Author’s response to reviews

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Development of breast cancer mortality considering the implementation of mammography screening programs – a comparison of western European countries

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Notes:

- All changes related to the comments were highlighted in yellow in the revised manuscript.
- We also added page and line numbers in the comments to avoid any misunderstanding.
- Additionally, we kept the track-changes for the important parts to be able to reconstruct the changes.

Reviewer 1: Jacques Fracheboud, M.D.

1. Consider to add in the Abstract Conclusions to add "(accelerated)" - between brackets - before "reduction of breast cancer mortality rates.

→ Thank you very much for suggesting this edit, the little nuance makes it more comprehensive.
2. Background, L9: consider to replace reference 5 (Moss et al.) by another RCT with focus on the 50-69 age group.

   Thank you for pointing this out. The UK Age trial might indeed not be the best example of an RCT focusing on the evaluation of the effectiveness of MSPs for the age range (50-69) we are analyzing. However, it was one of the largest and more recent RCTs performed and one of its objectives was to evaluate the effects of an MSP start at the age of 40. We believe that the insights and conclusion from the UK Age trial study help the reader to understand that this is another important aspect to think of when evaluating MSPs, even though we focused on the age range 50-69, which is more common among the western European countries we analyzed. We clarified the sentence and added an additional reference which evaluated the other Swedish RCTs conducted in Malmö, Stockholm and Goteborg. (p.3 li. 8-10)

3. Legend Table 1, 1st sentence: "more or less complete national screening" is still not very clear. The fact that everywhere in the country programme mammography has started (= 100% geographical coverage; e.g. Austria, Belgium, Germany, Italy) does not always mean that the total target population has been invited at least once (= 100% coverage by invitation; e.g. The Netherlands, Norway, Sweden, UK). This problem is tackled by "more or less"; I suggest to replace "national screening" by "national coverage".

   Thank you for pointing out this important detail. We rephrased the sentence by differentiating between geographical coverage and coverage by invitation as suggested.

4. In Switzerland, the coverage by invitation was in 2012 37% (Swiss Cancer Screening. Rapport de monitorage 2012. Bern: Swiss Cancer Screening, December 2015; www.swisscancerscreening.ch) and only recently reached more than 50%; it shall probably never reach 100%. I recommend to add a footnote for Switzerland in Table 1.

   Thank you for the suggestion. We added a footnote to explain the specific situation in Switzerland with the respective values found in the monitoring report from 2010-2015 on p.4 li.23.
Reviewer 3: Robert Smith

1. Page 2, line 8: References 3-5 work fine for covering the additional trials, but the authors should say "additional," rather than several. The Two county Trial was one of 4 trials conducted in Sweden (Malmo, Stockholm, and Gothenburg), and then there was the Edinburgh trial and the UK Age Trial in the UK. The word several only refers to two or three…and would not ever be used for 4 or more, whereas “additional" can refer to 1 more, or 100 more.

   → Thank you for the suggestion. We changed the wording accordingly and also added an additional reference (please see comment 2 for reviewer 1 as well).

2. Page 3, Table 1: About half of the counties in Sweden invite women aged 40+ to screening. If you've chosen to only examine women aged 50-70, you need to acknowledge that the policy of what age groups are invited varies by county, and that counties that invited women in their 40s will influence the data at age 50 compared with counties that begin issuing invitations at age 50 (incidence rates at age 50 will differ due to prior screening). There may be one or more countries in Europe that invite women to screening at age 40 or 45. You can check the most recent IARC Handbook for a description of screening programs.

   → Thank you for pointing out this important detail. Since we try to assess MSPs on a western European level in an ecological study approach, it will be difficult to consider all the intercountry or even intercounty differences in our analysis. We definitively agree that it is important to clarify these differences as much as possible and therefore added the information in the footnote for Sweden and Spain on p.4 li.18-22.

3. Page 4, line 24: It is common when listing the confounding variables that complicate the evaluation of the effectiveness of MSP in reducing breast cancer mortality….but what commonly isn't mentioned is the improvement in screening and diagnostic quality over the years. The evolution from film to digital systems has improved sensitivity in women with dense breast tissue, radiologists are considerably more skilled today than they were in the 90s, etc. It is worth mentioning, to avoid giving the impression that imaging has not changed to the benefit of patients, while treatment has.
We added this piece of information about how diagnostics have changed in parentheses on p.4 li.30. This will give the reader a better idea of how the situation on diagnostics has changed.

4. Page 4—one thing I notice is that each reviewer had some difficulty with the methodology, i.e., " our study focuses on the effect through the implementation of the MSP policy, rather than the isolated effect of the measure itself." I'd suggest reshuffling some of the sentences between lines 24 and 36…specifically (If I may)…..

Across Europe, a debate emerged on the effectiveness of MSPs with regard to their ultimate goal of reducing breast cancer mortality on the population level [18, 19]. Decreasing breast cancer mortality due to advances in diagnostics and treatment but also opportunistic screening and low MSP participation makes it difficult to analyze the isolated effect of a population wide MSP on breast cancer mortality [6, 9, 20]. [insert] Additional contributing factors such as attention or popularity in media, the public discussion of such an extensive health policy and consequences taken by individuals through the awareness are too heterogeneous between the different populations and are therefore analyzed as the aggregate effect of implementation. Thus, we chose an ecological study approach to compare the developments of breast cancer mortality across western European countries. Therefore, our study focuses on the effect through the implementation of the MSP policy, rather than the isolated effect of the measure itself.

Thank you for the suggestion. We adapted the edit and agree that it is more comprehensible to the reader now.

5. Page 8, line 27: I recommend replacing reference 29 with this one--Swedish Organized Service Screening Evaluation Group. Reduction in breast cancer mortality from organized service screening with mammography: 1. Further confirmation with extended data. Cancer Epidemiol Biomarkers Prev 2006;15:45-51. There were two papers (1 and 2) in this issue of CEBP, and they address outcomes of MSPS in 13 Swedish regions. Reference 29 only deals with 2 counties.
Thank you for suggesting this more recent and extensive reference for the Swedish regions. We have replaced the reference accordingly.

6. Page 9, line 30: There are few population data that show that unscreened women are benefiting significantly, and in an accelerated manner, from improvements in therapy, so the statement that it is more difficult today to show a benefit of screening than it was 30 years ago is misleading. There have been improvements in therapy and they have benefited women who unexposed to screening (as well as women exposed to screening), but these gains appear modest and do not compare with the advantage of early detection, then and now. The arguments advanced by Gotzsche and Welch (references 35, 36) are pure, speculation with no supporting evidence. Further, the recent analysis by Tabar, et al (reference 34) observed a 60% reduction in the incidence in fatal breast cancer (with each woman having 10 years of follow-up) comparing women exposed to screening with women not exposed to screening based on the year of diagnosis, which means that there is a direct comparison of an exposed and unexposed group, each receiving whatever therapy was the standard of care based on their stage at diagnosis in the diagnosis year. This evidence does not support the conclusion advanced by Gotzsche and Welch separately that mammography (more specifically, early detection) is becoming less relevant as treatment becomes better. There is no adjuvant or chemotherapy that overcomes the advantage of having a cancer diagnosed while small and still localized. While some of these are slower growing, others have been detected early in their natural history and will not have the opportunity to progress to a more aggressive, potential lethal breast cancer. As Tabar, et al noted, women who attend screening benefit substantially more from modern therapy than women who do not attend screening. If this were not true, the difference in the incidence of fatal breast cancers would steadily narrow. It didn't. Other incidence-based mortality analyses done by the Swedish group have shown mortality reductions over time in unexposed women, but it is not clear what fractions of these improvements are due to increased awareness (reporting symptoms earlier) or modern therapy. But the difference in the pre and post-screening era was only about one-third of the reduction observed in women who were exposed to screening. The authors should be cautious about casual observations that could be used to further this conjecture that the importance of the detection of occult disease by imaging is less and less important. The recent evidence aptly demonstrates that this isn't true. We would be fortunate if it were……but it isn't.

We generally agree with the reviewer to be cautious about the interpretation of observations. We removed this potentially misleading statement. Furthermore, we want to highlight that our study is intended to clarify or add to this discussion.
7. Page 10, line 7. The statement that the analysis is not based on incidence-based mortality was not an intent of the analysis (isolated effect of MSPs vs. overall effect) implies that unrefined mortality rates are just as useful for measuring the impact as refined mortality, where screened and unscreened cohorts are isolated. The point is, for the first 10 years after the program was initiated, about half of all breast cancer deaths are due to diagnoses before the program was launched. The effect this may have on the joinpoint analysis should be described.

→ Generally, we agree with the reviewer and therefore extended the sentence as follows:

“Furthermore, we did not use incidence-based mortality rates even though this may have shown a stronger decline since in the early years, most deaths have already been diagnosed before MSP implementation. However, this data is not directly available for all countries. Additionally, our study did not assess the isolated effect of the MSP itself, (…).”

However, there are problems when analyzing incidence-based breast cancer mortality on a population level. As shown in table 1, the MSPs were not implemented comprehensively across the countries within the same year. Therefore, in our ecological study, we would need county-specific incidence and mortality data, which are not available for most of the countries.

8. Page 10, line 26: The authors should cite the updated IARC estimate of the expected mortality reduction rather than the 2002 estimate.

→ Thank you for mentioning this aspect. We intended to include the 2002 data to show that between the 2002 and 2016 evaluation, regardless of all the recent controversial discussion, the results of the evaluation of effectiveness of MSPs remained the same. We decided to exclude the 2002 data though and have rephrased the sentence to focus on the 2016 review only.