Author’s response to reviews

Title: Hair Product Use, Age at Menarche and Mammographic Breast Density in Multiethnic Urban Women

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To the Editors of Environmental Health,

We appreciate the opportunity to submit our revised manuscript “Hair Product Use, Age at Menarche and Breast Density in Multiethnic Urban Women” to Environmental Health. We appreciate the reviewers’ overall compliments on our report and the thoughtful comments and suggestions that were made. Below, we have highlighted the major compulsory revisions and the minor and discretionary revisions suggested by the reviewers in the manuscript. The original reviewers’ comments are numbered and our responses are listed below. As a reminder, the original line numbers previously mentioned by reviewers have shifted due to manuscript edits.

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REVIEWER 1

Major Specific Comments:

1. I suggest that it would be more appropriate to put the primary emphasis on the race-adjusted results for age at menarche (e.g., in the abstract) rather than the minimally-adjusted results, given that race/ethnicity appears to be an important confounder in these analyses.
a. We concur and have now included the race/ethnicity adjusted findings for age at menarche in the abstract. However, we suggest cautious interpretation of these findings, as structural confounding could be at play. The key issue is that there is minimal overlap in hair product use between racial/ethnic groups. As such, this could lead to issues of making valid comparisons between groups, with impact on meaningful conclusions on associations adjusted for race/ethnicity. We now state this concern and the need to cautiously interpret the race-adjusted models in our Methods section. For this, we state: “Additionally, we adjusted for race/ethnicity. However, the additional adjustment for race/ethnicity could lead to structural confounding due to minimal overlap between racial/ethnic groups with respect to hair product use. As such, models adjusted for race/ethnicity should be interpreted with caution.”

2. Page 3, lines 31-51: Can you please clarify whether all women included in the analysis had no history of breast cancer at the time of interview/mammogram?

a. We include within the aforementioned lines the statement: “we excluded women who had a history of breast cancer.

3. Page 5, lines 5-6: Race/ethnicity is not mentioned as a potential confounder of the association of childhood hair product use and age at menarche in the Methods, although it appears a model including race/ethnicity was fit. Please include these details in the Methods section.

a. Race/ethnicity is mentioned in the Methods section as an a priori potential confounder on page 4, lines 13-14 in the original submitted manuscript. However, as mentioned above, we present this model with caution do to possible structural confounding due to minimal overlap by racial/ethnic groups with respect to hair product use. (See earlier comment).

4. It is not clear whether "childhood use" of hair products refers to any use before age 13, or any use before menarche. This introduces a concern about temporality of associations: some girls may have been <11 years old at menarche, but started using hair products between ages 11 and 13. Please clarify how the exposure variable was defined.

a. We thank the reviewer for bringing up this very important point on temporality. In the last paragraph in the Methods section, we highlight that women who were under age 11 at menarche all reported childhood hair product exposures prior to age 11.
5. Page 5, lines 40-45/Table 2: Race/ethnicity seems to meet the definition of a confounder in analyses of childhood hair product use and age at menarche, given that African American are more likely than white girls to use hair oils and other products and African American girls also have earlier menarche on average. In fact, after adjusting for race/ethnicity, the observed positive associations become attenuated. I strongly urge the authors to consider reporting the race-adjusted results as their primary results in the Abstract (and in Table 2 and Conclusions). It is helpful to see the results before adjustment for race/ethnicity, but race/ethnicity appears to be an important confounder here and relevant for interpretation of findings. In fact, the association for hair oils specifically remains borderline statistically significant (95% CI: 1.0, 5.5), even with relatively low power - this is an important finding and still supports the a priori hypothesis.

a. We concur that race/ethnicity is a possible confounder and have created greater emphasis around this point. However, we would like to balance this with the possibility that there is minimal overlap between racial/ethnic groups with respect to product use, which could lead to issues of structural confounding and a lack of meaningful interpretation of results, as mentioned earlier. As such, we present both models without race/ethnicity-adjustment and models with race/ethnicity adjustment. We also suggest cautious interpretation of the latter.

However, we do understand the reviewer’s concerns and while already included in the Methods section as an a priori confounder in our original submission, we have now added the race/ethnicity adjusted estimates into the abstract, Table 2, and included a sentence within the conclusion paragraph. We have also reported the association between childhood hair oil use and menarche for Hispanic women and African American women, separately. We also note that structural confounding may limit the findings in the Discussion section, as a significantly greater proportion of African-Americans reported use of hair products compared to women of other racial/ethnic groups. This has been added as part of our discussion of limitations in the Discussion section.

Minor Specific Comments:

1. * Title: "Breast density" could imply breast tissue density or mammographic density. Since breast density was assessed on mammograms (vs. MRI or DXA, for example), it would be more accurate to call this "mammographic breast density," at least in the title and the first time it is defined.

a. We have added “mammographic” to the title.
2. * Abstract, line 29: There is a typographical error: early age a menarche is given as ≥11 years, but I think it should be <11 years based on the Methods and Table 2.

   a. Corrected

3. * Page 2, line 60: If possible, it might be helpful to give specific estimates for how commonly these products are used in the general population (e.g., percent of women, preferably by race/ethnicity) vs. simply noting that use is "frequent and long-term."

   a. We have added more detailed quantification of hair product use from two large cohort studies in the Introduction.

4. * Page 3, line 49: The final sample size is given as 248, but this is confusing because on the next page, line 27, a larger sample size is given. At the end of that paragraph, it becomes clearer how the final sample size was calculated. I suggest excluding the first mention of the sample size from the first paragraph of the Methods section.

   a. These numbers have been removed for clarity.

5. * Page 3 [2], line 56: I'm a little confused about the assessment of timing of hair product use during childhood. Here, it seems that women were queried about use "before age 13," but based on information on Page 4, lines 15-16, it was also possible to calculate duration of childhood use. Were women asked about use at each age during childhood? Was any information collected about use between the ages of 13 and 20?

   a. We clarified in the Methods section, within the description of our exposure variable, that we calculated the duration of childhood use of hair oils based on the assumption that, once a woman reported the use of hair oils, she would continue to use them until age 13.

   b. We did not collect any information between the ages of 13 and 20.

6. * Page 4, lines 28-31: What was the timing of women's mammograms relative to interviews?
a. For the majority of women in the study, mammograms occurred after age 40 years. Questionnaire data on hair product use since age 20 occurred at a mean age of 46.8 years. As such, our exposure variable involved self-report of the ~20 years of follow-up from age 20 until the time of the questionnaire data collection. For ever use, once a woman reported use, she was considered to have used the product until the time of the mammogram.

b. Mammograms for the NY-MBCP were obtained on the same date as the interviews that collected epidemiologic risk factor data. Mammograms from NY-NCPP were taken closest to the time of the interview data collection. This information was provided in the Methods section.

7. * Page 4, lines 42-44: Was information on menopausal status or early life body fatness (e.g., childhood BMI) available? If menopausal status is available, it might be interesting to evaluate associations in premenopausal women only: one might expect a stronger effect in this group if the hypothesis is related to earlier life exposures. Childhood adiposity is a predictor of both age at menarche and breast density; could it be an uncontrolled confounder?

a. We thank the reviewer for raising this very salient point. We have included as a sensitivity analysis, the examination between childhood hair product use and age at menarche restricted to younger women. Young women have been independently defined as a) under age 50 and as b) not being postmenopausal. The details of the analysis and the findings can be found in the Statistics section of the Methods and Results section (first paragraph, 2nd to last paragraph). We have also included menopausal status to Table 1.

b. With respect to childhood adiposity, we believe obesity could be a potential mediator of the association between hair product use and earlier age at menarche, as some of the chemicals in these products could be obesogenic. That said, we agree with the reviewers that this might be an important factor to adjust for in the analysis, as it is also a predictor of the outcome. Unfortunately, this data is not available in the present study. We have now listed this as a limitation of the study.

8. * Page 4, line 56: Is "multivariable relative risk regression using the binomial link" simply "logistic regression"? For the sensitivity analysis modeling age at menarche as a continuous variable, was this linear regression? Was age at menarche normally distributed?

b. We have clarified the use of linear regression for the sensitivity analysis modeling age at menarche as a continuous variable. Yes, age at menarche was normally distributed in our study population.

9. * Page 5, lines 9-13: Were percent mammographic density and absolute mammographic density both normally distributed? If not, these variables (especially absolute density) may require transformation (e.g., log-transformation or square-root transformation) to meet the assumptions of the linear regression model.

a. Thank you for noting this. We have now log transformed mammographic percent density and total dense area as they were not normally distributed. We have changed all the results within the manuscript text and Table 3 accordingly; however, log transformation did not alter the data results nor interpretation.

10. * Page 6, lines 4-6: I think readers would find the actual results of the linear regression model for age at menarche of interest; please consider including the results here in the text (rather than indicating "data not shown").

a. We have added these results to the Results section.

11. * Page 6, lines 15-17 and Table 3: "After adjusting for confounders …." Why isn't race/ethnicity included in the multivariable model? Some recent research has suggested differences in percent mammographic density (adjusted for BMI) by race.

a. Given that parameters did not change with additional adjustment for race/ethnicity, we presented the more parsimonious models. We have added the following sentence “Estimates did not change with additional adjustment for race/ethnicity.”

12. * Page 6, lines 20-22: "… adult hair dye use was associated with higher percent density (beta 3.5; 95% CI: 0.6, 6.4) …" I respectfully disagree with this interpretation: given the wide confidence interval and the small beta, I don't think this result suggests strong evidence of a positive association. In fact, differences in percent mammographic density of less than 5
percentage points are not generally considered meaningful with respect to breast cancer risk. Similarly, in the Discussion (page 7, line 9), these results are suggested to be "consistent" with the literature showing positive associations between hair product use and breast cancer risk. I disagree; these generally null results for mammographic breast density suggest that the pathway from hair product use to breast cancer risk, if causal, may not operate through mammographic density.

a. We removed our statement regarding our findings with hair dye from the Discussion section.

13. * Page 6, lines 27-29: Readers may be interested in seeing the results for duration of hair dye use in a Supplementary table, if possible.

   a. We have placed the duration of hair oil use in the last paragraph of the results and provided more statistical information in the Methods section.

14. * Page 7, line 27: "Moreover …" There is a typographical error in this sentence.

   a. Thank you for catching this. We have corrected.

15. * Please be consistent in categorizing variables across tables and throughout the text. For example, age at menarche is dichotomized at <12 vs. 12+ in Table 1, but <11 vs. ≥11 in Table 2. It would be more helpful to see the distribution in Table 1 that corresponds to the way the variables were handled in the analysis.

   a. Thank you for this oversight and we have checked and corrected the manuscript and tables for consistency.

16. * Table 1, footnote: Does the p-value represent the test for differences between cohorts?

   a. Yes, this statement was added to the footnote
REVIEWER 2

1. Page 7, line 27: The third sentence on this paragraph starts without introduction of the second studied breast cancer risk factor, ie. breast density. Or the first sentence should say "We examined two breast cancer risk factors: age at menarche and breast density." The authors mentioned these two factors in the Intro but here in the Method the sentences are not clear and/or cohesive.
   a. In the Methods, the third paragraphs first sentence was modified to read as follows: We examined two breast cancer risk factors: AGE AT MENARCHE AND MAMMOGRAPHIC BREAST DENSITY.

2. Page 7, Line 42: I would suggest changing epidemiologic data for demographic data.
   a. We have changed wording to “sociodemographic”.

3. Page 8, line 4-9: This sentence is not clear. Were the confounders selected a priori or when they changed the estimate by more than 10%? By "selected" the authors referred that these two confounders were tested or included in the models?
   a. We have modified this sentence for added clarity.

4. Page 8, Lines 13-20. This sentence clarifies better my previous point. This sentence should proceed sentence in lines 4-9. If all these confounders were tested (change greater 10%), there is no need to establish a priory. These whole section of confounder selection needs to be more clear.
   a. To add clarity in the Methods section, we have removed “a priori” to emphasize that all confounders were tested by the 10% rule.

5. Page 8, Lines 40-45. I suggest adding these results to Table 2 as an additional column and present them as adjusted for demographic covariates models. Even though they are not statistically significant, it is important that the risk is still higher after this adjustment. Also, authors showed adjusted models for breast density in Table 3 but not for age at menarche (Table 2), I am not sure why.
a. See Reviewer 1, No. 5 response

6. Page 10, Line 27-29: Typo
a. See Reviewer 1, No. 14 response

7. Page 10, Line 58: or the sample size is too small to detect this association in the White women population.

a. We have added the statement following this statement: “However, these associations may be limited by small sizes”

8. Table 3: It is not clear what the authors modeled in the breast density models, percent density? This should be clear in Table 3 and in the Methods text.

a. The first column in Table 3 details Childhood hair product use by percent density and dense area and then again for adulthood hair product use.

b. Paragraph 3 in the Methods details how we measured mammographic breast density as percent density and total dense area.

Warm Regards,

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