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: 1 April 2009

Reviewer: Wendie Berg

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BMC Cancer
Early Detection of Breast Cancer….Nothacker et al

General comments: Screening breast ultrasound is a very important topic. The presentation of the material is good, though there are some errors in translation (not all of which are not detailed below). There are some factual misstatements of the literature, which is concerning. It is a bit too much of a summary without focus.

Specific issues:

Major Compulsory Revisions

1) Abstract, Introduction: I am not aware of literature to say that mammography particularly misses cancers smaller than 2 cm in size, except that cancers larger than 2 cm are typically clinically evident and not seen as “screened” cases. Please clarify.

2) Introduction, second paragraph, add reference to the American College of Radiology guideline for the performance of breast ultrasound, and to the Canadian guideline.

3) Introduction, third paragraph, first sentence: The goal is truly to detect node-negative cancers. This is more likely when tumors are closer to 1 cm, not 2. Greater emphasis should be placed on the node-negative aspect and the literature, as well as the number of cancers found on ultrasound which are invasive and node negative. These messages are lost in this manuscript.

4) Introduction, third paragraph, second sentence, when the authors state “suspicious findings”, do they mean cancers?

5) Methods, first paragraph, third sentence: This is a major issue. In normal screening programs approximately 15% of women have some family history of breast cancer. Women with known risks were not excluded from the evaluated screening ultrasound studies as implied. See comments re: ref. 46 below.

6) Methods, p. 6, what is meant by “number” and experience of sonographer? It is important that most of the studies (all but Kaplan) used physicians to scan for
ultrasound; only Kaplan used technologists. This is not clear in Table 2 or the Results.

7) Methods, p. 7, would it have changed the outcome of the searches if “ultrasound” or “sonography” were used or if “breast neoplasms” was not included?

8) Methods, p. 8, it is not obvious what is meant by “clinically irrelevant noninvasive” breast cancer. I believe it should say “overdiagnosis” not “overdiagnosing” in this sentence also. Indeed, in ref. 31, I believe that many of the 10% of cancers “overdiagnosed” were invasive. The authors of this manuscript do not distinguish invasive and noninvasive cancer detection rates on mammography and ultrasound, and that is an important issue to discuss also.

9) Results, p. 9, second paragraph: I do not believe any of the studies discussed enrolled consecutive screenees.

10) Results, p. 10, several of the series discussed did not limit the ultrasound to women with negative mammograms, yet it is stated in the second paragraph that they all did. Please revisit this issue.

11) Results, p. 10, as is discussed later, not all series limited ultrasound to “high breast density” (a nonstandard term—please define “dense” and stick with that)—indeed, as stated on p. 11 first sentence, three included all nonfatty breasts (i.e. they included those with minimal scattered fibroglandular density). ACR category 2 is not “dense”. This is confusing as presented throughout.

12) Results, p. 10, second paragraph, not sure about style of period instead of comma for n=1517, etc.

13) Results, p. 11, 0.3% and 1.1% absolute what?

14) Results, p. 11, “high familial risk” is not representative of what is in the papers. Please reevaluate this. Some had “any” relative with breast cancer for example.

15) Results, p. 11, last paragraph, emphasis on < 2 cm is perhaps a bit misguided. If the authors stick with this, rather than emphasis on one cm size, then they should discuss this issue more completely. Again, the node status is more important and not discussed.

16) Results, p. 12, second paragraph does not agree with what the papers present. Kolb presents sensitivity of 75.3% for ultrasound and specificity of 96.8%. It is possible to extract specificity from Kolb’s paper. He states an NPV of 99.7%, not 100%.

17) Results, p. 12, last paragraph: I don’t know what is meant by the PPV of 10.3 to 30%. PPV can mean several things. PPV1 is cancers/recalls for additional imaging. PPV2 is the PPV of biopsy (per BI-RADS). This needs to be clarified throughout.

18) Discussion—While some would argue that an RCT with mortality as an endpoint is needed, there is considerable strength to modeling breast cancer at this time. This should be discussed.

19) Discussion, p. 15, last paragraph, the PPV of biopsies prompted by US is not
a mean of 18.8%. It is closer to 11% across these series. The actual number of biopsies performed should be considered.

20) Discussion, p. 19, last bullet, see comments above re: modeling.

21) Table 3, 4th column, not clear what this PPV means. See above comment.

22) Table 3, 6th column, not clear what “relative” means nor what “-/” means in front of some of the numbers.

Minor Essential Revisions

1) Abstract, Introduction, second sentence: I believe this should read “Increased mammographic breast density has been identified as a marker strongly associated with increased risk of interval breast cancer, i.e. cancer detected between screening tests.

2) Abstract, Results, third sentence, should read “half” the PPV “of” biopsies due to mammography, not “twice”.

3) Introduction, first paragraph, I believe there are 750 lesions in the 1995 study of Stavros et al, not 622 as stated.

4) Introduction, third paragraph, first sentence: change “nodular” to “lymph node”.

5) References: There are a number of minor typographical errors.


7) Introduction, third paragraph, fourth sentence, insert “mammographic” in front of “screening”.

8) Introduction, fourth paragraph, add discussion of the American Cancer Society guidelines and any other published national guidelines on this issue either here or in Discussion. The emphasis is clearly German; I would like to see this slightly less focused on German practice per se, as this is truly a global issue.

9) Methods, p. 6, criteria: heterogeneously dense is 51-75% not 50-75%.

10) Results, p. 9, second paragraph, second sentence: What is meant by “almost consistently” or “undeterminable”?

11) Discussion, p. 14, second paragraph, first sentence, change “diagnostic” to “screening”. Again, not all studies limited ultrasound to those women with negative mammograms.

12) Discussion, p. 16, last paragraph, blinded to the “other” modality, not “blinded to the modalities”.

13) Discussion, p. 18, #1—mammographically dense not “mammographical”.

14) Discussion, p. 18, split the false positive issue into a second bullet.

15) Table 1, include papers by Hou, HF 2002 from Taiwan at least as having
been considered.

Discretionary Revisions

1) It would be nice to see discussion of issues in implementation in addition to the further research to be performed.

2) Many of the weaknesses of the studies discussed are addressed in reference 46. While I understand the concern about elevated risk vs average risk populations, all studies presented did include some women at increased risk (despite the authors’ statement to the contrary). Indeed, by the American Cancer Society criteria (Saslow et al 2007), dense breast tissue puts a woman at intermediate risk. Supplemental screening ultrasound is only seriously being considered in women with at least intermediate risk for breast cancer, and the vast majority of participants in ref 46 are in that category. Please reevaluate the exclusion of this work from this analysis, and reevaluate which population would truly be considered for supplemental ultrasound screening.

**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:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I have received equipment software support from Siemens. I am a consultant to Naviscan, Inc., and to MediPattern.