Reviewer's report

**Title:** Breast density in birth cohorts of Danish women: A longitudinal study

**Version:** 3 **Date:** 25 April 2013

**Reviewer:** Giske Ursin

**Reviewer's report:**

Response

This manuscript is much improved. However, in my opinion it still overstates the findings. Further, there are some serious limitations that the authors ought to acknowledge more clearly in the discussion. Doing so would substantially strengthen the manuscript. It is an intriguing finding, but the interpretation must be toned down and the limitations clearly stated.

Specifically – major concerns:

1. Concern regarding gliding assessment over time, and the possibility that the radiologist’s previous assessment can have affected the current one: This is a limitation of the design, and should be stated as such. The fact that 31% of the mixed density mammograms were, upon a reread reclassified as BI-RADS 1 seems high, and confirms my concern.

   The possibility of this type of bias, which some might call a reporting bias, should be added as a limitation in the discussion. This is a serious limitation of the paper, and may have resulted in systematic bias, i.e. failure to find an effect of age. It therefore needs to be spelled out clearly.

2. Sensitivity analysis confirming age- and birth cohort effects. It is not clear based on what is presented (or explained in the letter) why this confirmed the age-effect.

3. Potential for SES bias, in particular BMI: Since there is no data that BMI did not adversely affect drop-outs in the study, we do not know if that occurred. Again, this is a limitation that should be spelled out in the discussion.

4. There is something strange with these findings. I am concerned about the classification, and in particular the proportion of fatty to mixed dense. Why this is a reasonable method should be backed up further. Also this should be commented on in the discussion – as a limitation.

5. Background: The sentence “on perinatal exposures” should be omitted. This is still rather far-fetched, and in my mind detracts from the manuscript.

6. Discussion: General comment: The findings from this study should be toned even further down. Also see 1-4 above for limitations that need to be spelled out more clearly in the discussion.
7. The second sentence in the discussion is somewhat misleading. It sounds as if the authors have done a completely different analysis on individual data. What I think the authors mean is that they found that the age effect was not observable after adjusting for birth cohort.

8. There are several strong statements in the discussion that recall, reporting and selection biases were unlikely. The recall bias issue is not an issue and should be simply omitted. There might very well be strong reporting bias (see 1 above). This statement should be omitted, and a more thorough discussion of the possible for biases should be added. As for selection bias, see below.

9. The sentence on selection bias should also be altered – there might very well be selection bias, the authors simply do not have that information – see SES/BMI above.

10. Discussion – 3rd para, first sentence – needs to be reworded.

11. Note that the absence of known systematic changes does not mean that there were none. This sentence on page 13 should be altered.

12. The sentence that the true biological decline is not expected to be constant...is hard to follow with the double negative, and I disagree, there could be other gradual changes.

13. The discussion does not mention that the measure of density used is a rather crude measure. This should be acknowledged.

14. The change in % density from 44% to 34% (Verheus et al.) is not a small change. The sentence describing the "small" decreases related to menopausal status is therefore misleading and should be rewritten. The fact that no change was seen from age 50-51 to age 52-53 is a strange argument. This should be toned down as “evidence”.

15. Bottom paragraph on page 14: it would probably be better, or at least less controversial if the authors removed the "higher background burden...." and replace with " a number of factors". I suggest adding a comment that changes in formulation/dose of postmenopausal hormone therapy could have mattered.

16. The BCSC finding on page 15 is left hanging - it should be moved up or removed altogether.

17. There is no discussion of the general limitations with age-period cohort modeling. This should be added. Then the conclusion should sum up that this type of analysis have a number of limitations and must be interpreted with care.

Minor:
Suggest change mammographic density status to mammographic density category to make it easier to understand.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

no competing interests