Author’s response to reviews

Title: State of the evidence 2017: An update on the connection between breast cancer and the environment

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Author’s response to reviews:

I again thank the reviewer for her careful reading of our manuscript and for her thoughtful suggestions for making the report stronger and clearer. We have implemented her suggestions as discussed below.

In response to reviewer comments, changes since our original submission of EHNE-D-16-00286, ‘State of the Evidence 2017: An update on the connection between breast cancer and the environment – Revision 1’ are indicated in yellow highlight in the revised (Revision #2) manuscript.

Responses to specific comments:

• In the abstract, we have changed the declarative wording on the relationship over time between exposure to toxicants and increased rates of breast cancer. The revised wording is now more consistent with the language used throughout the rest of the report.

• On page 26, we clarified the point by adding, “The earlier, short-term finding…”

• In Table 3 we removed the CAS numbers.

• On page 59, we specified the size of the study, noting that it was small. Nevertheless, because there are so few studies examining the relationship between exposures to chemical toxicants and risk of developing breast cancer, we thought it was important to keep the study in our review.
• On pages 66 and 68-69, we have specified the number of controls in the respective case-control studies.

• On page 70, we added a brief phrase noting that, “no direct relationship can be inferred.” Similarly, in other places in the review when we present ecological data, we acknowledge the limitations of community-based (or county-based, etc) data in drawing conclusions about relationships between environmental factors and disease risk.

• On page 72, we rewrote the sentences to clarify the results of the study.

• On page 122 (now 123), we changed “’causes a significant increase in risk” to ”has been associated with an increase in risk”. We agree totally that the use of the term “cause” is inappropriate.

• On page 123, the reviewer suggested adding a phrase like, “Presumably because these younger women had a strong family history…” We did not make this change because the researchers tested for a possible difference in OR’s for women with a family history of breast cancer, as compared to those without such a family history. Although there was a higher OR for those with the family history of breast cancer, the difference was not statistically significant.

• On page 125, we have simplified the language of the second sentence to make the important point and get rid of the existing confusion.

• On page 126, we have acknowledged the ongoing controversy about possible relationships between cell phone use and brain tumors, while still positing that the data connecting EMF exposures and breast cancer is even weaker.

• We though long and hard about the suggestion to possibly include more specific comments on `methodological quality of the data being reported in the current review, presumably in comparison to our earlier report. We did add one brief and very general sentence addressing this. (“Not only has the corpus of the literature expanded in size over the past several years, but it has also been enhanced by greater depth, breadth and complexity.”) We also believe that our together, the discussions presented in our Methodology and Introduction sections address the strengths of the current literature (and changes over the past several years) in a bit more depth.

The remainder of the discussion, written (happily) in response to suggestions from the previous review, really is looking forward, starting with a review of the strength of some of the studies reported in the current review and then turning to methodological issues that still present challenges to making even stronger statement linking many environmental toxicant exposures to increased risk for developing breast cancer.
• With apologies for the sloppy (and repeated) error, all of the tables have been recreated to include the appropriate language for the carcinogenicity classifications as determined by IARC and NTP. Changes have been made in the tiles, bodies, and legends for these tables.

Additionally, with the text of the manuscript, we have move away from using ‘known carcinogen’ to designation as a ‘carcinogen’.

• We have corrected all the typographical and spelling errors pointed out by the reviewer. We have also done a tight read of this revision and found other ‘typos’, all of which we have corrected.