Reviewer's report

Title: Is there excess mortality in women screened with mammography? A meta-analysis of non-breast cancer mortality

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Reviewer: Arnaud Seigneurin

Reviewer's report:

The question of an excess of non-breast cancer mortality associated with mammography screening posed by the authors is very interesting. Indeed, these findings could be used to update the assessment of the risk/benefit balance of mammography screening.

The authors used an appropriate method to answer this question, a meta-analysis of randomised controlled trials.

However, I suggest mainly modifying the discussion with more comments on the main result of the study, i.e. the absence of an excess of non-breast cancer mortality associated with mammography screening.

• Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1. Discussion: I suggest focusing mainly the discussion on the findings of this meta-analysis. Indeed, the most part of the discussion concerns false positive results and overdiagnosis but not non-breast cancer mortality. The discussion about other side effects such as false positive results and overdiagnosis is interesting to assess the risk/benefit balance but this part could be shorter.

For example, the authors suggest (page 9) rewriting brochures considering the presence of false positive results, overdiagnosis and the results obtained in the Cochrane Library meta-analysis about the effect on overall mortality. This is an important discussion but not directly related to the absence of excess non-breast cancer mortality associated with mammography screening found in this study.

2. Discussion, page 10: "The literature shows high level of overdiagnosis"

The authors reported only articles which showed a high proportion of overdiagnosis whereas several other articles reported lower estimates (for example, Njor BMJ 2013, Puliti Eur J Cancer 2009, Duffy Journal of Medical Screening 2010, De Koning Breast Cancer Res 2006, Paci Breast Cancer Research 2006).

Indeed, the estimation of overdiagnosis is controversial in the literature mostly due to methodological issues (for example, adjustment required for lead time, how the evolution of breast cancer risk with successive birth cohorts is taken into account etc see Duffy British Journal of Cancer 2008) and the type of estimator used (see De Gelder Epidemiologic Reviews 2011). Such a discussion is
probably beyond the scope of the article but the authors could highlight the wide range of estimates in the literature. Moreover, the estimates given in the discussion are not necessarily comparable: increase of incidence due to overdiagnosis, proportion of overdiagnosis among breast cancers screened or diagnosed etc (see again De Gelder Epidemiologic Reviews 2011).

The authors provide a list of difficulties associated with the estimation of overdiagnosis (page 11). The accurate discussion of these difficulties is not directly related to the main question of their study (effect of screening on non-breast cancer mortality) and could consequently be shortened. However, if the authors want to discuss these points, I suggest categorizing the difficulties:

- Natural history not well-known for "the development of some tumoral lesions of the breast is not well known. Some authors suggest that the natural development of some invasive cancers detected during screening is spontaneously regressing,[47]"
- Improvement of the quality of mammography for "mammography quality is becoming more and more efficient"
- Lack of accurate data about mammography screening for "and in the case of France, the combination of mass and individual screening"
- and I would suggest to add the methodological issues, which is probably the main difficulty and the main cause of discrepancy between studies, with the difficulty to estimate the lifetime risk of breast cancer "there is an interaction between numerous known risk factors (e.g. hormone therapy, smoking) and unknown risk factors that depend on what year the women were born,"

and the adjustment required to take into account lead time.

3. In the Abstract, page 2: "This maximum percentage of mortality was calculated using the upper limit of confidence intervals in good-quality methodological studies. These findings were supported by those of the Cochrane Collaboration: out of 2,000 women screened for 10 years, 1 had prolonged life expectancy, and 10 received unnecessary treatment because they were healthy and would not have been diagnosed without screening."

Why an effect on mortality is supported by a number of unnecessary treatments received? This is rather a possible explanation considering that an unknown proportion of women unnecessary treated will die as a consequence of the treatment.

Actually, the authors considered that the excess mortality could be at maximum 12 deaths per 1,000 women (i.e. 24 per 2,000 women) and the Cochrane collaboration found that among 2,000 women screened for 10 years, 10 received unnecessary treatments. These 2 figures are difficult to compare because we don’t know if the excess mortality was calculated among women screened during 10 years. Moreover, the excess mortality (24 deaths) would be superior to the number of women unnecessary treated (10)!
This previous comparison carried out by the authors is probably not relevant as the main result of the meta-analysis is an absence of an increase of non-breast cancer mortality associated with screening: whatever the number of unnecessary treatments, they don't seem to involve more deaths.

• Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

4. Introduction section, page 3:

"Although a decrease has been observed in the standardised mortality ratio for breast cancer patients worldwide (6.8/100,000 women from 2000 to 2008),[2] the incidence of breast cancer nearly doubled in 25 years, from 56.8/100,000 women in 1980 to 101.5/100,000 women in 2005.[3]"

The authors should specify if 56.8/100,000 women in 1980 and 101.5/100,000 women in 2005 refer to standardized incidence rates (world population).

5. Methods section, page 5:

The methods section should indicate that the PRISMA statement was followed for the analysis.

6. Methods section, page 5:

"The main endpoint was non-breast cancer mortality at 13-year follow-up."

I was wondering if the 13-year follow-up was calculated from randomization. This information should be specified.

7. Results section, page 7:

The authors should refer to Table 2, Figures 1, 2 and 3 in the results section.

8. Results section, page 8:

"There was not any significant difference between the two groups, OR = 1.00 [0.98-1.03] ..."

This is probably an OR for non-breast cancer mortality but it should be clarified in the text.

9. Results section, page 8: the following sentence is unclear and should be rephrased.

"The following data were obtained after calculating the maximum quantification of screening the negative effect (i.e. the upper limit of deaths induced by screening if such negative effect exists)"

10. Discussion: the limits and strong points of the study are briefly discussed but this part could be longer. For example, the quality of the assessment of the cause of death in the different trials could be discussed more in details.

11. Discussion: the authors suggest in the discussion that overdiagnosis and overtreatment are possible explanations for an increase of mortality associated
with mammography screening. However, the results obtained in this meta-analysis show that no increase of mortality was observed. Consequently, comments on the possible causes of an increase of mortality are not very useful in the discussion.

12. To explain the result obtained, data about the mortality associated with the main types of treatments carried out for early stage breast cancer (which are more likely to be overdiagnosed) would be interesting. What is the mortality associated with localized surgery, radiotherapy and hormonotherapy which are the main treatments for early stage breast cancer? Such data from the literature could help discussing the results obtained. If these data show that the number of death related to these treatments is low, it would be consistent with the main findings of the study.

13. Discussion: a 13-year follow-up includes deaths related to short and middle term consequences of treatments (death during surgery etc..) but this length of follow-up may exclude some long term deaths related to mammography. For example, deaths related to radio-induced breast cancers (these deaths might however be negligible). Comments could be added about the length of the follow-up considered in the study and some long term deaths which might be excluded.

14. Discussion: based on the result of this study and previous meta-analysis, mammography screening is associated with a decrease of breast cancer mortality, no effect on overall mortality and no increase of non-breast cancer mortality. A possible explanation concerning these findings could also be added in the discussion. For example, the proportion of breast cancer deaths among the total number of deaths could be reported to see if a low number of deaths due to breast cancer could explain these previous findings.

15. Discussion: the authors suggest adding in the brochures data concerning the side effects of screening, especially the presence of false positive results and overdiagnosis. Based on their results, they should suggest adding their findings (no excess of non-breast cancer mortality associated with mammography screening) in the brochures.

16. Discussion section, page 10:
"In France, this rate is 12% for the initial screening."
A reference should be added.

17. Conclusion section, page 12:
The conclusion should be rephrased to be directly related to the main result of the meta-analysis carried out.
Indeed, the following sentences:
"Even so, recent studies recommend being careful and challenge the idea of mass screening with mammography in countries where screening has been used for a long time.[46-49] The concept of screening is appealing for lots of
caregivers and patients."

are not directly related to the findings of the study, i.e. no excess of non-breast cancer mortality with mammography screening.

Moreover, the need of individual modelling to assess the risk/benefit balance of screening is very interesting but it should be better related to the findings of this study and its limits or unanswered questions.

18. Discussion section, page 9: the following sentence is unclear and should be rephrased "Excess non-breast cancer mortality was excluded with the calculation of the limit quantification for a possible screening negative effect, with a maximum of 4% in the relative risk for women screened with mammography, i.e. 13 to 29 deaths induced for 100,000 screened women/year (upper limit of deaths induced by screening if such a negative effect exists, based on good methodological quality studies)."

19. References, page 13

Heading:
REFERENCES instead of "REFERNCES"

Reference number 3:

instead of

• Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

20. Introduction section, page 3
"In France, breast-cancer mortality is the leading cause of cancer death in women with 11,781 deaths in 2008.[2]"


21. Introduction section, page 3
"Apart from mass screening, personal screening continues to be used."

The authors could use the term individual screening instead of personal screening.

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests