added to the paragraph on confounders on Page 8 of the revised manuscript, as follows:

“Other potential confounders were identified from a directed acyclic graph(Shrier and Platt 2008) and included…”

REVIEWER 1, COMMENT 13. Page 9: Why was the ratio of the OR used to examine the cancer subtypes rather than interaction?

RESPONSE: Given that tumor subtype is only information pertinent to the case women, and not the controls, we cannot conduct a formal test for interaction to assess heterogeneity of associations across strata of breast cancer subtypes. Instead, we first used polytomous regression (where each breast cancer subtype group is simultaneously compared to the control group in a single model) to obtain the odds ratios corresponding to each breast cancer subtype. We can use these odds ratios obtained from a polytomous regression model to calculate the ratio of the odds ratios (Schlesselman JJ 1982), which is a method to assess heterogeneity of an association across tumor subtypes.
**REVIEWER 1, COMMENT 14.** Table II: The p for trend is statistically significant for synthetic log burning, but there does not appear to be a trend.

**RESPONSE:** The significant p for trend is simply stating that the slope of the trend with increasing years of use does not equal zero (i.e., rejecting the null hypothesis that the slope=0). Despite the lack of a completely monotonic relationship, all point estimates for increasing years of synthetic log burning are elevated above the null thus the slope of the line would not be equal to zero.

**REVIEWER 1, COMMENT 15.** Also – the text on Page 11 discussing Table II does not match the table (<6.9 years of synthetic log us).

**RESPONSE:** Thank you for catching the typo, the text should say \( \leq 6.9 \) years and has been corrected (Page 11 of the revised manuscript).

**REVIEWER 1, COMMENT 16.** Page 12 / Table III: the comparison of timing appears to be overstated given the overlapping confidence intervals.

**RESPONSE:** We have amended the text referring to Table IV (previously Table III) (Page 12 of the revised manuscript) to note the large confidence intervals (= imprecise) for women using synthetic logs prior to age 20 years.

“… rather than exposure occurring prior to age 20 years (OR=1.09, 95%CI 0.46, 2.59), which was imprecise due to large confidence intervals.”

**REVIEWER 1, COMMENT 17.** The potential limitation of recall bias is not adequately addressed. It seems plausible that participants might suspect synthetic logs to be more harmful than wood.

**RESPONSE:** Please note, that when the LIBCSP data was collected in the mid-1990s, most investigations had noted no association between cigarette smoking (a major source of PAHs) and breast cancer in women; however, a recent meta-analyses of cohort studies has now reported a modest positive association (Gaudet et al. 2013). Thus, despite the strong animal literature supporting a PAH-breast cancer link, in the mid-1990s epidemiologists were doubtful of an association in humans, and there was little or no information in the public press regarding a causal link. Additionally, this question was in the middle of a very lengthy questionnaire (which took an average of 101 minutes to complete (Gammon et al. 2002)) and it would be unlikely that either cases or controls would take specific note of these few relevant questions. Thus, it is unlikely, although possible, that other PAH-sources, such as synthetic logs, were suspected by case women would be more harmful than other materials. However, at the end of the LIBCSP questionnaire, participants were asked to provide information on what they thought caused breast cancer; similar proportion of cases and controls reported environmental contaminants (Teitelbaum et al. 2007). Thus, the likelihood that cases recalled their exposure to synthetic logs more strongly than controls, although possible, seems low. Thus, on Page 18 of the revised manuscript, we discuss that many LIBCSP women reported using synthetic logs for decades, suggesting it is unlikely that reports of this exposure are entirely due to recall bias (now on Page 18 of the revised manuscript). Nonetheless, we have augmented the discussion (Page 18 of the revised manuscript), as follows.

“It is unlikely at the time of data collection that cases would have suspected certain wood-based fuel materials would be more carcinogenic than others. In addition, this
study population had many long-term users of synthetic logs which suggest these results are not just an artifact of differential recall. Despite this, it is still possible that this association may have been impacted by recall bias.”

**REVIEWER 1, COMMENT 18.** The potential for selection bias should be addressed in the Discussion section.

**RESPONSE:** We have included in the discussion a statement on the possibility of selection bias, particularly among older control women which may have impacted our results (page 18 of the revised manuscript), as follows.

“There is also the possibility of the influence of selection bias, particularly among older control women who had a lower response rate. However, the mechanism by which stove/fireplace use would affect response rates among only elderly control women is unknown.”

**REVIEWER 1, COMMENT 19.** Possible residual confounding should be addressed in the Discussion section.

**RESPONSE:** We, too, were concerned about residual confounding, hence our model includes many breast cancer risk factors in an attempt to control for residual confounding. However, residual confounding is still a possibility. We have added to the discussion the possibility of residual confounding (page 18 of the revised manuscript) by an unknown factor as there is not much literature on predictors of stove/fireplace use in the home, as follows.

“There was also little existing literature on predictors of stove/fireplace use, which may result in residual confounding of the estimates. However, we included many known breast cancer risk factors in our adjustment sets in order to mitigate this concern.”

Level of interest:
An article whose findings are important to those with closely related research interests

Quality of written English:
Acceptable

Statistical review:
Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests
REVIEWER 2: Linda Birnbaum

Reviewer's report:

REVIEWER 2, COMMENT 1: This is a clearly written study demonstrating that indoor burning of synthetic logs is associated with an increased risk of breast cancer in the Long Island Breast Cancer Study. The results do suggest that synthetic logs, which generate more PAHs than wood, are problematic.

RESPONSE: We thank the reviewer for the positive comment on the writing of the manuscript.

REVIEWER 2, COMMENT 2: Their data suggest that more years of using such logs increases the risk, and that being an adult is more problematic than exposure before the age of 20. I find this quite problematic. When did synthetic logs come into common use? Certainly, not 40-50 or more years ago. The number of women who used synthetic logs before the age of 20 are very small in this study and I do not know if the study has the power to address this.

RESPONSE: We agree, synthetic logs likely were not commonly used among women in this study population prior to age 20. They were commercialized in 1931 and the now commonly-used petroleum-based artificial logs were not in use until 1963 (Shook 1999). This was addressed in the original version of the manuscript (page 17 of revised draft) and clarified to state:

“Synthetic logs were commercialized in 1931 with the petroleum-based synthetic logs being introduced in 1963 (Shook 1999). Thus, we cannot rule out the possibility that the older age of our population precluded many from being exposed to synthetic logs at an early age resulting in small sample sizes and unstable estimates.”

REVIEWER 2, COMMENT 3: I think that the suggested increase in risk prior to age 20 for any stove/fireplace is important - and likely just misses significance because of small numbers.

RESPONSE: Yes, we agree with the reviewer and can add emphasis on this result in the discussion (see Page 16).

“We did find a suggestive evidence that any indoor stove/fireplace use and wood burning prior to age 20 years, which encompasses age before first birth for approximately 90% of the LIBCSP study population, may be more relevant for future breast cancer risk than exposure that occurs after age 20 years. This is consistent with evidence from another PAH source, active smoking, which may be particularly important to breast cancer risk if the exposure is prior to the first pregnancy (Gaudet et al. 2013).”

REVIEWER 2, COMMENT 4: The exposure indice is quite crude - did you use a fireplace 3 times per year or more in a given year? I wonder how accurate that measure of exposure really is.

RESPONSE: This is definitely a limitation of this exposure assessment. We included evidence from another study population that found that those who reported using synthetic logs did so at least several times per month, which may suggest that “ever users” may tend to be relatively regular. This discussion was noted on the original version of the manuscript (now on Page 17 of the revised manuscript), as follows:
“In addition, although we did assess duration of exposure, we did not assess frequency of exposure to indoor stove/fireplace burning, which makes identifying and quantifying the association with those who are most highly exposed very difficult. One report found that those who burned synthetic logs did so relatively frequently (at least several times per month) (Gullett et al. 2003). Having information on frequency of use would better inform the results reported here.”

**REVIEWER 2, COMMENT 5:** While this population is largely white, is there a large number who are Ashkenazi Jews, who have a relatively high incidence of BRCA1 and 2 mutations... Was this examined?

**RESPONSE:** We do know that approximately 15% of cases and 17% of controls identified as being Jewish. After running a sensitivity analyses to address this comment, we did not find results to be stronger among Jewish women.

**REVIEWER 2, COMMENT 6:** There are several studies which demonstrate that there are critical windows of susceptibility for breast cancer. The work of Barbra Cohn, for example, has shown that the relationship between DDT and breast cancer involves exposure before the age of 14, and is strongest before the age of 4! While PAHs are genotoxic carcinogens, they may additional windows as well - childhood, puberty, pregnancy. In fact, was pregnancy when using stoves examined? PAHs can be estrogenic - or anti-estrogenic, as well as modulate multiple other nuclear receptor systems.

**RESPONSE:** Due to sample size concerns, we considered exposure prior to age 20 years which for this study population includes childhood, puberty and for 90% of the study population age before first birth. To address this comment, we did run analyses on the residence for where they had their first child and the results were similar to the overall analyses (estimates were close to the null for any stove/fireplace use, wood use and similarly elevated for synthetic logs).

**REVIEWER 2, COMMENT 7:** Ref. #11 - is NOT from a NCI group, but from scientists from several organizations who participated in a meeting on indoor cookstoves and reviewed the data on exposure to such and cancer. (2nd paragraph, p.13)

**RESPONSE:** We apologize for this oversight. The revised manuscript has been corrected (page 13 of the revised manuscript), as follows:

“a recent scientific review”

**Level of interest:**
An article of importance in its field

**Quality of written English:**
Acceptable

**Statistical review:**
No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests
References


