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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This is an interesting analysis of trends in registry data in countries with mammography screening programs (MSPs).

Introduction: The authors approach the issue of evaluating mammography screening programs as if it has received little attention, which is odd given the number of manuscripts cited from the Journal of Medical Screening 2012 supplement. Only one randomized controlled trial (RCT) is cited (the Swedish Two County Trial), whereas there were 9 RCTs conducted, and many more meta-analyses of the trials. Depending in inclusion and exclusion criteria, including age, a range of relative risks of death associated with invitation to screening have been observed, but still all are significant. More recent focus, since the 1990s has looked at the evaluation of service screening. The authors are correct that it is complex, but they do not describe the complexities in enough detail. To mention a few, there is the 1) time of introduction, rate of population inclusion, and rate of uptake; 2) the age group invited and the attendance rate of the mature program; 3) quality of screening and the screening interval; 4) isolating screened and unscreened cohorts; censoring deaths from women who die in the evaluation period, but were diagnosed prior to the introduction of screening, and prior to their invitation to screening; 5) duration of follow-up; 6) trends in incidence, including birth cohort and period effects, 7) etc, etc, etc. Having said that, many countries have made the effort to evaluation their programs, and the introduction, thin on the RCTs, is further vague on the studies that have taken place in Sweden, Norway, the UK, Netherlands, Denmark, Italy, etc. There are numerous citations, but they are covered in the new IARC Handbook (15).1 It is odd that the 2002 IARC handbook is cited, and the NEJM summary (reference 32) is cited, but not the new handbook. Evaluation methods, specifically incidence-based mortality analysis,2, 3 and the incidence rate of fatal breast cancers,4 address these challenges, and specifically, have been conducted on a population basis with attention to both invitations to screening and exposure to screening in the target group; the difficulty achieving this attention to detail complicates trend analyses and in general can lead to an underestimate of the benefit. Further, disentangling wild type screening and the influence of therapy are the only challenges described in the use of trend data….there are many more issues to address, and failure to address these issues leads to stunningly flawed articles with incorrect conclusions, such as reference 33. The further irony here is that reference 33 is exactly the sort of article that, had it even its methodology had been competent, and it had concluded that mammography was beneficial, the methodology would have been judged to be insufficient to adopt mammography screening on a population basis. Only favorable results from an RCT would be acceptable. Well,
we have those. And yet, Autier, et al. challenges the results of the RCTs based on a poorly designed ecological study.

Methodology: There have been good trend studies, and the methodological issues are described by Moss, et al. in reference 21. In this analysis, there is no adjustment for deaths that occur in the evaluation period but were diagnosed before screening was initiated, deaths among women in their 50s due to a diagnosis in the 40s (in most countries women would not have been invited) and there is no adjustment for trends in incidence, nor are these factors mentioned as limitations.

Discussion: The opening sentence suggests that this analysis is answering a vexing question, although tentatively ("...the implementation of MSPs has contributed to the reduction of breast cancer mortality."). It would be more appropriate to concluded that the analysis of mortality trends further supports the extensive literature on the effectiveness of mammography screening programs, and is in contrast with trend analyses that question the effectiveness of MSPs. With respect to the influence of therapy, there are studies that have compared women exposed to screening and women not exposed to screening and have shown both the positive effects of new therapies over time in reducing deaths in women who did not attend screening, but more to the point, the morality reductions are considerably greater in the women who attended screening. This observation was recently demonstrated more conclusively in reference 4 below. Regarding overdiagnosis, it is not relevant in this instance because the study is focused on mortality. Women who are overdiagnosed do not die from breast cancer.

Page 9, line 18. The working group for the IARC Handbook 15 was a different group than the one that worked on Handbook 7.

I would recommend against citing reference 33. It is deeply flawed and does not credibly challenge the evidence for the effectiveness of mammography.

In general, this manuscript should not treat the efficacy of mammography screening as a still open question; rather, it should focus on the ability of population registry data to be used to evaluate MSPs that commonly target less than half of the female population and have variable attendance rates.

References
Are the methods appropriate and well described?  
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No

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Yes

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