Reviewer’s report

Title: Breast Density in Birth cohorts of Danish Women: A Longitudinal Study

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Reviewer: Giske Ursin

Reviewer’s report:

This is a well written article on an interesting issue. As the authors state, there are very few previous data on this, and thus the authors should be complimented for addressing this issue.

MAJOR COMPULSORY CHANGES:

However, there are some inherent weaknesses with the design that make the interpretation of these findings challenging. These weaknesses could be better described, and taken into account in the discussion and interpretation of findings. The findings and conclusions from this study should be toned down to reflect these challenges.

The authors use mammographic density data obtained at different time periods to determine whether the changes over time are predominantly due to age or cohort effects. The problem is that the density is not assessed all at one time, but at each screening. Therefore changes in film, technique, equipment and assessment over time could have affected the mammographic density readings. How this was in Denmark during this time period is not discussed. This can be a challenge because if there were systematic changes then this could have caused some of the findings that are attributed to cohort effects.

An added problem is that the assessment (whether a woman had a fatty breast or not) appears to have had clinical implications, i.e. if a woman was found to have mixed or dense breasts, then she would be called in for a two-view mammography at the subsequent screening, otherwise only one view. This may be why there are essentially no declines in % of women with mixed/dense breasts from their first image in their early 50s to ten years later (diagonal in Table 2). This is a problem with the design and may be why there are no changes with age within one cohort, which we would have expected based on other studies.

It also seems possible that a radiologist’s previous assessment of each woman could have affected the current assessment – again this reflects the challenge with this design. There was no way of doing this blinded, because obviously either the radiologist had two views (i.e. previously this was assessed as mixed/dense) or there was one view (previously this was assessed as fatty). Thus, this appears to be another challenge.

In Copenhagen there was an added radiologist towards latter part of the period. It
is not clear how similar the two radiologists were, nor on whether there was any attempt to keep the definitions the same over time.

Copenhagen coverage decreased from 70 to 61% during study period. Was it predominantly higher or lower socioeconomic status women that stopped attending? Would the ones that dropped out be expected to have lower SES in general (higher BMI), and thus could it have been the low mammographic density women that dropped out, which compounded the problem with this design?

The authors do not discuss the linear versus non-linear components of these models displayed in Table 4. Some more space could have been allocated to modeling and interpreting the non-linear parts of these various effects. In particular, it looks as if it is particular the younger cohorts that are different.

There is no explanation on how the modeling in Table 4 are done – how were the adjustments made? With linear terms? Categorical terms?

What happens if the age effects are modeled only with the linear cohort effects? These analysis should be done and discussed.

How did various age adjustments affect the birth cohort results? Only as a linear term? Why would this be adequate given the menopause issue? The authors should discuss this and the inherent assumptions, results and challenges with various adjustments.

The part on perinatal exposures having an effect should be omitted or modified. This evidence is tenuous at best, and even if there are such effects, it is not clear how strong they might be or if they are even close to effects of other lifestyle factors. The focus in the introduction on whether these (of all) factors have changed over time and caused the observed changes is therefore somewhat strange. This should be rewritten, and the abstract, discussion and conclusion should be modified accordingly. The authors could alter it to state that changes throughout a woman’s life can have caused any cohort effects, to better fit with what we currently know about mammographic density.

Breast density is an unfortunate term that implies something with the consistency of the breast, and is often misunderstood by women and investigators outside of the field. Please use mammographic density throughout.

MINOR:

In the description of the Copenhagen reevaluation study – when N is less than 100 – it would probably be better with both % and N.

Level of interest: An article of importance in its field

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