Reviewer's report

Title: Early detection of breast cancer: Benefits and risks of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue. A systematic Review

Version: 2 Date: 30 March 2009

Reviewer: Nehmat Houssami

Reviewer's report:

Major Compulsory Revisions:

General comments

The paper is too long and should be reduced in length – irrelevant details have been included in some sections. There are some errors in spelling of author names (eg. Crystal/ Christal) and language errors that require editing. The rest of my comments will focus mostly on content issues.

Specific comments:

1 -Abstract – the abstract is a critical part of the manuscript, yet it does not capture well the essence of the quality appraisal, see comment re Results in abstract.

2- Intro - ‘Mammographic breast density has been identified as a marker strongly associated with the risk of breast cancer detected by screening or between screening tests’ should be expressed with more clarity. I suggest: ‘Mammographic breast density is a marker of increased risk of breast cancer, and is associated with a higher risk of an interval cancer in mammography screening’.

3- Methods – ‘A systematic search and review of studies involving mammography and breast ultrasound for diagnosis of breast cancer was conducted’. Do you mean to say ultrasound for ‘diagnosis’ or ‘screening’?

4- Results: this section of abstract should commence with a clear statement that there were no RCTs of ultrasound in breast screening, and that all studies were of intermediate level of evidence (3b) at best (You bring this up at end of the paragraph but it should be stated upfront). You should also say that ‘few studies included adequate follow-up of subjects with negative or benign findings’. Then go on to reporting the detection data. This allows the reader to understand the extent/quality of evidence before seeing the actual data.

Manuscript

5- Introduction: This is very long, contains excessive and frequently irrelevant information, and overall detracts from the manuscript. It should be reduced to only a couple of paragraphs that are relevant/essential for the focus of your manuscript: your work is about adjunct ultrasound (US) in screening, please try
to stick to that aspect of breast US. Instead, you have given in the introduction a background about US in diagnosis, characterisation of solid nodules, an introduction to BI-RADS, German guidelines etc etc. With all due respect to the issues you cover in the Introduction and the US pioneers whose work you mention, most of these details are not necessary, so please get to the point and condense this section. Make sure you retain the relevance of breast density in terms of breast cancer risk and increased likelihood of interval cancers in screening.

6-the issue of adjunct screening US in women with mammography-dense breast is of international interest, so I think you might want to de-emphasise the German guidelines as the driver of this work (state that only once) and do not repeat it in the conclusion.

Methods
7- “Types of study” (p5): most of this is not necessary! A simple reference to the levels of evidence system and/or QA system you applied would suffice.

Description of inclusion and exclusion criteria is overly detailed and should be more concise.

Results
8- The paragraph under ‘Results of literature search’ is not needed – most of the text is already covered in Fig 1 and Table 2, why repeat it all here? I would just say this is represented in Fig 1 and exclusions are in T2, a summary line.

The rest of the results section is relevant but could/should be condensed, since T3 has most of the key data. Most readers will prefer to use a summary table rather than read excessive text.

Discussion
“Methodological”
9- ‘The target measure breast cancer mortality rate, was not reported in any of the studies’. I agree BUT I think it is not quite correct to state it as such, even though I understand what you mean. A better way of saying this is: ‘None of the studies of US in breast screening were RCTs, therefore studies were not designed to provide evidence on screening benefit in terms of mortality reduction’.

10- Berg’s study (2008, JAMA) – you have approached this study in a very unusual way in that (1) you have described it as a RCT incorrectly, assigned it the wrong level of evidence category in T1, and (2) decided to exclude it on the basis of its high risk population (I accept that is reasonable), BUT (3) you then detail the study and its findings in 2 entire pages in the Discussion!! Clearly, you regard this as a highly relevant study (and it is very relevant), but I think you can mention it in less detail if you have already decided it is not eligible for your SR. Irrespective of how you choose to include it, it is not a RCT of the intervention. The study is a well-designed prospective trial with randomisation of the sequence of imaging BUT all women had US screening as well as mammography. At
analysis, combined mammography plus ultrasound was compared to mammography alone. So, it is not a RCT of US or not.

“Content”
11- P 14: ‘…. the choice of study populations is explicable’ – unclear

12- Conclusion (1)’ the median size of the cancers thus identified being 9-11 mm’ – was this a pooled estimate calculated from your systematic review? Or was this inferred from the review by Berg? If the former, then how did you calculate it? If the latter, it is not appropriate to have it as a primary conclusion.

Tables
13- Table 1: Berg et al 2008: you refer to this as RCT – this is not correct. See my earlier comment on this.

14- Table 3: This is a key table in terms of summarising the evidence from the selected studies, so I think it is important to be sure you have not omitted relevant data. Please verify data for the following 2 studies:
- Crystal et al., 2003, From memory, this study included symptomatic/clinically-referred women and women at high risk due to varying reasons? – if so, then this may be against your defined inclusion criteria for eligible studies - so I think this should be checked and reported if appropriate since it will overestimate the PPV and detection rate, and may account for the higher reported PPV.
- Corsetti et al., 2008; in the column where you describe malignant histology and for some studies you report tumour size descriptives – for Corsetti et al you had ‘no details’ – refer to Table 2 in publication for pT data, these could be included instead, although a mean size was not reported.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

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

Declaration of competing interests:
None.