Reviewer’s report

Title: Development of breast cancer mortality, considering the implementation of mammography screening programs - a comparison of western European countries

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Reviewer: Robert Smith

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PUBH-D-18-01877R1 Development of breast cancer mortality, considering the implementation of mammography screening programs - a comparison of western European countries

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.

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.

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.

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.

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.

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.

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.

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

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

No

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