Author’s response to reviews

Title: Exposure to Hazardous Air Pollutants and Risk of Incident Breast Cancer in the Nurses' Health Study II

Authors:

Jaime Hart (jaime.hart@channing.harvard.edu)
Kimberly Bertrand (kab15@bu.edu)
Natalie DuPré (ncd121@mail.harvard.edu)
Peter James (pjames@hsph.harvard.edu)
Verónica Vieira (vvieira@uci.edu)
Trang VoPham (tvopham@hsph.harvard.edu)
Maggie Mittleman (mmittlem@wellesley.edu)
Rulla Tamimi (rulla.tamimi@channing.harvard.edu)
Francine Laden (francine.laden@channing.harvard.edu)

Version: 1 Date: 29 Jan 2018

Author’s response to reviews:

Dear Dr. Stayner,

Thank you for the opportunity to revise our article “Exposure to Hazardous Air Pollutants and Risk of Incident Breast Cancer in the Nurses' Health Study II" (ENHE-D-17-00283)" for Environmental Health. We believe that the comments from the reviewers have helped to improve and clarify our paper. All comments are answered below, with page and paragraph references to the version of the manuscript with changes tracked.

All authors have had an opportunity to read and edit the revised version of the manuscript and all have consented to its resubmission. We look forward to working with you on this submission. Thank you for your consideration.

Sincerely,

Jaime Hart
Reviewer #1

This study evaluates breast cancer risk associated with modeled Hazardous Air Pollutants among the nationwide Nurses Health Study II cohort, applying the methods used in the California Teachers Study.

I appreciate the value of applying the methods used by the California Teacher's Study (CTS). However, I think it would be better to also think through ways in which those methods could be adapted or improved in this dataset.

C1. Please replace the term "replicate" throughout. It is conceptually important in environmental health to understand that human studies cannot be exactly repeated. In this study, specifically, we know that breast cancer is influenced by exposures during windows of susceptibility in the life cycle and that the disease includes subtypes that are more/less common by menopausal status, so we expect that analysis in the mostly premenopausal Nurses II is not the same as the mostly older CTS.

R1. We agree with the reviewer’s point, and have removed references to “replication” throughout.

C2. The differences between the two studies in parity and age distribution are substantial, and I recommend noting this early in the article, so that readers can keep this in mind throughout. Otherwise, readers who are not already familiar with CTS do not encounter this important "design difference" until the discussion.

R2. As requested, we have pointed out the differences in the cohorts earlier in the manuscript. However, as opposed to discussing age, we have made the point that CTS is mostly composed of postmenopausal women, as opposed to the mostly premenopausal NHSII.

Page 3, para 2: “Two recent analyses based in the California Teachers Study (CTS) cohort (a study of mostly postmenopausal women, of whom 26% were nulliparous) have focused on Hazardous Air Pollutants (HAPs) as another potential group of environmental risk factors for breast cancer”

Page 4, para 1: “The results of these two previous studies suggest that HAPs may be a previously unidentified risk factor for breast cancer, and that these associations should be examined in other cohorts with a larger geographic scale and among women of different ages. Therefore, the purpose of our study was to assess the impacts of HAPs among a nationwide cohort of mostly premenopausal women, the Nurses’ Health Study II (NHSII).”

C3. Are you able to consider the effects of occupational exposures to the same chemicals? Some of the HAPs are likely exposures in hospitals, and other carcinogens and endocrine disruptors are, too. For example, when did the ethylene oxide standards go into effect? Are the nurses likely exposed to this sterilant? Please discuss nurses' exposures to these and other mammary carcinogens and EDCs, and how this relates to the study design.
R3. Unfortunately, we do not have information on chemical exposures at work among NHSII participants. We have noted this key point as a limitation of our study.

Page 11, para 2: “Importantly, for this population, who may have been exposed to some of these chemicals as nurses, we are unable to adjust for exposures to these chemicals at work, as NHSII does not have information on workplace chemical exposures.”

C4. P 5, line 36 "Women were excluded from the current study if they had been diagnosed with cancer … during follow-up." Obviously, women with breast cancer weren't excluded, so maybe you mean other cancers?

R4. We have rephrased this text to indicate that women with any cancer (including breast, but excluding non-melanoma skin cancer) were excluded if diagnosed before the baseline questionnaire, and were censored after developing any non-breast, non-melanoma cancer during follow-up.

Page 4, para 2: “Women were excluded from the current study if they had been diagnosed with cancer (other than non-melanoma skin cancer) before returning the baseline questionnaire. Women were censored during follow-up if they were diagnosed with a cancer other than breast or non-melanoma skin cancer.”

C5. p. 6. In this study, women are aged 25-42 at the beginning of the exposure period (residential histories start in 1989). Past breast cancer research suggests that exposure to carcinogens early in life is most important, before the first full-term pregnancy when the breast becomes mature. Does NHSII have adequate power to analyze risk limited to exposure before the first pregnancy?

R5. Unfortunately, we do not have sufficient power to examine the impact of exposures before first pregnancy in the NHSII, as most first pregnancies in the cohort occurred before enrollment, when information on residential address at the Census tract level is not available.

C6. P 6, line 54. The use of only 2002 HAPs data is explained, but this remains a limitation. How much does this matter - do locations change very much in rank order across time periods dating back to earlier years?

R6. In response to this, and other Reviewer comments, we have added a sensitivity analysis looking at the limited number of HAPs available in the 1996 NATA to determine if similar patterns were observed with breast cancer. We have also included a supplemental table with the correlations between the 1996 and 2002 measures for the tracts included in the analyses to directly answer this question.
Page 8, para 1: “As noted above, we conducted sensitivity analyses using estimates from the 1996 NATA to determine if the choice of predictions affected our results. We also assessed Pearson and Spearman correlations between the 1996 and 2002 predictions of each HAP.”

Page 9, para 4: “The Pearson correlations between exposures based on the 1996 and 2002 NATA assessments, although statistically significant, tended to be small to modest (Supplemental Table S5). However, based on the Spearman correlations, the rank ordering of Census tracts did appear to be relatively consistent between the two time points. Models using the values from 1996 assessment had generally similar patterns as those using the 2002 values (Supplemental Table S6).”

C7. How does the distribution of absolute exposure levels in NHSII compare with CTS (Garcia Figure 1)? Off the top of my head, I might think more CTS women are exposed to substantial air pollution than would be found nationwide.

R7. Although direct comparisons cannot be made because exact ranges were not presented in the paper by Garcia et al., our ranges of exposure appear to be very comparable.

C8. P 7, line 39. Diesel exhaust contains many mammary gland carcinogens, and this should be mentioned in addition to classifying diesel as estrogen-disrupting. For example, search for "diesel" in the Mammary Carcinogens Database: http://sciencereview.silentspring.org/mamm_search.cfm.

R8. This is an excellent point and we have clarified throughout to add diesel to the list of mammary carcinogens.

C9. Potential confounders. In addition to my comment above about chemical exposures in nursing, it seems important to consider the possible role of shiftwork. How might that confound or modify this analysis?

R9. As requested, we have added shiftwork to the lists of potential confounders considered and included in the fully adjusted models (and revised results in all tables accordingly). It does not appear to be an important confounder (see examples in Supplemental Figure S1).

C10. P 8, line 43. Do you have data on exposure to environmental tobacco smoke? What about models limited to smokers? It seems like these could be important to further evaluate in a study of air pollutants.

R10. Unfortunately, there is no information available on ETS exposures in NHSII. However, as requested, as a complement to Supplemental S3 (in never smokers), we have added an additional Supplemental Table (S4) restricted to smokers and detailed this additional model in the Methods and Results. We edited the Results section to read:
“Patterns of association with each of the HAPs were similar, although somewhat further from the null, in models restricted to women who were premenopausal (Supplemental Table S2). Results were also similar in models restricted to never smokers (Supplemental Table S3) or ever smokers (Supplemental Table S4).”

C11. p. 8, line 51-52. Please clarify the description of the study population "throughout follow-up." The women are aged 25-42 at recruitment in 1989. Follow-up extends to 2011, when they would be aged 47-64. Please clarify the definition of the average age 44.4, so people understand what "throughout follow-up" means. Similarly, % premenopausal. CTS describes its study population at baseline (1995). It appears CTS women are older. 63% of CTS cases and 49% of non-cases are menopausal. 23% of CTS cases and 26% of non-cases are nulliparous. These differences between the NHSII and CTS study populations are relevant to hypotheses about effects of pollutant exposures.

R11. Table 1 shows the characteristics of the study population essentially weighted by person-time (which is what is being used directly in the proportional hazards model). As almost all of the covariates vary over time, we believe it is important to show this, as opposed to the population at baseline (which is more appropriate for variables that do not time vary).

C12. p. 9, line 18. You may be interested to know that there is elevated breast cancer risk on Cape Cod in locations affected by 2,4,dinitrotoluene from explosives at a military base. https://www.ncbi.nlm.nih.gov/pubmed/12003750?dopt=Abstract

R12. We are aware of this paper, and thank the Reviewer for reminding us. We struggled with including a comprehensive and coherent discussion of all 32 chemicals examined. However, in response to this comment and comments from the other reviewers, we have expanded our discussion to include additional papers focused on some of the specific compounds that yielded interesting results, as well as the Reviewer’s recently published comprehensive review on chemical exposures and breast cancer where it was appropriate.

C13. p.9, line 56 If indeed diesel increases breast cancer risk, even with relatively modest HR, this would be of major public health importance, because diesel exposure is so widespread, breast cancer is so common, and diesel is a modifiable exposure. In general, the use of the word "only" seems unhelpful.

R13. We agree that if replicated in other studies the modest increases in breast cancer with exposures to diesel would have substantial public health implications. However, given the large number of compounds examined, we have opted to be cautious in the interpretation of any given compound and instead present all exposures for the reader to assess. However, we agree that the "only" was unhelpful and have removed it. We have also specifically expanded our discussion of diesel in the discussion and noted that given the large number of exposed women, it could have a major public health impact.
C14. p. 12, line 27. Missing "on."

R14. We have corrected this typographical error.

C15. p. 12, line 45. Mention occupational exposures.

R15. As requested, we have added that a limitation of this study is our inability to consider exposures to these compounds in the workplace.

C16. p. 13, line 27. You mean "not"?

R16. We did (thank you for the catch) and have made the change.

C17. Did you consider analyzing mixtures other than diesel?

R17. We did not consider any other mixtures.

C18. The footnote in the supplemental tables S2 and S3 seems to be copied from Table 2, but the supplemental tables show two different models, one not fully adjusted, so this is confusing.

R18. We have modified the footnote to give the variables included in both the basic and adjusted models.

C19. In the methods, you say "each variable (or set of variables) was added to models adjusted for age and calendar period to assess confounding, but we don't learn how that led to the inclusion of the large set of variables in the multivariable models."

R19. We have both revised the text in question and included a supplemental figure to show the impact of the inclusion of specific confounders (or groups of confounders) on sample effect estimates.

Reviewer #2

The authors present an analysis of hazardous air pollutants in association with incident breast cancer in the Nurses' Health Study. The findings suggest varied associations for different pollutants. Overall, this is an interesting study, however, I would like to see some additional context for the research and have some questions on the analysis.
Abstract:

The authors conclude that long term exposures to HAPs in adulthood are not consistently associated with breast cancer. However, only 2002 estimates of HAPs were used from the NATA data, therefore, it cannot be considered long term exposures.

Response: We have removed “long-term” as requested.

Introduction:

A comment for the overall paper, the authors focus on the two particular studies that utilize the California Teachers Study as comparisons, particularly in the introduction and discussion. Are these the only two studies to consider HAPs and breast cancer outcomes? It would be helpful to have a more comprehensive background section siting additional references that consider HAPs and breast cancer outcomes is needed.

Response: The Reviewer (and other reviewers) make an excellent point. We struggled with writing a coherent and concise Discussion if we included previous studies of all 32 chemicals examined and focused on the CTS findings as they are the only prospective cohort that has examined the impact of all of these exposures with breast cancer incidence. However, in response, we have expanded our discussion to include additional papers focused on some of the specific compounds that yielded interesting results, as well as findings from a recently published comprehensive review on chemical exposures and breast cancer.

Methods:

The exposure utilizes the 2002NATA data, however, it is not clear from the description, the time frame in which women were diagnosed with breast cancer. Therefore, it not clear if the exposure is preceding the outcome with a sufficient lag period for cancer development. I would suggest including some descriptive information on date of cancer diagnosis. In addition, the authors should consider limiting the analysis to cases diagnosed a sufficient time following the exposure utilized.

Response: The 2002 NATA estimates were appended to all addresses 1989-2011 (so they did change if women moved) and cases could be diagnosed at any point during follow-up (so both prospectively and retrospectively in regards to the NATA date). We agree that timing is important and in response to this and other comments, we have added a sensitivity analysis using the available data from the 1996 NATA (Supplemental Table S7) and have reported the correlations of 12 HAPs available in 1996 and 2002 (Supplemental Table S6). We have added the following text to the Results section: “The Pearson correlations between exposures based on the 1996 and 2002 NATA assessments, although statistically significant, tended to be small to modest (Supplemental Table S5). However, based on the Spearman correlations, the rank ordering of Census tracts did appear to be relatively consistent between the two time points.
Models using the values from 1996 assessment had generally similar patterns as those using the 2002 values (Supplemental Table S6).

There are several confounders which are utilized in the analysis. Several of these confounders seem as though they may be highly correlated (such as height and BMI and median household income and median home value). I am concerned that the models may be over adjusted. The statistical analysis does not describe any model building or assessment of model fit. I would suggest that the authors provide more justification, both from the literature and statistically for this particular analysis, for the inclusion of all of these confounders.

Response: We have now added additional information on our model building approach. Our primary models are the basic models stratified only by current age and time period and our fully adjusted models include all a priori assessed confounders. However, to show the impact (or, more explicitly, lack of impact) of different confounders (or groups of confounders), we have added a supplemental figure showing selected effect estimates in models including different potential confounders.

Page 9, para 2: “Measures of area-level SES and parity and age at first birth appeared to be the only relevant confounding variables in most models (Supplemental Figure S1).”

The authors also mention adjusting for age and calendar period. Is that age at diagnosis, at the beginning of the study, or current age? What is the calendar period, month, season, quarter? And what is the reason for including the calendar period?

Response: We have clarified that we are using time-varying current age and the current two-year questionnaire period in all models. We stratify by calendar period to both meet the assumptions of proportional hazards, to adjust for secular trends in diagnosis, and to control for any other temporal trends (including changes in actual HAPs levels relative to the 2002 values) in exposure or outcome that are not controlled for with the other potential confounders.

In the statistical analysis it is mentioned that quartiles of exposure were used since dose-responses were not linear. I would recommend that this be described in more detail. How was this assessed and which HAPs demonstrated non-linear responses? Additionally, the statement following says p-values for trend were obtained using the median value for quartile of exposure. However, I would recommend not focusing on the p-value for the trend and including the estimates of trend as well so that the reader can assess the dose-response regardless of statistical significance.

Response: Below we have included a table indicating which of the HAPs had dose-responses the deviated from linearity and providing the highly unstable dose-response estimates for those that did not statistically significantly deviate. Given the very large confidence intervals, we would prefer not to include this in the Supplement Material, but will defer to the wishes of the Reviewer.
Supplemental Table S5: Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for an interquartile range (IQR) increase in each HAPs exposure on risk of incident invasive breast cancer 1989-2011 among women in the Nurses’ Health Study II cohort.

<table>
<thead>
<tr>
<th>Hazardous Air Pollutant</th>
<th>Non-Linear?</th>
<th>IQR (µg/m³)</th>
<th>HR (95% CI) per IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammary Carcinogens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2-Dibromo-3-Chloropropane</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,4-Dinitrotoluene</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,4-Toluene Diisocyanate</td>
<td>No</td>
<td>4.96E-05</td>
<td>1.00 (0.00, 52,292,610,210.72)</td>
</tr>
<tr>
<td>2-Chloroacetoephone</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>No</td>
<td>6.06E-03</td>
<td>0.99 (0.01, 122.38)</td>
</tr>
<tr>
<td>Benzene (Including Benzene From Gasoline)</td>
<td>No</td>
<td>1.10E+00</td>
<td>0.97 (0.92, 1.02)</td>
</tr>
<tr>
<td>Benzidine</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbon Tetrachloride</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroprene</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diesel Engine Emissions</td>
<td>No</td>
<td>6.10E-01</td>
<td>1.01 (0.43, 2.38)</td>
</tr>
<tr>
<td>Ethylene Dibromide (Dibromoethane)</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethylene Dichloride (1,2-Dichloroethane)</td>
<td>No</td>
<td>1.39E-03</td>
<td>1.00 (0.00, 2,222.32)</td>
</tr>
<tr>
<td>Ethylene Oxide</td>
<td>No</td>
<td>5.31E-03</td>
<td>1.01 (0.05, 21.00)</td>
</tr>
<tr>
<td>Ethyldiene Dichloride (1,1-Dichloroethane)</td>
<td>No</td>
<td>8.85E-04</td>
<td>1.00 (0.00, 41,806.66)</td>
</tr>
<tr>
<td>Hydrazine</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylene Chloride (Dichloromethane)</td>
<td>No</td>
<td>2.00E-01</td>
<td>1.00 (0.90, 1.11)</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O-Toluidine</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propylene Dichloride (1,2-Dichloropropane)</td>
<td>No</td>
<td>1.36E-03</td>
<td>1.00 (0.00, 439,188,086.76)</td>
</tr>
<tr>
<td>Propylene Oxide</td>
<td>No</td>
<td>3.02E-04</td>
<td>1.00 (0.00, 18,514.94)</td>
</tr>
<tr>
<td>Styrene</td>
<td>No</td>
<td>4.00E-02</td>
<td>1.00 (0.77, 1.29)</td>
</tr>
<tr>
<td>Vinyl Chloride</td>
<td>No</td>
<td>3.94E-03</td>
<td>1.00 (0.06, 16.92)</td>
</tr>
<tr>
<td>Vinylidene Chloride (1,1-Dichloroethylene)</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen Disruptors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diesel Engine Emissions</td>
<td>No</td>
<td>6.10E-01</td>
<td>1.01 (0.43, 2.38)</td>
</tr>
<tr>
<td>Arsenic Compounds (Inorganic)</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biphenyl</td>
<td>No</td>
<td>1.43E-04</td>
<td>1.00 (0.00, 302,447,192,795.12)</td>
</tr>
<tr>
<td>Bis(2-Ethylhexyl)Phthalate (Dehp)</td>
<td>No</td>
<td>4.60E-04</td>
<td>1.00 (0.00, 1,978.21)</td>
</tr>
<tr>
<td>Dibutulphthalate</td>
<td>No</td>
<td>3.38E-04</td>
<td>1.00 (0.24, 4.12)</td>
</tr>
<tr>
<td>Dimethyl Formamide</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Nitrophenol</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selenium Compounds</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All fully adjusted models are adjusted for time-varying current age and calendar period by stratification and include terms for race, family history of breast cancer, history of aspiration or biopsy confirmed benign breast disease, age at menarche, parity and age at first birth, menopausal status and postmenopausal hormone use, oral contraception use, recent
mammogram, height, BMI at age 18, difference between current BMI and BMI at age 18, physical activity, overall diet quality (including alcohol consumption), alcohol consumption at age 15 and age 18, current smoking status, shift work, individual-level SES (marital status, living arrangements, household income), area-level SES (Census tract median home value and median income), and Census region of residence.

a Diesel exhaust and Styrene are both potential estrogen disruptors and mammary carcinogens.

Results:

I would recommend including estimates of trend, and not only p-values, in the results tables.

Response: See response above.

Discussion:

As mentioned earlier, the discussion focuses on the two CTS studies. However, there is no comparison of results to any other studies which assess HAPs and breast cancer outcomes. Therefore, it is not clear how these results compare to other studies in this area.

Response: As noted above, we have rewritten the Discussion to more broadly compare our findings to those in the literature where other studies were available.

The limitations of the use of NATA data are mentioned however, no references are provided and it is not clear if these limitations are specific to this study or if this is a common challenge of using NATA and geographic level exposures.

Response: These limitations are noted in the EPA documentation for use of the NATA assessments and not specific to this analysis. We have added a reference to this documentation.

Minor Comments:

Page 7, line 40 - the parentheses are not necessary around the ER as the acronym has been established previously.

Page 10, line 33 - 36 - the acronyms ER+/PR+ and ER-/PR- are used for the first time and not described or mentioned earlier in the paper. Additionally, here the authors use ER+ and throughout the paper elsewhere they use ER-positive. Please be consistent.

Response: We thank the reviewer for these comments and have changed the text to first define each of the acronyms and then use them thereafter.
Reviewer #3

In article 'Exposure to Hazardous Air Pollutants and Risk of Incident Breast Cancer in the Nurses' Health Study II' authors aim to reproduce results from two studies based on California Teacher's Study (CTS) where associations between several HAPS and estrogen disruptors with breast cancer incidence was reported. Authors find little agreement with CTS study, and generally weak support for increased risk of breast cancer with any HAPs, with associations being weak positive, and going in both directions (positive and negative). Study is well designed and clearly written and presented, based on a well-established NHSII cohort, with excellent data on breast cancer incidence, subtypes by ER status, risk factors, and good data on HAPs. However, authors need to discuss several issues which may help elucidate differences between CTS and NHSII study, before study can be accepted. My specific comments can be seen below:

Comment 1: My main concern in the study design is the choice of exposure matrix for HAPs for year 2002, the reason being that earlier studies in CTS based their funding on HAPs data from the same year. The NATA had data available from HAPs assessment in 1996, 1999, 2002 and 2005. Authors write that EPA cautions against comparing concentrations against NATA due to differences in methodology. Did author's consider different criteria to choose which NATA data to use, for example based on the quality of data, if there are any validation studies of HAPs predictions for different years available? Although methods are different, I would argue that three is added benefit in trying different windows of exposure. Perhaps focusing on the earliest data from 1996 would have been more optimal, since easiest exposures are probably the most relevant for breast cancer development, as authors do point out in discussion. Can authors discuss a bit further?

Response 1: In response to this and comments from other Reviewers, we have included sensitivity analyses using the 1996 version of the NATA for the 12 HAPs available on both the 1996 and 2002 NATA. We have also expanded our discussion of the linear and rank order correlations of the HAPs across the NATAs. Text has been added to describe these analyses in the Methods (Page 6, para 1: “In sensitivity analyses to determine if the choice of NATA influenced results, we also conducted analyses using the 1996 NATA.” and Page 7, para 3: “As noted above, we conducted sensitivity analyses using estimates from the 1996 NATA to determine if the choice of predictions affected our results. We also assessed Pearson and Spearman correlations between the 1996 and 2002 predictions of each HAP.”), Results (Page 9, para 4: “The Pearson correlations between exposures based on the 1996 and 2002 NATA assessments, although statistically significant, tended to be small to modest (Supplemental Table S5). However, based on the Spearman correlations, the rank ordering of Census tracts did appear to be relatively consistent between the two time points. Models using the values from 1996 assessment had generally similar patterns as those using the 2002 values (Supplemental Table S6.”) and additional tables (Supplemental Tables S5 and S6) have been included in the Supplemental Material.

Comment 2: Page 11, line 9: Authors state that 'Women in the CTS were also likely to be parous (26% versus 18%)?' This seems to be mistake, it should be nulliparous, according to statistics in Table 1.
Response 2: We thank the Reviewer for catching this mistake and have corrected it.

Comment 3: Author point out the differences between CTS and NHSII cohorts, one being number of postmenopausal women in two cohorts, which is much higher in CTS. They speculate that HAPs may be more relevant for postmenopausal women, but could have they tested this (effect modification analyses) in their data, for selected HAPs and estrogen disruptors?

Response 3: Unfortunately, we do not have enough postmenopausal cases yet to be able to conduct the analyses requested.

Comment 4: Can author discuss in little more detail geographical differences between the two studies, CTS based on California and NHSII, being a nationwide study, as this is an important possible explanation for different findings in two studies. Are concentrations of HAPs higher/lower in California then rest of the country/states represented in NHSII? Is NATA data assessment for HAPS possibly better for California (number of measurements, etc.), if there are any validation studies possible?

Response 4: As shown in Supplemental Table S1, our ranges of exposures are very comparable to those from the CTS, indicating that this is not likely an explanation for the differences in findings between the two studies. The same methods are used to conduct the NATA nationwide, however, it is possible that the underlying information used to create the predictions may vary geographically. However, we do not feel that there is enough information to speculate on this issue, and that the differences between the two cohorts are a more likely explanation for the differences in findings. However, we do not have enough cases in CA alone to perform robust sensitivity analyses to directly assess this.