Early detection of breast cancer: benefits and risks of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue: a systematic review

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CRD summary
This review assessed the risks and benefits of supplemental ultrasound breast cancer screening, in women with negative mammography and dense breast tissue. It concluded that ultrasound can detect small, otherwise occult, breast cancers, but there are potential adverse effects from additional biopsies. The authors' conclusions are reasonable, but should be interpreted cautiously, given weaknesses in the review and limited data.

Authors' objectives
To assess the risks and benefits of supplemental breast cancer screening with breast ultrasound, in women with negative mammographic screening with dense breast tissue.

Searching
PubMed, DARE and the Cochrane Library were searched from January 2000 to August 2008; search terms were reported.

Study selection
Studies that had adequate design (“poor quality case-control” studies were excluded) and adequate population (asymptomatic, primarily healthy women), and that assessed breast ultrasound as a supplemental screening technique for breast cancer, were eligible for inclusion. Included studies were required to use an ultrasound transducer frequency of over 5MHz. Included studies had to report breast density according to the Breast Imaging Reporting And Data System (BI-RADS) American College of Radiology (ARC) categories and/or quantification.

The median age of participants, where reported, was 47.6 to 60.7 years. All ultrasound positive results were confirmed histologically; one study reported use of follow-up as the reference standard in patients with negative ultrasound results. Studies included patients both with and without a history of malignancy. Two studies assessed women with breast tissue in categories ACR 3 (heterogeneously dense - high density, 51 to 75% gland parenchyma) to ACR 4 (extremely dense - very high density, more than 75% gland parenchyma); the other studies evaluated women with breast tissue in categories ACR 2 (scattered fibroglandular densities - average density, 26 to 50% gland parenchyma) to ACR 4.

The authors did not state how many reviewers performed the inclusion screening.

Assessment of study quality
The authors did not state that they assessed study validity, but some comments on methodological quality were included in the results.

Data extraction
Data were extracted on percentage of carcinomas identified by breast ultrasound, cancer detection rates by breast density category, size and stage of detected carcinomas, biopsy rate as a result of ultrasound, and the positive predictive value for the detection of additional malignancies for ultrasound prompted biopsies.

The authors did not state how data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Studies were combined in a narrative synthesis.

Results of the review
Six cohort studies, five of which enrolled consecutive patients, were included in the review. The total number of
participants assessed in the included studies was 29,772 (range 1,517 to 9,157).

Overall cancer detection rates, as a percentage of the population screened, reported for supplemental ultrasound ranged from 0.23 to 0.41% (six studies). The proportion of the total number of cancers diagnosed, which were detected by ultrasound ranged from 15% to 34% (four studies). The detection rates in ACR (American College of Radiology) category 2 breast tissue ranged from 0 to 0.4% (three studies), for ACR category 3 tissue detection rates ranged from 0.27% to 0.4% (three studies), and for ACR category 4 tissue detection rates ranged from 0.1% to 1.1% (three studies).

The mean size of identified tumours was 9.9mm, and 90% had negative lymph node status.

Biopsy rates ranged from 2.3 to 4.7% (five studies), with positive predictive values of 8.4 to 13.7% (four studies).

**Authors’ conclusions**

Supplemental breast ultrasound in the population of women with mammographically dense breast tissue (ACR 3 and 4) permitted detection of small, otherwise occult, breast cancers. Potential adverse impacts for women in this intermediate risk group were associated with an increased biopsy rate.

**CRD commentary**

The review addressed a clearly stated research question. Inclusion criteria were reported, but some were poorly defined. The literature search was limited and no details of language or publication status restrictions were reported, so it was possible that relevant publications may have been missed. Reporting of the review process was limited and no formal assessment of the methodological quality of included studies was reported. Therefore, it was not possible to assess the potential for error and/or bias.

The use of a narrative summary was appropriate to the studies included. Additional study details were reported in supplemental tables online (see URL for Additional Data field). The available data, on the performance of supplemental ultrasound screening, were limited; no sensitivity and specificity data were reported and the false positive and false negative results that would be generated by ultrasound were therefore unknown. Whilst the authors’ conclusion that supplemental ultrasound could detect small, otherwise occult, breast cancers, was a reasonable interpretation, it is perhaps worth noting that (based on the reported biopsy rates) approximately ten biopsies would be needed for every additional cancer detected by ultrasound.

Given the limitations in the review methods and available data, the authors’ conclusions should be interpreted cautiously.

**Implications of the review for practice and research**

**Practice**: The authors stated that, since the study populations had very broad age ranges, which included younger women, the impact of supplemental ultrasound in the context of a mammography screening program, including only women in the age group of 50 to 69 years, could be reduced.

**Research**: The authors stated that there is a need for prospective validating studies of risk-adjusted, second-line, supplemental breast ultrasound screening in women with dense breast tissue (ACR types 3 and 4), performed in the setting of established population-based mammography screening-programs. Validation studies should report the sensitivity, specificity and negative predictive value of breast ultrasound, as well as the positive predictive value; a uniform assessment system (such as the ultrasound BI-RADS categories) should be used, so that the reasons for biopsy can be described accurately. Quality of life and cost-effectiveness analyses should be performed.

**Funding**

German Cancer Aid and the German Society of Senology, Update of the Guideline - Early Detection of Breast Cancer in Germany - Model Project for the Updating of Stage-3-Guidelines in Germany 2008, grant funding code 107374.

**Bibliographic details**

Nothacker M, Duda V, Hahn M, Warm M, Degenhardt F, Madjar H, Weinbrenner S, Albert US. Early detection of
breast cancer: benefits and risks of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue: a systematic review. BMC Cancer 2009; 9:335

PubMedID
19765317

DOI
10.1186/1471-2407-9-335

Original Paper URL
http://www.biomedcentral.com/1471-2407/9/335/abstract/

Other URL
http://ukpmc.ac.uk/abstract/MED/19765317

Additional Data URL
http://www.biomedcentral.com/content/supplementary/1471-2407-9-335-S2.DOC
http://www.biomedcentral.com/content/supplementary/1471-2407-9-335-S3.DOC

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Breast Neoplasms /diagnosis /pathology /radiography /ultrasonography; Early Diagnosis; Female; Humans; Mammography; Middle Aged; Risk Assessment; Ultrasonography, Mammary

AccessionNumber
12010000594

Date bibliographic record published
10/03/2010

Date abstract record published
14/07/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.