

Peer Review File

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Reviewer A

Comment 1: This commentary on mammography screening in women aged 70 years and above seems rather superficial and formulaic. In particular, the treatment of the likely effect on breast cancer mortality could be improved. It makes no sense whatever to take the attitude that screening is highly effective at age 69 but we have no idea whether it works at age 70. Breast cancer does not respect your 70th birthday.

Reply 1: The need to establish the efficacy of medical interventions in subgroups defined by age is a long established part of accepted medical practice before introducing such interventions. Screening women over the age of 70 should therefore not occur unless it is proven to be beneficial in this group

Comment 2: In relation to the above it is worth noting that this is only a real issue in developed countries where women have high life expectancy. In the UK, at age 70, a woman has around 17 expected years of life left. This is relevant both to the potential mortality benefit and to potential overdiagnosis.

Reply 2: The high life expectancy of women age 70 is already mentioned in the first sentence. The quantification suggested has been added.

Comment 3: The authors quote but do not reference a RR of 1.18 associated with screening in women aged 70 and over from the Swedish trials. This is either wrong or from incomplete data. As I understand it, the only Swedish trial screening women over age 70 is the two-county trial, which reported relative risks of 0.76 and 0.73 in the two counties (Tabar et al, *Radiol Clin N Amer* 2000; 38: 625-51).

Reply 3: The RR risk given by the referee for the two counties trial relates to all age groups in the trial not women aged over 70. The RR of 1.18 is neither wrong or incomplete but is in the overview of the Swedish randomized trials which is referenced (Nystrom et al *Lancet* 2002).

Comment 4: The treatment of overdiagnosis reports some circumstantial evidence of the likelihood of substantial overdiagnosis. Rather than arguing from such evidence, are there no explicit estimates of overdiagnosis? Duffy et al (*Stat Methods Med Res* 2010; 19: 547-55)

estimated that increasing the upper age limit from 70 to 73 in the UK programme would lead to approximately one additional overdiagnosed case per thousand

Reply 4: Over diagnosis has only been measured directly in women under 70 as there was only one study (Malmo 1) which never screened the control group so overdiagnosis could be directly measured. Unfortunately this group did not include women aged over 70. Given this lack of direct measurement in women aged over 70, inference from life expectancy, tumour biology and lead time is the best that can be done. The AgeX trial should be able to give robust information on this topic in a few years time.

Comment 5: The authors may be overoptimistic about the Agex trial which ceased recruiting with the COVID pandemic, and is now only in follow-up. It is not clear whether it is of sufficient size to deliver a definitive result.

Reply 5: The AgeX trial randomized 2 million women aged over 70 making it by far the largest RCT of mammographic screening in history, in addition the high cancer incidence will give the trial additional power compared to a similar size trial of younger women. I therefore find it difficult to see why it should not be sufficient size to deliver a definitive result.

Comment 6: It is stated that radiologist 'enjoy' reading mammograms from older women. Is enjoy the correct word here?

Reply 6: I agree that enjoy is not the correct word here, I have reworded the sentence
Changes in the text Radiologists also find reading screening mammograms in older women satisfying

Comment 7: The English would benefit from careful editing.

Reply 7: The manuscript has been carefully re-read and the English corrected.

Reviewer B

Comment 1: I think the major omission in this paper is the lack of any mention of what the patients want. There is also no mention of how life expectancy and competing medical issues factor into the decision to get screened. The paper seems to be saying that the decision to get screened or not is a societal, health system, or clinician one rather than a decision made by a woman.

Reply 1: The referee appears to have overlooked that there is an entire paragraph on attitudes of older women to screening. The decision of individual women to be screened or not

screened becomes an issue when it has been shown to be beneficial on a societal level and is offered routinely. We have not currently reached that stage.

Comment 2: It is hard to lump everyone over 70 together. Women between 70-74 are much different than women between 80-85, for instance. So, making a policy for all women over 70 may not be accurate.

Reply 2: I agree that if screening is shown to be effective in women over 70 additional work will need to be done to identify groups most likely to benefit vs those most likely to be harmed. A sentence to this effect has been added.

Changes in the text: If screening is shown to be effective in women over 70, additional work will need to be done to identify groups most likely to benefit vs those most likely to be harmed.

Comment 3: Discussion of the endpoint of screening programs-- decrease in breast cancer mortality-- is also very, clinician-centric. If we ask women, what is their end point.-- would they agree.

Reply 3: I am not aware of any other end point of the value for screening other than decreasing breast cancer mortality.

Comment 4: The discussion of pending results of the AgeX trial is interesting, but again, this trial completely took the patient out of the decision making. It also took the clinician out of the decision making sphere, which is surprising.

Reply 4: This is a comment which does not appear to require a response

Comment 5: Attitudes toward screening are likely different based on country of origin. Shouldn't a screening program take that into account?

Reply 5: I agree that attitudes to screening are important once efficacy has been shown and implementation is planned or is being discussed. We are not at that point in this age group as yet.

Comment 6: You state that radiologists enjoy reading mammograms in older women-- is there a citation for this statement? It may be more accurate to state that mammograms in older women are easier to read.

Reply 6: This sentence has been rephrased

Changes in the text: Radiologists also find reading screening mammograms in older women satisfying

Comment 7: I think it would be interesting to add a table with call back rates and negative biopsy rates by age.

Reply 7: Such a table has been added

Reviewer C

Comment 1: Introduction, 1st paragraph, line 16, older women and wider society should be defined.

Reply 1: Older women has now been defined as women > 70yrs, I am not sure how wider society can be defined so I have used the phrase society as a whole instead.

Comment 2: Introduction, 2nd paragraph, line 19, the authors should provide data to back up the statement that radiologists enjoy reading screening mammograms in older women.

Reply 2: Enjoy has now been changed and a data showing improved screen reading outcomes is provided.

Comment 3: In line 24 and throughout the paper, years should be added after 70.

Reply 3: This has been done

Comment 4: In the sentence starting in line 26, and throughout the paper, I suggest that the authors not use the term harms, but, rather, use the term negative consequences.

Reply 4: The use of the term harms to describe the negative consequences of mammographic screening is very widespread and accepted and so this has not been altered.

Comment 5: Introduction, 3rd paragraph, lines 29 and 32, I suggest Office of National Statistics.

Reply 5: This has been changed as suggested

Comment 6: In Screening of older women: evidence for benefit, 1st paragraph, line 39, is therefore can be cut. In line 41, doesn't should be changed to does not.

Reply 6: These changes have been made as suggested

Comment 7: In Screening of older women: evidence for benefit, 2nd paragraph, line 47, the sentence should start with Mortality.

Reply 7: Changed as suggested

Comment 8: In Overdiagnosis when screening older women, 1st paragraph, complete sentences should be used.

Reply 8: This section has been revised to include complete sentences.

Changes in the text(Inserted text): There are a number of reasons why screening women aged over 70 years would lead to a higher overdiagnosis rate than that found when screening younger women including decreased life expectancy, the presence of more indolent cancers and less masking by breast density leading to a greater lead time.

Comment 9: In Overdiagnosis when screening older women, 3rd paragraph, in line 63, I suggest: dying of causes other than breast cancer. In line 67, that should be added after means.

Reply 9: The suggested edits have made

Comment 10: In Overdiagnosis when screening older women, 4th paragraph, line 73, tomosynthesis should be tomosynthesis' In line 74, spiculate should be spiculated.

Reply 10: The suggested edits have made

Comment 11: In Impact of overdiagnosis on older women, line 79, the authors did not make it clear that a significant proportion of the cancers detected in women over 70 years represent overdiagnosis.

Reply 11: This sentence has been rephrased

Changes in the text (Added text): It is therefore clear that a higher proportion of screen detected cancers in women aged over 70 years represent overdiagnosis compared to women aged 50-69 years.

Comment 12: In line 92, that should be added before providing.

Reply 12: Edit suggested has been made