Effective Health Care Program

Comparative Effectiveness Review
Number 47

Noninvasive Diagnostic Tests for Breast Abnormalities: Update of a 2006 Review

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The information in this report is intended to help healthcare decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Noninvasive Diagnostic Tests for Breast Abnormalities: Update of a 2006 Review

Structured Abstract

Objectives. To systematically review the literature on the diagnostic accuracy of noninvasive imaging technologies proposed to be useful as part of the workup after recall of women with suspicious breast abnormalities identified on routine screening. This report is an update of a Comparative Effectiveness Review originally published in 2006.

Data Sources. We searched the medical literature, including PubMed and Embase, from December 1994 through September 2010. We included diagnostic cohort studies that enrolled the patient population of interest and used current generation scanners and protocols of the noninvasive imaging technologies of interest. We excluded case-control studies, meeting presentations, and very small (<10 patients) studies.

Review Methods: We abstracted data from the included studies and used a bivariate mixed-effects binomial regression model for meta-analysis. We used the summary likelihood ratios and Bayes' theorem to calculate the post-test probability of having a benign or malignant lesion. We explored heterogeneity in the data with meta-regressions using standard methodology. We graded the strength of evidence supporting each major conclusion as high, moderate, low, or insufficient. The grade was developed by considering four important domains: the risk of bias in the evidence base (internal validity, or quality of the studies), the consistency of the findings, the precision of the results, and the directness of the evidence.

Results. We identified 41 studies of magnetic resonance imaging (MRI). The summary sensitivity of MRI was 91.7 percent (95% CI: 88.5 to 94.1%) and the summary specificity was 77.5 percent (95% CI: 71.0 to 82.9%). The estimate of accuracy was judged to be supported by a moderate to low strength of evidence (low for the estimate of specificity due to the lack of precision as reflected in the wide confidence interval). Bayes' theorem and the summary estimates of accuracy suggest that only women with a pre-MRI suspicion of malignancy of 12 percent or less will have their post-MRI suspicion of malignancy change sufficiently to suggest that a change in patient management may be appropriate.
We identified seven studies of positron emission tomography (PET). The summary sensitivity of PET was 83.0 percent (95% CI: 73.0 to 89.0%) and the summary specificity was 74.0 percent (95% CI: 58.0 to 86.0%). The estimate of accuracy was judged to be supported by a Low strength of evidence. Bayes' theorem and the summary estimates of accuracy suggest that only women with a pre-PET suspicion of malignancy of 5 percent or less will have their post-PET suspicion of malignancy change sufficiently to suggest that a change in patient management may be appropriate.

We identified 10 studies of scintimammography. The summary sensitivity of scintimammography was 84.7 percent (95% CI: 78.0 to 89.7%) and the summary specificity was 77.0 percent (95% CI: 64.7 to 85.9%). The estimate of accuracy was judged to be supported by a Low strength of evidence. Bayes' theorem and the summary estimates of accuracy suggest that

only women with a pre-scintimammography suspicion of malignancy of 5 percent or less will have their post-scintimammography suspicion of malignancy change sufficiently to suggest that a change in patient management may be appropriate.

We identified 21 studies of B-mode grayscale ultrasound, six studies of color Doppler ultrasound, and seven studies of power Doppler ultrasound. For B-mode grayscale, summary sensitivity was 92.4 percent (95% CI: 84.6 to 96.4%) and the summary specificity was 75.8 percent (95% CI: 60.8 to 86.3%); for color Doppler, summary sensitivity was 88.5 percent (95% CI: 74.4 to 95.4%) and summary specificity was 76.4 percent (95% CI: 61.7 to 86.7%); for power Doppler, summary sensitivity was 70.8 percent (95% CI: 47 to 86.6%) and summary specificity was 72.6 percent (95% CI: 59.9 to 82.5%). These estimates of accuracy were all judged to be supported by a Low strength of evidence. Bayes' theorem and the summary estimates of accuracy suggest that only women with a pre-ultrasound suspicion of malignancy of 10 percent or less will have their post-ultrasound suspicion of malignancy change sufficiently to suggest that a change in patient management may be appropriate.

Conclusions. The use of noninvasive imaging, in addition to standard workup of women recalled for evaluation of an abnormality detected on breast cancer screening, may be clinically useful for diagnostic purposes only for women with a low (less than 12%) pretest suspicion of malignancy. When choosing which noninvasive imaging technology to use for this purpose, the evidence appears to suggest that diagnostic B-mode grayscale ultrasound and MRI are more accurate than PET, scintimammography, or Doppler ultrasound. The utility of these findings, however, depend on whether clinicians can identify women with a pretest suspicion of malignancy in the ranges necessary for the tests to affect management. Several of the expert reviewers of this report did not think this is currently possible.

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Executive Summary

Background

Breast cancer is one of the most common malignancies of women, with approximately 200,000 new cases diagnosed every year in the United States.[1] Some breast cancers are identified by physical examination (either self-examination or an examination performed by a physician). Population-wide screening programs that use x-ray mammography to examine asymptomatic women for early signs of breast cancer are also in common use.[2-4] If a suspicious area is seen on x-ray mammography, women are usually recalled for further examination. The results of these examinations are used to make decisions about further management: return to normal screening/return for short-interval followup/refer for biopsy. In current standard practice the examinations conducted after recall usually consist of diagnostic mammography and possibly ultrasound. More and more often women are being sent for additional imaging during recall workup. Extensive diagnostic ultrasound examinations and MRI are currently the most commonly chosen additional imaging added to the workup, but other imaging technologies are offered by some practitioners.

It is important to triage recalled women into the correct management pathway. Women with readily treatable early-stage cancers who get mistakenly triaged into "return to normal screening" may experience a significant delay in diagnosis and treatment of the cancer. However, the majority of women who are recalled for further assessment after a screening mammography do not have cancer, and significant numbers of healthy women are referred for biopsy or short-interval followup after recall and diagnostic mammography.[5,6]

A number of noninvasive imaging technologies have been developed and proposed to be useful as part of the workup after recall. This evidence review focuses on additional noninvasive imaging studies that can be conducted (in addition to standard workup) after discovery of a possible abnormality on screening mammography or physical examination. These studies are intended to guide patient management decisions. In other words, these imaging studies are not intended to provide a final diagnosis as to the nature of the breast lesion; rather, they are intended to provide additional information about the nature of the lesions such that women can be more appropriately triaged into the correct management pathway. It is important to evaluate the evidence to see if women do or do not benefit from the addition of these imaging modalities to the standard workup after recall on breast cancer screening.

Because there are no available studies that directly evaluate whether women benefit from additional imaging in this context, we addressed this important question indirectly. First we evaluated the accuracy of the imaging tests in distinguishing between "benign" and "malignant" breast lesions. Inaccurate tests will lead to suboptimal management decisions and less than desirable patient outcomes. The accuracy of the noninvasive imaging tests was primarily measured in terms of sensitivity and specificity. Sensitivity is a measure of how accurately the test can identify women with cancer; specificity is a measure of how accurately the test can identify women who do not have cancer. A test with high sensitivity will rarely misclassify women with cancer as not having cancer, and a test with high specificity will rarely misclassify women without cancer as having cancer.

The accuracy of a test can also be expressed in a more clinically useful measure, namely, likelihood ratios. When making medical decisions, a clinician can use likelihood ratios and test results to estimate the probability of an individual woman having breast cancer. Clinicians use

individual patient characteristics (such as age and family history) and features seen on the diagnostic mammogram (such as microcalcifications or distortions) to estimate a woman's risk of malignancy. This estimate is known as a "pre-test" or "prior" probability. The clinician can then use the likelihood ratios (that express the accuracy of the test) to decide if an additional imaging test will be helpful in guiding management decisions. For example, if a clinician estimates a woman's risk of malignancy as greater than 50 percent, most likely the use of any additional imaging test, even a very accurate imaging test, will not change the clinician's management recommendation of a biopsy, and therefore additional imaging will not be beneficial to the woman. However, if a clinician estimates a woman's risk of malignancy as being uncertain or close to a clinical threshold (2%), the likelihood ratios can be used to estimate whether the results of an additional test are likely to change management decisions and possibly affect patient outcomes.

After establishing the accuracy of the various imaging tests, we used the summary likelihood ratios to prepare simple models of various clinical scenarios. In doing so, we attempted to indirectly address the implicit question of whether women benefit from the addition of noninvasive imaging tests to standard workup after recall for evaluation of a possible breast abnormality detected by screening mammography or physical examination.

This report is an update of a Comparative Effectiveness Review (CER) of the same title originally published in 2006.[7] In addition to an update of the literature, the Key Questions have been revised and additional noninvasive imaging tests have been added.

Methods

Topic Development and Scope

The topic was selected for update by the Effective Health Care program. The Key Questions were posted for public comment. A Technical Expert Panel was assembled to provide expert input, and a protocol for updating the review was developed by the EPC authors and approved by the Agency for Healthcare Research and Quality.

Patient Population

The patient population of interest is the general population of women participating in routine breast cancer screening programs (including mammography, clinical examination, and self-examination) who have been recalled after discovery of a possible abnormality and who have already undergone standard workup (which usually includes diagnostic mammography and/or ultrasound) . In other words, the patient population of interest consists of women who have or might receive a Breast Imaging-Reporting and Data System (BI-RADS®) rating of 0, or 3 to 5, after standard workup. Some of the women evaluated may have had an ultrasound examination before being examined using the technology under study, including the women being evaluated by diagnostic ultrasound. Although not explicitly stated in the studies, in most cases this prior ultrasound seemed to be used primarily to identify women with simple benign cysts, who were then not included in the study. Populations that were not evaluated in this review include: women thought to be at very high risk of breast cancer due to family history or breast cancer (BRCA) gene mutations; women with a personal history of breast cancer; women presenting with overt symptoms (such as pain or nipple discharge); and men.

Interventions

The noninvasive diagnostic tests evaluated were ultrasound (conventional B-mode grayscale, harmonic, tomography, color Doppler, and power Doppler); magnetic resonance imaging (MRI, with gadolinium-based contrast agents) with or without computer-aided diagnosis (CADx); positron emission tomography (PET, with 18-fluorodeoxyglucose [FDG]), with or without concurrent computed tomography (CT) scans (including positron emission mammography [PEM]); scintimammography (with technetium-99m sestamibi [MIBI]), including Breast Specific Gamma Imaging (BSGI).

Comparators

The accuracy of the noninvasive diagnostic tests were evaluated by a direct comparison with histopathology (surgical or biopsy specimens) or with clinical followup, or a combination of these methods. In addition, the relative accuracy of the different tests under evaluation were directly and indirectly compared as the evidence permitted.

Outcomes

Outcomes of interest are diagnostic test characteristics; namely, sensitivity, specificity, and likelihood ratios. Because predictive values vary as the prevalence of disease changes, we did not calculate predictive values. Adverse events related to the procedures, such as radiation exposure, discomfort, and reactions to contrast agents, were also be discussed as the evidence permitted. Our literature searches did not identify any relevant studies that directly reported the impact of the diagnostic tests on patient-oriented outcomes. Therefore, we used the estimates of accuracy and various clinical scenarios to address the implicit, very important question of whether women benefit from the use of these noninvasive imaging tests.

Timing

Any duration of followup, from same day interventions to many years of clinical followup, were evaluated.

Setting

Any care setting was evaluated, including general hospitals, physician's offices, and specialized breast imaging centers.

Study Selection

We searched the medical literature, including PubMed and Embase, from December 1994 through September 2010. We included diagnostic cohort studies that enrolled the patient population of interest and used current generation scanners and protocols of the noninvasive imaging technologies of interest. We excluded case-control studies, meeting presentations, and very small (<10 patients) studies. Data were abstracted from the included studies.

Strength of Evidence

We graded the strength of evidence supporting each major conclusion as high, moderate, low, or insufficient. The grade was developed by considering four important domains: the risk of bias in the evidence base (internal validity, or the quality of the studies), the consistency of the findings, the precision of the results, and the directness of the evidence.

Data Analysis

We used a bivariate mixed-effects binomial regression model for meta-analysis of data.[8,9] We used summary likelihood ratios and Bayes' theorem to calculate the post-test probability of having a benign or malignant lesion. In cases where a bivariate binomial model could not be fit, we meta-analyzed the data using two random-effects models, one for sensitivity and one for specificity.[10] We explored heterogeneity in the data with meta-regressions using standard methodology.[9]

Peer Review and Public Commentary

The draft received comments from peer reviewers, and from members of the public through an open public comment period.

Results

Magnetic Resonance Imaging

We identified 41studies of MRI that included a total of 3,882 patients with 4,202 suspicious breast lesions.[11-51] We combined the data reported by all 41 studies into a bivariate binomial mixed-effects model. The summary sensitivity was 91.7 percent (95% CI: 88.5 to 94.1%) and the summary specificity was 77.5 percent (95% CI: 71.0 to 82.9%). The estimate of accuracy was judged to be supported by a moderate to low strength of evidence (low for the estimate of specificity due to the wide confidence interval). The dataset was very heterogeneous (I^2 = 98.4%). We explored the heterogeneity with meta-regression and found that the prevalence of disease in the study population and whether or not the image readers were blinded was statistically significantly correlated with the results. Subgroup analyses found that MRI was less sensitive for evaluation of microcalcifications (84.0% vs. 91.7% summary sensitivity).

The probability that a woman actually has cancer (invasive or in situ) even after a finding of "benign" on MRI depends on her probability of having cancer before undergoing the test. Bayes' theorem and the summary likelihood ratios indicate that if a woman with an estimated 5 to 10 percent chance of having cancer undergoes MRI and has a finding of "benign" she will then have an estimated 1 percent chance of having cancer; a woman with an estimated 20 percent chance of having cancer who has a finding of "benign" on MRI will then have an estimated 3 percent chance of having cancer; and a woman with an estimated 50 percent chance of having cancer who has a finding of "benign" on MRI will then have an estimated 10 percent chance of having cancer.

Positron Emission Tomography

We identified seven studies of PET[34,35,41,52-55] and one study of PET/CT[16] that met our inclusion criteria. The studies of stand-alone PET included 308 women with 403 suspicious breast lesions. We combined the data reported by the seven studies of PET into a bivariate binomial mixed-effects model. The summary sensitivity was 83.0 percent (95% CI: 73.0 to 89.0%) and the summary specificity was 74.0 percent (95% CI: 58.0 to 86.0%). The estimate of accuracy was judged to be supported by a Low strength of evidence. The dataset contained moderate heterogeneity (I^2 = 64.0%). We explored the heterogeneity with meta-regression and

did not identify any possible causes. Subgroup analyses found that PET was more sensitive for evaluation of palpable lesions.

The probability that a woman actually does have cancer (invasive or in situ) even after a finding of "benign" on PET depends on her probability of having cancer before undergoing the test. Bayes' theorem and the summary likelihood ratios indicate that if a woman with an estimated 5 percent chance of having cancer undergoes PET and has a finding of "benign" she will then have an estimated 1 percent chance of having cancer; a woman with an estimated 20 percent chance of having cancer who has a finding of "benign" on PET will then have an estimated 6 percent chance of having cancer; and a woman with an estimated 50 percent chance of having cancer who has a finding of "benign" on PET will then have an estimated 19 percent chance of having cancer.

Scintimammography

We identified 10 studies of scintimammography[14,56-64] and one study of BSGI[19] that met our inclusion criteria. The studies included a total of 1,064 suspicious lesions. We combined the data reported by all 11 studies into a bivariate binomial mixed-effects model. The summary sensitivity was 84.7 percent (95% CI: 78.0 to 89.7%) and the summary specificity was 77.0 percent (95% CI: 64.7 to 85.9%). The estimate of accuracy was judged to be supported by a low strength of evidence. The dataset was very heterogeneous (I^2 = 93.0%). We explored the heterogeneity with meta-regression and did not identify any possible causes.

The probability that a woman actually does have cancer (invasive or in situ) even after a finding of "benign" on scintimammography depends on her probability of having cancer before undergoing the test. Bayes' theorem and the summary likelihood ratios indicate that if a woman with an estimated 5 percent chance of having cancer undergoes scintimammography and has a finding of "benign" she will then have an estimated 1 percent chance of having cancer; a woman with an estimated 20 percent chance of having cancer who has a finding of "benign" on scintimammography will then have an estimated 5 percent chance of having cancer; and a woman with an estimated 50 percent chance of having cancer who has a finding of "benign" on scintimammography will then have an estimated 17 percent chance of having cancer.

Ultrasound

We identified a total of 31 diagnostic cohort studies of ultrasound. Of these, there were 21 studies of B-mode grayscale ultrasound,[18,26,65-83] six studies of color Doppler ultrasound,[78,80,84-87] and nine studies of power Doppler ultrasound.[65,72,75,77,86,88-91] We combined the data reported by these studies into bivariate binomial mixed-effects models. For B-mode grayscale, summary sensitivity was 92.4 percent (95% CI: 84.6 to 96.4%) and the summary specificity was 75.8 percent (95% CI: 60.8 to 86.3%); for color Doppler, summary sensitivity was 88.5 percent (95% CI: 74.4 to 95.4%) and summary specificity was 76.4 percent (95% CI: 61.7 to 86.7%); for power Doppler, summary sensitivity was 70.8 percent (95% CI: 47 to 86.6%) and summary specificity was 72.6 percent (95% CI: 59.9 to 82.5%). These estimates of accuracy were all judged to be supported by a low strength of evidence. The datasets were heterogeneous. We explored the heterogeneity of the largest dataset (21 studies of B-mode) with meta-regression and found that whether the studies blinded the image readers and accounted for inter-reader differences were statistically significantly associated with the results.

The probability that a woman actually does have cancer (invasive or in situ) even after a finding of "benign" on ultrasound depends on her probability of having cancer before

undergoing the test. Bayes' theorem and the summary likelihood ratios indicate that if a woman with an estimated 5 to 10 percent chance of having cancer undergoes B-mode grayscale ultrasound and has a finding of "benign" she will then have an estimated 1 percent chance of having cancer; a woman with an estimated 20 percent chance of having cancer who has a finding of "benign" on B-mode grayscale ultrasound will then have an estimated 2 percent chance of having cancer; and a woman with an estimated 50 percent chance of having cancer who has a finding of "benign" on B-mode grayscale ultrasound will then have an estimated 9 percent chance of having cancer.

Discussion

According to the American College of Radiology, the threshold of suspicion of malignancy at which management of women changes is 2 percent.[92] After recall and workup, women with a suspicion of malignancy greater than 2 percent are generally recommended to undergo tissue sampling of some kind (biopsy), and women with a lower suspicion of malignancy are triaged into imaging management pathways (short-interval followup or return to regular screening). We used the 2 percent threshold to explore the clinical usefulness of the various noninvasive imaging technologies as add-ons to the current standard of care; namely, if a woman was recalled for evaluation after a screening mammography, and received standard-of-care workup versus standard-of-care workup plus the noninvasive imaging technology, would use of the noninvasive imaging technology be likely to alter the recommendations for care after the workup?

For all of the technologies evaluated in this assessment, only women with a low suspicion of malignancy after standard-of-care workup might be expected to experience a change in management decisions as a result of additional noninvasive imaging. A woman with a ≤12 percent suspicion of malignancy who has benign findings on MRI could have her suspicion of malignancy drop below the 2 percent threshold, and therefore she might be assigned to short-interval imaging followup management rather than tissue sampling management; a woman with a 1 percent suspicion of malignancy who has benign findings on MRI could have her suspicion of malignancy drop to near 0 percent and therefore she might be assigned to return to normal screening rather than short-interval followup imaging; a woman with a 1 percent suspicion of malignancy who has malignant findings on MRI could have her suspicion of malignancy increase to 4 percent and therefore she might be assigned to tissue sampling management rather than short-interval followup. The equivalent thresholds of pre-test suspicion of malignancy at which additional imaging may change management are: for B-mode grayscale ultrasound, 1 to 10 percent; for scintimammography, 1 to 5 percent; and for PET, 1 to 5 percent.

Therefore, if the 2 percent threshold is chosen, the use of noninvasive imaging in addition to standard workup may be clinically useful for diagnostic purposes only for women with a low suspicion of malignancy. When choosing which noninvasive imaging technology to use for this purpose, diagnostic B-mode grayscale ultrasound and MRI appear to be more accurate than PET, scintimammography, or the other types of ultrasound (e.g., Doppler) that were evaluated in this comparative effectiveness review.

Women thought to be at moderate to high risk of malignancy after standard workup will not have their estimate of risk of malignancy change sufficiently after further noninvasive imaging to affect management decisions. For many patients the suspicion of malignancy will not be able to be estimated with sufficient precision for clinicians to feel comfortable recommending return to normal screening (rather than a biopsy or short-interval followup) solely on the basis of additional noninvasive imaging. Estimates of risk of malignancy are based on features of the

mammographic images, patient characteristics, patient history, and patient family history. Several of our expert reviewers did not think such precise estimation of risk is feasible using currently available methods. Potential harms of noninvasive imaging, such as radiation exposure, also need to be considered when deciding whether to perform these tests.

Changes Since 2006

This CER is an update of a CER finalized in 2006.[7] The updated results are, in general, very similar to the findings of the 2006 report. For MRI, in 2006 we found that the sensitivity was 92.5 percent and the specificity was 75.5 percent; the updated evidence base supported estimates of 91.7 percent sensitivity and 77.5 percent specificity. In both reports, MRI was found to be less sensitive (approximately 85%) for evaluation of microcalcifications than for evaluation of lesions in general. For PET, in 2006 we found that the sensitivity was 82.2 percent and the specificity was 78.3 percent; the updated evidence base supported estimates of 83.0 percent sensitivity and 74.0 percent specificity. In the updated report we attempted to evaluate the accuracy of PET/CT, but only one study that met the inclusion criteria was identified.

For scintimammography, the updated evidence base identified a sensitivity of 84.7 percent, much higher than the sensitivity estimate from 2006 of 68.7 percent. Specificity was estimated at 84.8 percent in 2006, and at 77.0 percent in the update; however, the confidence intervals around the updated estimate of specificity are wide. It is possible that improvements in the technology in the last few years improved the sensitivity of the technique.

For ultrasound, in 2006 we evaluated a relatively small set of studies of B-mode grayscale ultrasound, and estimated a sensitivity of 86.1 percent and a specificity of 66.4 percent. The update included a significantly expanded evidence base on B-mode grayscale ultrasound, and identified a sensitivity of 92.4 percent and specificity of 75.8 percent. In the update we included numerous other types of ultrasound, including power and color Doppler ultrasound, that were not studied in the 2006 report.

Remaining Issues

The conclusions of quantitative accuracy were for the most part rated as being supported by low strength of evidence, due primarily to the imprecision of the estimates (wide confidence intervals around the estimates of accuracy); the publication of additional diagnostic accuracy studies are likely to increase the precision of the estimates of accuracy, which may upgrade the strength of evidence rating. There was also considerable heterogeneity (inconsistency) in the majority of the evidence bases, which contributed to the low strength of evidence rating. Most likely the heterogeneity was due to slight differences in imaging methodology or patient populations across studies; future research intended to tease out factors affecting the accuracy of imaging may be helpful to the clinician when deciding whether a test may be a useful addition to standard workup for management of a particular patient.

However, the publication of additional diagnostic accuracy studies is unlikely to affect the implications of the conclusions. The conclusions of diagnostic accuracy lead indirectly to a conclusion that only women with a low (1 to 12%) suspicion of malignancy will experience a "change in management" (which may or may not be beneficial) from the use of these noninvasive diagnostic tests. Improving the precision of the estimates of accuracy or upgrading the strength of evidence rating in response to the publication of more diagnostic accuracy studies will not affect the indirect conclusion. Studies that address the issue of how to establish more

accurate estimates of malignancy from diagnostic mammography for an individual patient may be more clinically relevant than additional diagnostic accuracy studies.

A limitation of the current evidence base that should be addressed in future research is the patient population being evaluated. Many of the currently available studies were conducted only on women who had been scheduled for biopsy after standard workup, and therefore the patient population studied is not truly representative of the entire patient population of interest. Additional studies that enroll women referred for short-interval followup after standard workup are needed to confirm that the findings of this assessment do apply to the patient population of interest.

In addition, the majority of studies did not report data separately for different categories of breast lesions or patient characteristics. Future research should focus on the accuracy of noninvasive imaging technologies for discrete categories of lesions, such as nonpalpable lesions classified as BI-RADS 3, or for discrete categories of women, such as women older than age 75. Information from more granular groupings of women will allow estimates of test accuracy to be more immediately clinically useful.

Future research efforts should also focus on studies that report the impact of the use of noninvasive imaging on patient-oriented outcomes such as quality of life, and on evaluation of newer noninvasive imaging technologies.

Conclusions

Our key findings are summarized in Table A. In conclusion, the use of noninvasive imaging in addition to standard workup after recall for evaluation of a breast lesion detected on screening mammography or physical examination may be clinically useful for diagnostic purposes only for women with a low (1 to 12%) suspicion of malignancy. When choosing which noninvasive imaging technology to use for this purpose, diagnostic B-mode grayscale ultrasound and MRI appear to more accurate than PET, scintimammography, or Doppler ultrasound. However, whether these findings are clinically relevant hinges on whether clinicians can identify those women who, after standard workup after recall, have a risk of malignancy in this range. Several expert reviewers of this report expressed doubt about the feasibility of such precise estimation.

Table A. Summary of key findings

Technology	Summary Sensitivity	Summary Specificity	Pretest Probability of Malignancy Threshold[a]	Strength of Evidence
B-mode grayscale 2D ultrasound	92.4% (84.6 to 96.4%)	75.8% (60.8 to 86.3%)	1 to 10%	Low
MRI	91.7% (88.5 to 94.1%)	77.5% (71.0 to 82.9%)	1 to 12%	Moderate (sensitivity) to Low (specificity)
Scintimammography	84.7% (78.0 to 89.7%)	77.0% (64.7 to 85.9%)	1 to 5%	Low
PET	83.0% (73.0 to 89.0%)	74.0% (58.0 to 86%)	1 to 5%	Low

[a] The threshold at which use of the noninvasive imaging test may change the post-test probability of malignancy sufficiently to trigger a change in patient management.

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Introduction

Background

Breast Cancer

Breast cancer is the second most common malignancy of women.[1] The American Cancer Society estimates that in the United States in 2010, 54,010 women were diagnosed with new cases of in situ cancer, 207,090 women were newly diagnosed as having invasive breast cancer, and there were 39,840 deaths due to this disease.[1] In the general population, the cumulative risk of being diagnosed with breast cancer by age 70 is estimated to be 6 percent (lifetime risk of 13%).[93,94]

The most common type of breast cancer, accounting for over 85 percent of cases diagnosed, is ductal carcinoma.[95] Ductal carcinoma arises within the ducts of the breast from the cells lining the ducts. Early-stage breast cancer confined to the inside of the duct is referred to as ductal carcinoma in situ (DCIS). Later stages of ductal carcinoma that have invaded or broken through the walls of the ducts into nearby tissues may be referred to as invasive or infiltrating ductal carcinoma. Cases of invasive ductal carcinoma that are found to be well-differentiated specific subtypes (such as mucinous, medullary, tubular, or papillary) are much rarer than the common "otherwise not specified" type of invasive ductal carcinoma.

Another type of invasive carcinoma is lobular carcinoma. Lobular carcinoma is similar to ductal carcinoma, first arising in the terminal ducts of the lobules and then invading through the walls of the ducts and invading nearby tissues. Other rare types of potentially life-threatening breast tumors include papillary carcinoma, inflammatory breast cancer, and sarcomas, among others.[95]

A number of different breast lesions have been described that, while not malignant, are believed to predispose to the development of invasive breast carcinomas. These lesions include atypical ductal hyperplasia (ADH), papillary lesions, radial scars, atypical lobular hyperplasia (ALH), and lobular carcinoma in situ (LCIS).[96] However, the most commonly reported breast abnormalities diagnosed after screening are benign: benign fibrocystic changes, cysts, and benign fibroadenomas.

Breast Cancer Diagnosis

Breast cancer is usually first detected by feeling a lump on physical examination (either self-examination or an exam conducted by a health practitioner) or by observing an abnormality during x-ray screening mammography. Survival rates depend on the stage of disease at diagnosis. At stage 0 (carcinoma in situ) the 5-year survival rate is close to 100 percent. The five-year survival rate for women with stage IV (cancer that has spread beyond the breast) is only 23 percent.[1] Because early breast cancer is asymptomatic, the only way to detect it is through screening of asymptomatic women. Mammography is a widely accepted and used method for breast cancer screening.[2-4] Meta-analyses of large clinical trials have demonstrated that mammography screening reduces breast cancer mortality.[97,98]

Mammography uses x-rays to examine the breast for clusters of microcalcifications, circumscribed and dense masses, masses with indistinct margins, architectural distortion compared with the contralateral breast, or other abnormal structures. The United States Preventive Services Task Force (USPSTF) has recently recommended routine screening

mammography every two years for women aged 50 to 74, with decisions to screen women under the age of 50 made on an individual basis.[4] After identification of a possible abnormality on screening mammography or physical examination, women typically undergo additional imaging studies (diagnostic mammography and/or ultrasound) and a physical examination. If these studies suggest the abnormality may be malignant, a biopsy of the suspicious area may be recommended.

The American College of Radiology has created a standardized system for reporting the results of mammography, the Breast Imaging-Reporting and Data System (BI-RADS®).[99-101] There are seven categories of assessment, each with an accompanying clinical management recommendation:

0 Need additional imaging evaluation and/or prior mammograms for comparison
1 Negative
2 Benign finding
3 Probably benign finding. Initial short interval followup suggested.
4 Suspicious abnormality. Biopsy should be considered.
5 Highly suggestive of malignancy. Appropriate action should be taken.
6 Known biopsy-proven malignancy. Appropriate action should be taken.

Noninvasive breast imaging tests have multiple uses, including image-guidance of biopsy procedures, searching for multifocal lesions in a woman diagnosed with or at high risk of breast cancer, and screening women at high risk of breast cancer. This evidence review specifically focuses only on the use of noninvasive imaging studies that can be conducted after the discovery of a possible abnormality on screening mammography or physical examination- studies intended to guide patient management decisions. In other words, these studies are not intended to provide a final diagnosis as to the nature of the breast lesion; rather, they are intended to provide additional information about the nature of the lesion such that women can be appropriately triaged into "biopsy/watchful waiting/return to normal screening intervals" care pathways.

It is important to accurately triage women into the correct care pathway. Women with readily treatable breast cancers who get incorrectly triaged into "return to normal screening care pathways" may experience a significant delay in diagnosis and treatment of the cancer. However, the majority of women who are recalled for further assessment after a screening mammogram do not have cancer. Elmore et al. estimated that the cumulative risk for a woman having a false-positive finding on screening mammography is close to 50 percent after 10 years of yearly screenings.[5] In addition, diagnostic mammography performed after a mammographic screening recall often leads to identification of a "probably benign" (BI-RADS 3) lesion. Women with "probably benign" lesions are usually referred for short-interval repeat mammography examinations, meaning that they wait for three to six months before being re-tested. Many women experience considerable emotional distress and anxiety during this waiting period.[102] If an available noninvasive diagnostic test could assist clinicians in evaluating women recalled for further investigation after mammographic screening, namely, in assisting in accurately distinguishing between "benign," "probably benign," and "probably not benign" lesions, then some women could avoid having to spend several months wondering if they have cancer or not.

The majority of women who traditionally have been referred for biopsy also do not have cancer. Studies in the U.S. generally find that only 20 to 30 percent of women who undergo biopsy are diagnosed with breast cancer.[6,103] Exposing large numbers of women who do not have cancer to invasive procedures may be considered an undesirable medical practice. In conclusion, current workup after recall results in a large number of false-positives. If additional tests could

reduce the false-positive rate without increasing the false-negative rate then it is possible that women could benefit from adding these tests to standard workup.

Because there are no available studies that directly evaluate whether women benefit from additional noninvasive imaging, we addressed this important question indirectly. First we evaluated the accuracy of the imaging tests in distinguishing between "benign" and "malignant" breast lesions. Inaccurate tests will lead to sub-optimal management decisions and less than desirable patient outcomes. The accuracy of the noninvasive imaging tests was primarily measured in terms of sensitivity and specificity. Sensitivity is a measure of how accurately the test can identify women with cancer; specificity is a measure of how accurately the test can identify women who do not have cancer. A test with high sensitivity will rarely misclassify women with cancer as not having cancer, and a test with high specificity will rarely misclassify women without cancer as having cancer.

The accuracy of a test can also be expressed in a more clinically useful measure, namely, likelihood ratios. When making medical decisions a clinician can use likelihood ratios and test results to estimate the probability of an individual woman having breast cancer. Clinicians use individual patient characteristics (such as age and family history) and features seen on the diagnostic mammogram (such as microcalcifications or distortions) to estimate a woman's risk of malignancy. This estimate is known as a "pre-test" or "prior" probability. The clinician can then use the likelihood ratios (that express the accuracy of the test) and Bayes' theorem to decide if an additional imaging test will be helpful in guiding management decisions.

After establishing the accuracy of the various imaging tests we used the summary likelihood ratios to prepare simple models of various clinical scenarios to attempt to indirectly address the implicit question of whether women benefit from the addition of noninvasive imaging tests to standard work-up after recall for evaluation of a possible breast abnormality detected by screening mammography or physical examination. This information may be useful to clinicians in deciding when, or if, it is clinically appropriate to use various types of noninvasive technologies to evaluate breast abnormalities.

Because women with a previous history of breast cancer and women known to be at high risk of breast cancer (due to carrying BRCA1 and BRCA2 mutations or having a very strong family history of breast cancer) have a very different risk profile than the rest of the population, we did not evaluate the use of noninvasive technologies for such women in this review. Instead, we focused on the use of noninvasive imaging technology for women from the general population who present with an abnormal finding by screening mammography or physical examination. We also (as the evidence permitted) examined the influence of age; the size and morphological characteristics of the lesion; and other key clinical risk factors on the accuracy of the noninvasive imaging methods.

Noninvasive Imaging

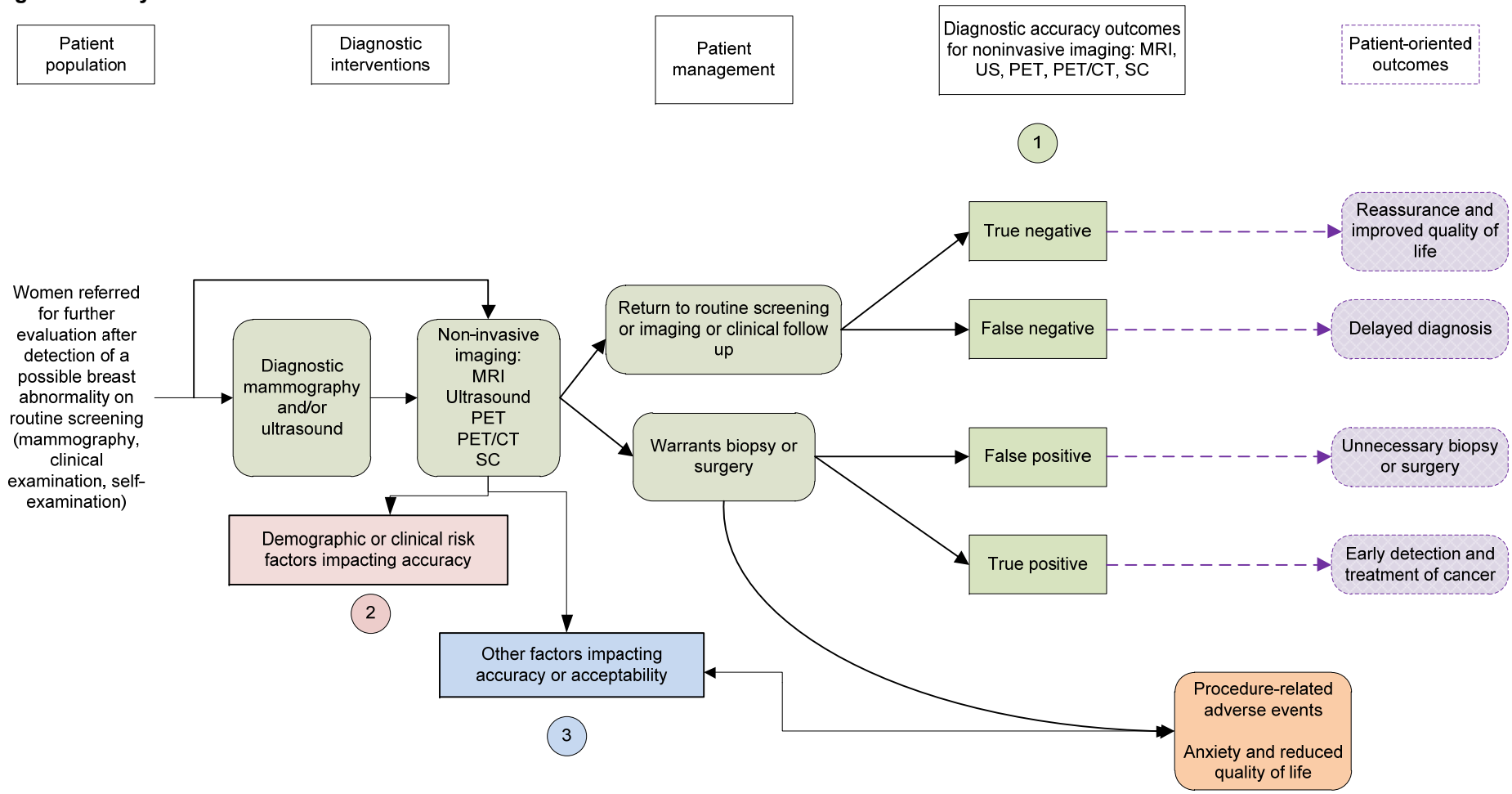
Noninvasive imaging technologies generally fall into two primary groups: technologies that examine the anatomy, or physical structure, of the breast; and technologies that detect abnormal metabolic patterns. Some noninvasive imaging technologies are slightly invasive in that they require the infusion or injection of a tracer or contrast agent; and some technologies expose patients to radiation. Each of the noninvasive technologies considered in this review is briefly introduced in the Results section of this report.

Conceptual Framework

The analytical framework (Figure 1) demonstrates the links between patients, tests, interventions, and outcomes. The numbers on the diagram refer to the Key Questions (see next section) and their placement in Figure 1 illustrates the many links separating the Key Questions from the patient-oriented outcomes. Fryback and Thornbury have proposed a six-level model of assessing diagnostic efficacy.[104] Level 1 is analytic validity; Level 2 is diagnostic accuracy; Level 3 is diagnostic thinking; Level 4 is impact on choice of treatment; Level 5 is patient-oriented outcomes; and Level 6 is societal impact. Demonstration of efficacy at each lower level is logically necessary, but not sufficient, to assure efficacy at higher levels. Patients and health-care providers are generally most interested in studies that evaluate the impact of diagnostic tests on Level 5, patient-oriented outcomes, and on Level 4, impact on choice of treatment. However, studies that directly link diagnostic tests to patient-oriented outcomes are expensive, require very long followup, and are difficult to conduct. In the absence of direct evidence, the effect of diagnostic tests on patient-oriented outcomes can sometimes be estimated by creating indirect chains of evidence by evaluating other levels. Our literature searches did not identify any relevant studies that directly reported the impact of the diagnostic tests on patient-oriented outcomes.

Therefore, we chose to approach this project by conducting a systematic review of the diagnostic accuracy of various noninvasive methods of evaluating breast abnormalities (Level 2). After establishing the accuracy of the tests, we constructed an indirect chain of evidence in an attempt to address Level 4 (impact on choice of treatment or use of additional diagnostic tests), and where possible Level 5 (impact on patient-oriented outcomes). We used the estimates of accuracy and the usual clinical scenario to address the implicit, very important question of whether women benefit from the additional use of these noninvasive imaging tests.

Figure 1. Analytical framework



CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography; SC = scintimammography
Note: Figure 1 depicts the Key Questions within the context of the patient population, diagnostic tests, subsequent interventions, and outcomes. In general, the figure illustrates how the use of additional noninvasive imaging tests may affect decisions about patient management, and how such decisions may impact patient outcomes. The Key Questions are depicted within the figure as numbers inside circles. Outcomes illustrated but not directly examined in this report are indicated by dashed lines.

Diagnostic Test Characteristics

No diagnostic test is perfect. Studies of test performance compare test results on a group of individuals, some of whom have the disease and some of whom do not. Each individual undergoes the experimental test as well as a second reference test to determine "true" disease status. The relationship between the diagnostic test results and disease status is described using diagnostic test characteristics. It is important that the reference test is very accurate in measuring "true" disease status, or else the performance of the experimental diagnostic test will be poorly estimated.

Sensitivity and Specificity

The results of the experimental and reference standard test and their relationship are commonly presented as two-by-two (2x2) tables (see Table 1). From the 2x2 table, sensitivity and specificity are readily calculated:

Sensitivity = TP/(TP+FN)

Specificity = TN/(FP+TN)

Table 1. Example of a 2x2 table

		Disease	
		Present	Absent
Test Results	Positive	True positives (TP)	False positives (FP)
	Negative	False negatives (FN)	True negatives (TN)

Sensitivity and specificity are test properties that are useful when deciding whether to use the test. Sensitivity is the proportion of people with the disease who have a positive test for the disease. A test with high sensitivity will rarely misclassify people with the disease as not having the disease (the test rarely has false-negative errors). Specificity is the proportion of people without the disease who have a negative test. A test with high specificity will rarely misclassify people without the disease as diseased (the test rarely has false-positive errors).

Predictive Values and Likelihood Ratios

To make sense of a diagnostic investigation, a clinician needs to be able to make an inference regarding the probability that a patient has the disease in question according to the result obtained from the test. Sensitivity and specificity do not directly provide this information. The predictive values and likelihood ratios can also be directly calculated from a 2x2 table:

Positive predictive value = TP/(TP+FP)

Negative predictive value = TN/(FN+TN)

Positive likelihood ratio = (TP/(TP+FN))/(FP/(FP+TN))

Negative likelihood ratio = (FN/(TP+FN))/(TN/(FP+TN))

The positive predictive value of a test is the probability of a patient having the disease following a positive test result. The negative predictive value is the probability of a patient not having the disease following a negative test result. Predictive values describe the probabilities that positive or negative results are correct for an individual patient. However, predictive values depend on the prevalence of disease in the population. A study that enrolled a patient population with a disease prevalence of 70 percent may report a positive predictive value of 80 percent. If a clinician tests a patient from a population with a disease prevalence of 70 percent, and the test

comes back positive, the clinician knows the patient has an 80 percent chance of having the disease in question. However, if the patient comes from a population with a disease prevalence of 20 percent, the clinician cannot apply the results of the study directly to this patient.

Because sensitivity and specificity are difficult to directly apply to clinical situations, and predictive values vary markedly as a function of disease prevalence (i.e., may be different for each patient subpopulation) a combined measure of diagnostic performance, the likelihood ratio, is a more clinically useful diagnostic test performance measure. Negative likelihood ratios measure the ability of the test to accurately "rule out" disease, and positive likelihood ratios measure the ability of the test to accurately detect disease.

Likelihood ratios are independent of prevalence and therefore can be directly applied in the clinic to update an individual's estimated chances of disease according to their test result. Likelihood ratios can be used in Bayes' theorem to calculate post-test odds of having a disease from the pre-test suspicion of the patient's odds of having that disease. Clinicians may be familiar with simple nomograms that allow a direct visualization of post-test chances of disease given a positive or negative test result, without the need to go through the tedious calculations of Bayes' theorem; see, for example, the interactive form of the nomogram provided by the Center for Evidence-based Medicine at http://www.cebm.net.

When making medical decisions a clinician can use likelihood ratios and the test results to estimate the probability of an individual woman having breast cancer. Clinicians use individual patient characteristics such as age, family history, and personal history; and features seen on the diagnostic mammogram, such as microcalcifications or distortions, to estimate a woman's risk of malignancy. This estimate is known as a "pre-test" or "prior" probability. The clinician can then use the likelihood ratios (that express the accuracy of the test) to help decide if an additional imaging test will be helpful in guiding management decisions. For example, if a clinician estimates a woman's risk of malignancy as "very high >50 percent" or "very low <1 percent" most likely the use of any additional imaging test will not change the clinician's management recommendations, and therefore additional imaging will not be beneficial to the woman. However, if a clinician estimates a woman's risk of malignancy as being uncertain or in an intermediate area, the likelihood ratios can be used to estimate whether an additional test is likely to change management decisions.

Scope and Key Questions

This systematic review was commissioned by the Agency for Healthcare Research and Quality (AHRQ) to address the following Key Questions:

Key Question 1. What is the accuracy (expressed as sensitivity, specificity, predictive values, and likelihood ratios) of noninvasive tests for diagnosis of breast cancer in women referred for further evaluation after identification of a possible breast abnormality on routine screening (mammography and/or clinical or self-detection of a palpable lesion)? The noninvasive tests to be evaluated are:

- Ultrasound (conventional B-mode, color Doppler, power Doppler, tissue harmonics, and tomography)
- Magnetic resonance imaging (MRI) with breast-specific coils and gadolinium-based contrast agents, with or without computer-aided diagnosis (CADx)
- Positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG) as the tracer, with or without concurrent computed tomography (CT) scans

- Scintimammography (SMM) with technetium-99m sestamibi (MIBI) as the tracer, including Breast Specific Gamma Imaging (BSGI)

Key Question 2. Are there demographic (e.g., age) and clinical risk factors (e.g., morphologic characteristics of the lesion) that affect the accuracy of the tests considered in Key Question 1?

Key Question 3. Are there other factors and considerations (e.g., safety, care setting, patient preferences, ease of access to care) that may affect the accuracy or acceptability of the tests considered in Key Questions 1 and 2?

This report is an update of a Comparative Effectiveness Review (CER) of the same title originally published in 2006. The Key Questions have been revised and additional diagnostic tests have been added to the list of tests to be evaluated. The 2006 version of the CER only evaluated B-mode ultrasound, MRI (without CADx), PET (without CT), and full-body scintimammography.

Methods

Topic Development

AHRQ requested an update of the evidence report Effectiveness of Noninvasive Diagnostic Tests for Breast Abnormalities.[7] The original report was finalized in February 2006. Due to technological advances and continuing innovation in the fields of noninvasive imaging, the conclusions of the original report are possibly no longer relevant to current clinical practice. Consequently, the topic was selected for update. The EPC recruited a technical expert panel (TEP) to give input on key steps including the selection and refinement of the questions to be examined. The expert panel membership is provided in the front matter of this report.

Upon AHRQ approval, the draft Key Questions were posted for public comment. After receipt and consideration of the public commentary, ECRI Institute finalized the Key Questions and submitted them to AHRQ for approval. These Key Questions are presented in the Scope and Key Questions section of the Introduction.

ECRI Institute created a work plan for developing the evidence report. The process consisted of working with AHRQ and the TEP to outline the report's objectives, performing a comprehensive literature search, abstracting data, constructing evidence tables, synthesizing the data, and submitting the report for peer review.

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design and/or methodologic approaches do not necessarily represent the views of individual technical and content experts.

The topic development procedure employed the "PICOTS" approach; namely, carefully and clearly defining the Patients, the Intervention(s), the Comparator(s), the Outcomes, the Timing of followup, and the Setting of care.[105]

Patients

The patient population of interest is the general population of women participating in routine breast cancer screening programs (including mammography, clinical examination, and self-examination). who have been recalled after discovery of a possible abnormality and who have already undergone standard work-up, which may include diagnostic mammography and/or ultrasound (BI-RADS 0, and 3 to 5). Populations that will not be evaluated in this review include: women thought to be at very high risk of breast cancer due to family history or BRCA mutations; women with a personal history of breast cancer; women with overt symptoms such as nipple discharge or pain; and men.

Interventions

The noninvasive diagnostic tests to be evaluated are:

- Ultrasound (conventional B-mode, harmonic, tomography, color Doppler, and power Doppler)
- Magnetic resonance imaging (MRI) with breast-specific coils and gadolinium-based contrast agents, with or without computer-aided diagnosis (CADx)

- Positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG) as the tracer, with or without concurrent computed tomography (CT) scans, and positron emission mammography.
- Scintimammography with technetium-99m sestamibi (MIBI) as the tracer, including Breast Specific Gamma Imaging (BSGI).

Technologies that were proposed for evaluation but, after discussion by the TEP, were not included, are: elastography; molecular breast imaging; scintimammography using tracers other than MIBI; PET using tracers other than FDG; digital tomosynthesis mammography; computer-aided diagnostic x-ray mammography; breast thermography; electrical impedance tomography; and optical breast imaging. The primary reasons that the TEP decided to not include these technologies in the current CER was a) insufficient robust evidence available about the technology at this time; b) no devices that employ the technology are currently available or approved in the United States; and/or c) the technology is primarily intended to be used in the screening setting.

Comparators

The accuracy of the noninvasive imaging tests was evaluated by a direct comparison to histopathology (biopsy or surgical specimens) or to clinical followup, or a combination of these methods. In addition, the relative accuracy of the different tests under evaluation was evaluated by directly and indirectly comparing the tests (as the reported evidence permitted).

Outcomes

Outcomes of interest are diagnostic test characteristics, namely, sensitivity, specificity, and likelihood ratios. Adverse events related to the procedures, such as radiation, discomfort, and reactions to contrast agents, were also discussed.

Timing

Any duration of followup, from same-day interventions to many years of clinical followup, was evaluated.

Setting

Any care setting was acceptable, including general hospitals, physician's offices, and specialized breast imaging centers.

Search Strategy

The medical literature was searched from December 1994 through September 2010. The full strategy is provided in Appendix A. In brief, we searched 10 external and internal databases, including PubMed and EMBASE, for clinical trials addressing the Key Questions. To supplement the electronic searches, we also examined the bibliographies/reference lists of included studies, recent narrative reviews, and scanned the content of new issues of selected journals and selected relevant gray literature sources.

Study Selection

We selected the studies that we consider in this report using *a priori* inclusion criteria. Some of the criteria we employed are geared towards ensuring that we used only the most reliable evidence. Other criteria were developed to ensure that the evidence is not derived from atypical patients or interventions, and/or outmoded technologies.

Studies of diagnostic test performance compare results of the experimental test to a reference test. The reference test is intended to measure the "true" disease status of each patient. It is important that the results of the reference test be very close to the truth, or the performance of the experimental test will be poorly estimated. For the diagnosis of breast cancer, the "gold standard" reference test is open surgical biopsy. However, an issue with the use of open surgical biopsy as the reference standard in large cohort studies of screening-detected breast abnormalities is the difficulty of subjecting women with probably benign lesions to open surgical biopsy. Furthermore, restricting the evidence base to studies that used open surgery as the reference standard for all enrolled subjects would eliminate the majority of the evidence. Therefore, we have chosen to use a combination of clinical and radiologic followup as well as core-needle biopsy and open surgical biopsy as the reference standard for our analysis, although we acknowledge that this decision may cause our analysis to over-estimate the accuracy of the noninvasive tests.[106]

We used the following formal criteria to determine which studies would be included in our analysis. Many of our inclusion criteria were intended to reduce the potential for spectrum bias. Spectrum bias refers to the fact that diagnostic test performance is not constant across populations with different spectrums of disease. For example, patients presenting with severe symptoms of disease may be easier to diagnose than asymptomatic patients in a screening population; and a diagnostic test that performs well in the former population may perform poorly in the latter population. The results of our analysis are intended to apply to a general population of women participating in routine breast cancer screening programs (mammography, clinical examination, and self-examination programs) and therefore many of our inclusion criteria are intended to eliminate studies that enrolled populations of women at very high risk of breast cancer due to family history, or populations of women at risk of recurrence of a previously diagnosed breast cancer.

1. The study must have directly compared the test of interest to core-needle biopsy, open surgery, or clinical followup of the same patient.

   Although it is possible to estimate diagnostic accuracy from a two-group trial, the results of such indirect comparisons must be viewed with great caution. Diagnostic cohort studies, wherein each patient acts as her own control, are the preferred study design for evaluating the accuracy of a diagnostic test.[107] *Studies may have performed biopsy procedures on all patients, or may have performed biopsy on some patients and followed the other patients with clinical examination and mammograms. Fine-needle aspiration of solid lesions is not an acceptable reference standard for the purposes of this assessment.*[108-111]

   Retrospective cohort studies that enrolled all or consecutive patients were considered acceptable for inclusion. However, retrospective case-control studies and case reports were excluded. Retrospective case-control studies have been shown to overestimate the accuracy of diagnostic tests, and case reports often report unusual situations or individuals that are unlikely to yield results that are applicable to general practice.[106,107] *Retrospective case studies (studies that selected cases for study on the basis of the type of*

lesion diagnosed) were also excluded because the data such studies report cannot be used to accurately calculate the overall diagnostic accuracy of the test.[106]

2. The studies must have used current generation scanners and protocols of the selected technologies only. Other noninvasive breast imaging technologies are out of the scope of this assessment.

   Studies of outdated technology and experimental technology are not relevant to current clinical practice. Definitions of "outdated technology" and "current technology" were developed through discussions with experts in relevant fields. Definitions of "current technology to be included" are defined in Table 2.

Table 2. Noninvasive current technologies to be evaluated

Technology	Cutoff Publication Date (to present) To Exclude Outdated Technology	Other Inclusion Criteria
Ultrasound	1994	
Magnetic resonance imaging (MRI)	2000	Must have used specific breast coils, and used gadolinium-based contrast agents
Computer Aided Detection (CAD) MRI	2005	Must have used specific breast coils, and used gadolinium-based contrast agents. CAD systems must be FDA approved for diagnostic breast cancer use, and are defined as stand-alone third-party packages that may be added to standard MRI systems to assist interpretation of the images.
Positron emission tomography (PET)	2000	FDG (fluorodeoxyglucose) as the PET tracer; includes positron emission mammography systems (PEM).
Combined PET/computed tomography (CT) systems	2000	FDG as the PET tracer
Scintimammography (SMM)	2005	Includes breast specific gamma imaging (BSGI) and also single photon emission tomography (SPECT); only studies that used sestamibi, also called MIBI, also called Technetium-99m sestamibi, as the tracer.

3. The study enrolled female human subjects.

   Animal studies or studies of "imaging phantoms" are outside the scope of the report. Studies of breast cancer in men are outside the scope of the report. However, studies of predominantly female patients that enrolled one or two men were considered acceptable.

4. The study must have enrolled patients referred for the purpose of primary diagnosis of a breast abnormality detected by routine screening (mammography and/or physical examination).

   Studies that enrolled women who were referred for evaluation after discovery of a possible breast abnormality by screening mammography or routine physical examination were included. Studies that enrolled subjects that were undergoing evaluation for any of the following purposes were excluded as being out of scope of the report: screening of asymptomatic women; breast cancer staging; evaluation for a possible recurrence of breast cancer; monitoring response to treatment; evaluation of the axillary lymph nodes; evaluation of metastatic or suspected metastatic disease; or diagnosis of types of cancer

other than primary breast cancer. Studies that enrolled patients from high-risk populations such as BRCA1/2 mutation carriers, or patients with a strong family history of breast cancer, are also out of scope. If a study enrolled a mixed patient population and did not report data separately, it was excluded if more than 15 percent of the subjects did not fall into the "primary diagnosis of women at average risk presenting with an abnormality detected on routine screening" category.

5. Study must have reported test sensitivity and specificity, or sufficient data to calculate these measures of diagnostic test performance; or (for Key Question 3) reported factors that affected the accuracy of the noninvasive test being evaluated.

   Other outcomes are beyond the scope of this report.
6. Fifty percent or more of the subjects must have completed the study.

   Studies with extremely high rates of attrition are prone to bias and were excluded.
7. Study must be published in English.

   Moher et al. have demonstrated that exclusion of non-English language studies from meta-analyses has little impact on the conclusions drawn. Juni et al found that non-English studies typically were of lower methodological quality and that excluding them had little effect on effect size estimates in the majority of meta-analyses they examined. Although we recognize that in some situations exclusion of non-English studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary for translation of studies to identify those of acceptable quality for inclusion in our reviews.[112,113]
8. Study must be published as a peer-reviewed full article. Meeting abstracts were not included.

   Published meeting abstracts have not been peer-reviewed and often do not include sufficient details about experimental methods to permit one to verify that the study was well designed.[114,115] *In addition, it is not uncommon for abstracts that are published as part of conference proceedings to have inconsistencies when compared to the final publication of the study, or to describe studies that are never published as full articles.*[116-120]
9. The study must have enrolled 10 or more individuals per arm.

   The results of very small studies are unlikely to be applicable to general clinical practice. Small studies are unable to detect sufficient numbers of events for meaningful analyses to be performed, and are at risk of enrolling unique individuals.
10. When several sequential reports from the same patients/study are available, only outcome data from the most recent report were included. However, we used relevant data from earlier and smaller reports if the report presented pertinent data not presented in the more recent report.

The abstracts of articles identified by the literature searches were screened for possible relevance in duplicate by four analysts. All exclusions at the abstract level were approved by the lead research analyst. The full-length articles of studies that appeared relevant at the abstract level were then obtained and three research assistants examined the articles to see if they met the inclusion criteria. All exclusions were approved by the lead research analyst. The excluded articles and primary reason for exclusion are shown in the Appendixes.

Data Abstraction

Standardized data abstraction forms were created and data were entered by each reviewer into the SRS© 4.0 database (see Appendixes). Three research assistants abstracted the data. The first fifty articles were abstracted in duplicate. All conflicts were resolved by the lead research analyst.

Study Quality Evaluation

We used an internal validity rating scale for diagnostic studies to grade the quality (internal validity) of the evidence base (see Appendixes). This instrument is based on a modification of the QUADAS instrument with reference to empirical studies of design-related bias in diagnostic test studies.[106,121] Each question in the instrument addresses an aspect of study design or conduct that can help to protect against bias. Each question can be answered "yes," "no," or "not reported," and each is phrased such that an answer of "yes" indicates that the study reported a protection against bias on that aspect.

Responses to the questions in the quality assessment instrument for each study are presented in the Evidence Tables in Appendix C.

Strength of Evidence Assessment

We applied a formal grading system that conforms with the CER *Methods Guide* recommendations on grading the strength of evidence.[122,123]

The overall strength of evidence supporting each major conclusion was graded as High, Moderate, Low, or Insufficient. The grade was developed by considering four important domains: the risk of bias in the evidence base, the consistency of the findings, the precision of the results, and the directness of the evidence.

The risk of bias (internal validity) of each individual study was rated as being Low, Medium, or High; and the risk of bias of the aggregate evidence base supporting each major conclusion was similarly rated as being Low, Medium, or High. We used our inclusion/exclusion criteria to eliminate studies with designs known to be prone to bias from the evidence base. Namely, case reports, case-control studies, and retrospective studies that did not enroll all or consecutive patients were not included for analysis. Because we eliminated all studies with a High risk of bias from the evidence base, we consider the remaining evidence base to have either a Low or Medium risk of bias.

We initially used an internal validity rating instrument for diagnostic studies to grade the internal validity of the individual studies (see section above Study Quality Evaluation). However, after we had conducted meta-regressions investigating the correlation between key individual items on the quality rating instrument and the results reported by the studies (see Appendix D for details), we consistently found that the majority of the items on the instrument had no statistically significant correlation with the reported results (with one exception, discussed below). We therefore concluded that the quality instrument was not adequately capturing the potential for bias of the studies in our sample (after eliminating study designs known to be prone to bias, such as retrospective case-control studies and case reports during the inclusion/exclusion process). Unlike studies of interventions, diagnostic cohort studies are quite simple in design, with one group of patients acting as their own controls. As long as all enrolled patients receive both the diagnostic test and the reference standard test, opportunities for bias (due to study design or conduct) to affect the results are limited. As mentioned above, we eliminated all

studies with a High risk of bias due to their study design from the evidence base. We did not identify any obvious design flaws in the remaining studies that suggested they were at Medium risk of bias; therefore, we rated all of the included studies, and the aggregate evidence bases, as being at Low risk of bias.

Meta-regressions did identify a statistically significant correlation between blinding of image readers to patient clinical information and the reported results of studies of MRI and ultrasound. Studies that blinded image readers to patient clinical information generally reported the blinded image readers had less accurate findings. It may, therefore, be that lack of blinding is a design flaw that is biasing the results. However, an alternative interpretation, which we favor, is that blinding image readers to patient clinical information is an artificial construct that will rarely if ever occur in clinical practice; therefore, non-blinded studies are generating an estimate of accuracy that is closer to the "real" accuracy that can be obtained in clinical practice. The majority of the studies are either non-blinded or did not specifically state whether they were blinded, leading us to believe that our aggregate pooled summary estimate of accuracy is close to the "real" accuracy of the technologies as used in routine clinical practice.

We rated the consistency of conclusions supported by meta-analyses with the statistic I^2.[124,125] Datasets that were found to have an I^2 of less than 50 percent were rated as being "Consistent"; those with I^2 of 50 percent or greater were rated as being "Inconsistent"; and datasets for which I^2 could not be calculated (e.g., a single study) were rated as "Consistency Unknown."

For qualitative direct comparisons between different diagnostic tests, we rated conclusions as consistent if the effect sizes were all in the same direction. For example, when comparing the accuracy of ultrasound without a contrast agent to the accuracy of ultrasound with a contrast agent, if the estimates of sensitivity of the individual studies are consistently higher for studies that used a contrast agent, then the evidence base would be rated as "consistent."

We defined a "precise" estimate of sensitivity or specificity as one for which the upper AND lower bound of the 95 percent confidence interval was no more than 5 points away from the summary estimate; for example, sensitivity 98 percent (95% CI: 97 to 100%) would be a precise estimate of sensitivity, whereas sensitivity 95 percent (95% CI: 88 to 100%) would be an imprecise estimate of sensitivity. Precision could be rated separately for summary estimates of sensitivity and specificity for each major conclusion.

For qualitative direct comparisons between different diagnostic tests, the conclusion is "Precise" if the confidence intervals around the summary estimates being compared do not overlap. We did not derive any formal conclusions (or formally rate the strength of evidence for any speculative statements) about indirect comparisons between different diagnostic tests.

According to the *Methods Guide*,[122]

The rating of directness relates to whether the evidence links the interventions directly to health outcomes.

For studies of diagnostic test accuracy, the evidence should always be rated as "Indirect" because the outcome of test accuracy is indirectly related to health outcomes. However, the Key Questions in this particular comparative effectiveness review do not ask about the impact of test accuracy on health outcomes. We therefore did not incorporate the "Indirectness" of the evidence into the overall rating of strength of evidence for these Key Questions because they did not ask about health outcomes.

Overall Rating of Strength of Evidence

The initial rating is based on the risk of bias. If the evidence base has a Low risk of bias, the initial strength of evidence rating is High; if the evidence base has a Moderate risk of bias, the initial strength of evidence rating is Moderate; if the evidence base has a High risk of bias, the initial strength of evidence rating is Low. For this particular comparative effectiveness review, as explained above, the rating of risk of bias was Low for all evidence bases, and therefore the initial strength of evidence rating is High. The remaining two domains are used to up- or down-grade the initial rating as per the following flow charts:

Consistent, Precise: High

Inconsistent, Precise: Moderate

Consistent, Imprecise: Moderate

Inconsistent, Imprecise: Low

"Consistency Unknown," Precise: Low

"Consistency Unknown," Imprecise: Insufficient

Evidence bases judged to be too small to support an evidence-based conclusion (e.g., one or two small studies) were simply rated "Insufficient" without formally considering the various domains. Further details about grading the strength of evidence may be found in the *Evidence* Tables section of the Appendixes.

Applicability

The issue of applicability was chiefly addressed by excluding studies that enrolled patient populations that were not a general population of asymptomatic women participating in routine breast cancer screening programs. We defined the population of interest as women at average risk of breast cancer participating in routine breast cancer screening programs (including mammography, clinical examination, and self-examination) who had been recalled after discovery of an abnormality and who had already undergone a standard work-up (diagnostic mammography and/or ultrasound and/or physical examination). We excluded studies that enrolled women thought to be at very high risk of breast cancer due to personal history, family history, or known carriers of BRCA mutations, and also excluded studies that enrolled patients presenting with overt symptoms such as nipple discharge or pain.

Data Analysis and Synthesis

The majority of studies reported data on a per-lesion rather than a per-patient basis, and therefore we analyzed the data on a per-lesion basis assuming that statistical assumptions about data independence were not being violated. Because the number of lesions was usually very similar to the number of patients (i.e., the vast majority of patients only had one lesion) we do not believe that this assumption will have a significant impact on the results.

We performed a standard diagnostic accuracy analysis. For the diagnostic accuracy analysis:

- True negatives were defined as lesions diagnosed as benign on imaging that were found to be benign by the reference standard;
- False negatives were defined as lesions diagnosed as benign on imaging that were found to be malignant (invasive or in situ) by the reference standard;
- True positives were defined as lesions diagnosed as malignant (invasive or in situ) on imaging that were found to be malignant (invasive or in situ) on the reference standard

- False positives were defined as lesions diagnosed as malignant that were found to be benign on the reference standard.

We meta-analyzed the data reported by the studies using a bivariate mixed-effects binomial regression model as described by Harbord et al.[8] All such analyses were computed by the STATA 10.0 statistical software package using the "midas" command.[9] The summary likelihood ratios and Bayes' theorem were used to calculate the post-test probability of having a benign or malignant lesion. In cases where a bivariate binomial regression model could not be fit, we meta-analyzed the data using a random-effects model and the software package Meta-Disc.[10] Meta-regressions were also performed with the STATA software and the "midas" command. We did not assess the possibility of publication bias because statistical methods developed to assess the possibility of publication bias in treatment studies have not been validated for use with studies of diagnostic accuracy.[126,127]

Diagnostic tests all have a trade-off between minimizing false-negative and minimizing false-positive errors. False-positive errors that occur during breast screening diagnostic workups are not considered to be as clinically relevant as false-negative errors. Women who experience a false-positive error will be sent for unnecessary procedures, and may suffer from anxiety and a temporarily reduced quality of life, as well as morbidities related to the procedures. However, women who experience a false-negative error may suffer morbidities, reduced quality of life, and possibly even a shortened lifespan from a delayed cancer diagnosis.

Likelihood ratios can be used along with Bayes' theorem to directly compute an individual woman's risk of actually having a malignancy following a diagnosis on imaging. However, each individual woman's post-test risk varies by her pre-test risk of malignancy. Simple nomograms are available for in-office use that allow clinicians to directly read individual patients' post-test risk off a graph without having to go through the tedium of calculations. Predictive value is another commonly used measure of errors; however, negative and positive predictive values are specific to specific populations of women. Predictive values vary by the prevalence of disease in each specific population and should not be applied to other populations with different prevalences of disease. For this reason, we have avoided the use of predictive values in this systematic review.

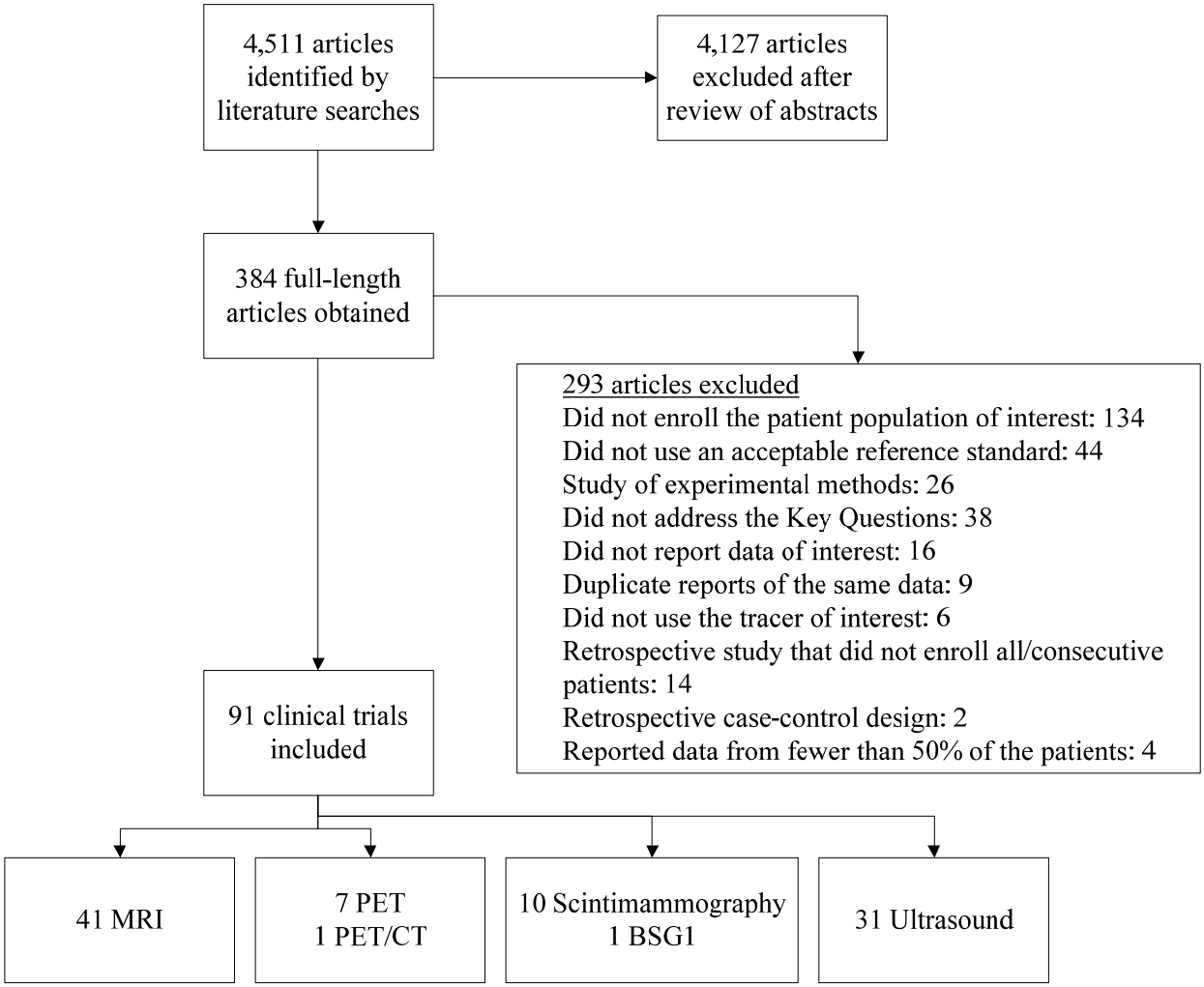
Peer Review and Public Commentary

A draft of the completed report was sent to the peer reviewers and representatives of AHRQ. The draft report was posted to the Effective Health Care Web site for public comment. In response to the comments of the peer reviewers and the public, revisions were made to the evidence report, and a summary of the comments and their disposition has been submitted to AHRQ, and will be made publicly available within 3 months of publication of this final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

Results

Our literature searches identified a total of 4,511 possible articles. After review of the abstracts, we selected 384 for further review as full-length articles to determine whether they met the inclusion criteria. The study selection process is summarized in Figure 2. Full details of excluded articles and reasons for exclusion are shown in the Appendixes. The included articles are described throughout this Results section. We have organized the Results section by type of noninvasive test rather than by Key Question.

Figure 2. Study selection process



Magnetic Resonance Imaging

Background

Technology

Magnetic resonance imaging (MRI) systems use strong magnetic fields and radiofrequency energy to translate hydrogen nuclei distribution in tissues into computer-generated images of the

structure of the interior of the breast. MRI does not expose patients to radiation. However, the procedure is not completely noninvasive because often contrast agents are infused to improve the resolution of the images.

MRI systems are usually described primarily in terms of strength of the magnet, in the unit Tesla (T). Systems in commercial use for breast imaging usually vary from 0.5T to 3.0T. In general, increasing the strength of the magnet increases the spatial resolution of the images. MRI systems that use field strengths below 1.0T are usually open gantries and are primarily used for patients who cannot be accommodated inside the bore of a higher field strength magnet due to claustrophobia. An additional reason for the use of open gantry systems is that MRI-guided invasive procedures, such as biopsies, are much easier to perform than in closed systems.[128]

Surface coils are routinely used in MRI to increase the efficiency of signal detection and, by extension, the image quality. Dedicated breast coils have been available for some time and are considered a prerequisite for breast imaging.[129] The dedicated breast coils allow the patient to lie prone with her breasts in close proximity to the coils. Some coils are designed to immobilize the breasts with compression. The compression reduces the volume to be imaged (and therefore reduces image acquisition time) and moves the coils closer to the tissue and helps prevent patient movement (so image quality is improved).[130,131] Coils are described by the number of channels they contain. In general, increasing the number of channels improves the signal to noise ratio.[130,132,133] Eight-channel breast coils are considered standard equipment for breast MRI examinations.

While all suppliers of MRI equipment provide suggested protocols for different examination types, it is common for users to customize these. The degree of protocol customization largely depends on the clinical users, both radiologists and technologists. Even in tightly controlled studies with a limited number of institutions all using equipment supplied by the same manufacturer, differences in technique have been observed.[134]

MR images are susceptible to a number of artifacts that could cause image distortion and false interpretations. In particular, breast MR images are prone to artifacts caused by sternal wires and prosthetic cardiac valves.[135] Also, respiratory motion can be a problem, although when the patient is prone the effect is reduced.[135] Interpretation of the images is a subjective procedure that requires specialized training.[136,137] Computer-based tools to partially automate the interpretation procedure are available and may reduce subjectivity and decrease time required for image interpretation.[138]

The use of contrast agents for MRI breast examinations is considered standard procedure. Gadolinium-based paramagnetic contrast agents accumulate in the vascular system and can aid in visualizing tumors by highlighting areas containing a dense blood vessel network. There are currently five slightly different gadolinium-based contrast agents in common clinical use: gadobenate dimeglumine, gadopentetate dimeglumine, gadodiamide, gadoteridol, and gadoversetamide.[139] These agents differ slightly in molecular structure; all, however, consist of the heavy metal gadolinium bound to a chelating molecule.[140] Different agents may have different imaging properties.[141,142] When using conventional gadolinium contrast agents, the exact dose used does not appear to be particularly relevant to image quality when used in the normal range (0.1 to 0.2 mmol/kg). When contrast is taken up by a lesion, one of three characteristic enhancement and wash-out curves are usually observed: continuous enhancement, rapid enhancement followed by a plateau, or rapid enhancement followed by rapid wash-out. Rapid wash-out is considered indicative of malignancy.[136] In premenopausal women, the normal parenchyma can demonstrate enhancement that can decrease the specificity of breast MRI

studies.[143,144] The amount of enhancement depends on the stage in the menstrual cycle. Therefore, in order to ensure accurate results, an MRI study should if possible be performed during the second week of the menstrual cycle when proliferative changes are at their lowest level.

For the purposes of this assessment, only MRI conducted on a 0.5 to 3T system using dedicated breast coils and gadolinium-based contrast agents has been considered. These requirements were selected because they describe the systems and methods currently considered to be "standard practice" for breast imaging; other systems and methods would be unlikely to produce results that would be applicable to current clinical practice.[145]

Patient Safety and Comfort

A number of well-known safety hazards exist when a patient is undergoing an MRI exam. Examples include: patient heating, pacemaker malfunction, dislodgment of metallic implants, peripheral nerve stimulation, acoustic noise, and radio frequency induced burns.[146-151] Precautions are taken at MRI facilities to routinely screen patients for possible contraindications. Patients are routinely asked to wear earplugs and are given an emergency call button. No adverse effects have been conclusively identified in association with the magnetic fields to which patients are exposed during routine MRI scanning.[152-155] Therefore, so long as routine precautions are followed, breast MRI can be considered a safe exam for most patients.

A search for reports of patient discomfort did not find any reports of severe discomfort. In fact, in order to decrease patient motion, it is important that the patient be as comfortable as possible.[135] Breast compression does increase the level of discomfort, but the amount is not significant, particularly when compared to the compression that is exerted during x-ray mammography exams.

Gadolinium-based contrast agents are generally considered to be very safe for most patients; some patients may experience allergic reactions which are generally mild.[156,157] However, in 2007, FDA requested that manufacturers include a new warning on the labeling of all gadolinium-based contrast agents which are used to enhance MRI.[139] The new labeling warns that the use of these agents increases the risk of development of nephrogenic systemic fibrosis (NSF) in patients with pre-existing acute or chronic severe renal insufficiency or renal dysfunction due to recent liver transplantation or hepatorenal syndrome.[158-160] NSF is a progressive, disabling, and potentially fatal disorder that leads to deposition of excessive connective tissue in the skin and internal organs. The condition was previously unknown; the typical patient is a middle-aged individual with severe renal disease who first exhibits skin changes 2 to 4 weeks after undergoing an MRI examination that used gadolinium-based contrast agents.[160]

Accreditation Factors

General-purpose MRI systems are cleared for marketing by United States Food and Drug Administration (FDA) under the 510(k) process. Accessories such as breast coils are cleared separately, also under the 510(k) process. Imaging devices are usually not cleared for specific indications; they are cleared for marketing for all indications in the entire body or in specified parts of the body.

There is no nationwide compulsory accreditation for MRI facilities. The American College of Radiology does administer a voluntary accreditation program.[161]

Findings From 2006 Review

Our CER from 2006 included 19 prospective diagnostic cohort studies of MRI (published between 1991 and 2004) that studied a total of 2181 suspicious breast lesions.[30-32,34,35,40-42,44-46,141,162-168]

We found that for suspicious lesions in general, at a fixed 95 percent sensitivity, the specificity of MRI was 62.8 percent. At the mean threshold of the studies, the sensitivity was 92.5 percent and the specificity was 72.4 percent. For lesions with microcalcifications, our analysis found that the sensitivity of MRI was 85.9 percent and the specificity was 75.5 percent.

Evidence Base

Our literature searches identified 41 diagnostic cohort studies of MRI (published 2000 through 2009) that studied a total of 3882 patients with 4,202 suspicious breast lesions.[11-51] The majority of the studies used 1.5T magnets (33 studies) and gadopentetic acid enhancement (26 studies). The studies and patients are described in detail in the Appendixes, and listed at the end of this subsection on MRI in Table 4.

Key Question 1. What is the accuracy of MRI for diagnosis of breast cancer in women referred for further evaluation after identification of a possible breast abnormality on routine screening (mammography and/or clinical or self-detection of a palpable lesion)?

We combined the data reported by all 41 studies into a bivariate binomial mixed model. The data were extremely heterogeneous ($I^2 = 98.4\%$). The summary sensitivity of MRI for all lesions was 91.7 percent (95% CI: 88.5 to 94.1%) and the summary specificity was 77.5 percent (95% CI: 71.0 to 82.9%). These summary estimates are fairly similar to our 2006 estimates of the accuracy of MRI (at the mean threshold the sensitivity was 92.5%, and the specificity was 72.4%).

We investigated the heterogeneity with meta-regression. The variables investigated were: the strength of the magnet, the type of contrast agent used, whether the study enrolled all/consecutive patients or not, whether the study was prospective in design or not, whether all diagnoses were verified by histopathology or not, whether any financial conflicts of interest from the funding source existed or not, whether the study was multi- or single-centered, whether readers were blinded to clinical information or not, whether the study accounted for inter-reader differences or not, the geographical setting of the study, whether the study was clearly affected by spectrum bias or not, and the prevalence of disease. The prevalence of disease in the study population and whether or not readers were blinded to clinical information were both found to be statistically significantly correlated with the accuracy data reported by the studies ($p = 0.02$ and 0.03, respectively). However, in subgroup analyses there was a statistical correlation between blinding of readers and prevalence of disease. Graphical analysis of prevalence of disease by accuracy failed to reveal any consistent pattern; therefore it is possible that the correlation between prevalence of disease and accuracy is an artifact caused by the correlation between blinding and enrollment of a population with a higher prevalence of disease. Studies that reported they had blinded readers to clinical information had a lower sensitivity than non-blinded studies (86.8% vs. 93.9%) but approximately the same specificity (74.7% vs. 78.0%).

Key Question 2. Are there demographic (e.g., age) and clinical risk factors (e.g., morphologic characteristics of the lesion) that affect the accuracy of the tests considered in Key Question 1?

Two studies reported the accuracy of MRI by patient age.[30,44] One of these two studies (Bluemke et al.[30]) investigated the relative accuracy by premenopausal status vs. post-menopausal status of the patients, and reported virtually no difference in either sensitivity or specificity between groups. The other study (Imbriaco et al.[44]) reported the accuracy of MRI for women 50 years of age and older vs. younger women, and found that MRI was more sensitive (100% vs. 92.9%) in younger women, but had virtually the same specificity (75.0%) in both age groups.

Eight of the studies enrolled patients who had been referred for further investigation after identification of microcalcifications on mammography.[20,22,23,25,30,39,46,51] When combined in a bivariate mixed-effects model the data from these eight studies had very low heterogeneity ($I^2 = 3.86\%$). The summary sensitivity of MRI for microcalcifications was 84.0 percent (79.5 to 88.3%) and the summary specificity was 79.4 percent (71.5 to 85.6%). The summary sensitivity of MRI for evaluation of microcalcifications is considerably lower than the sensitivity of MRI for evaluation of any/all lesions (84.0% vs. 91.7%). The specificity for microcalcifications is approximately the same (79.4% vs. 77.5%). Two studies also directly compared the sensitivity of MRI for evaluation of microcalcifications vs. other types or all types of lesions (Bluemke et al.[30] and Van Goethem et al.[51]) and reported similar results: the sensitivity of MRI for evaluation of microcalcifications is approximately 85 percent, which is considerably lower than the sensitivity of MRI for evaluation of all/other types of lesions; whereas the specificity of MRI for evaluation of microcalcifications is approximately 77 percent, which may be slightly higher than the specificity of MRI for evaluation of all/other types of lesions.

Two studies evaluated the accuracy of MRI for dense breasts vs. all or non-dense breasts (Bluemke et al.[30] and Wiberg et al.[40]), and reported virtually no difference in the accuracy of MRI for evaluation of these different categories of breast tissue.

One study enrolled only patients with lesions classified as BIRADS 3 before investigation by MRI (Gokalp and Topal[24]); however, only one enrolled patient (out of 43 total) was found to have a malignancy and therefore the patient population is too small to draw conclusions about the accuracy of MRI for probably benign lesions.

One study each investigated the accuracy of MRI for lesions broken down by palpable vs. non-palpable (Bluemke et al.[30]) and large lesion vs. small lesion (Imbracio et al.[44]).

Key Question 3. Are there other factors and considerations that may affect the accuracy or acceptability of MRI?

One study reported the accuracy of MRI images interpreted with and without a Computer Aided Diagnosis (CAD) software system.[12] The study reported virtually no difference in either sensitivity (77.4% vs. 78.9%) or specificity (73.2% vs. 73.2%) with or without CAD assistance.

Previously Published Systematic Reviews

We identified three systematic reviews of the use of MRI to evaluate women with prior clinical findings that suggest the possibility of breast cancer; two were published prior to the release of the 2006 version of this report. The methods and conclusions of these reviews are summarized in Table 3. The authors of two of the systematic reviews concluded that the negative

predictive value of MRI is too low for this indication, and therefore patients did not benefit from being examined by MRI after mammography; the authors of the third review (Peters et al.) did not speculate on the clinical utility of MRI.[169]

Table 3. Other published technology assessments of MRI

Study	Methods	Conclusions
Peters et al. 2008[169]	Systematic review of the literature on the diagnostic performance of contrast-enhanced MRI for breast lesions. The review included studies published 1985 through 2005, and identified 44 studies of 3101 women who had both MRI and breast biopsies. Summary ROC was fitted, and bivariate analyses were performed.	The summary sensitivity of MRI was 90% (95% CI: 88 to 92%), and the specificity was 72% (95% CI: 67% to 77%). Meta-regressions found that the prevalence of cancer in the population being studied affected the accuracy, as did the criteria used to identify lesions as malignant.
The Blue Cross/Blue Shield Technology Evaluation Program, published in 2002[170] and then updated in 2004[171]	Systematic review of the literature on the use of MRI to evaluate suspicious breast lesions in order to avoid biopsies. The review included 25 prospective studies and 14 retrospective studies. Reported data were described and a small, informal cost-benefit analysis was performed.	Reported sensitivity for MRI ranged from 91% to 99%; specificity ranged from 31% to 91%; and negative predictive value ranged from 56% to 99%. The authors of the review pointed out that in many of the populations studied, small breast lesions had been specifically excluded, and therefore the diagnostic performance of MRI in the clinic, where smaller lesions are often encountered, may be less accurate than predicted from these studies. The authors of the review performed a small, informal cost-benefit analysis and concluded that the negative predictive value of MRI was too low, even under the best possible conditions, to recommend the use of MRI for this indication. The potential benefit of sparing patients from unnecessary biopsy was not found to outweigh the potential harm of missed or delayed diagnosis of breast cancer.
Hrung et al. 1999[172]	A systematic review focused on women presenting with either a lesion that was palpably abnormal, or a BIRADS category 4 lesion detected by mammography. The review included 16 studies published between 1994 and 1997. Quality of the studies was rated on a 10-point scale (1 = highest quality, 10 = poorest quality). The data from the included studies were combined meta-analytically using the method of Littenburg and Moses.[173] The authors then conducted a cost-effectiveness analysis.	The mean quality score of the included studies was 3.0, indicating low quality. The optimal operating point of MRI, chosen to have a sensitivity of 95%, was found to have a specificity of 67%. Breast MRI is cost-effective relative to needle core biopsy only if MRI performance achieves a sensitivity and specificity of 93%, and needle core biopsy performance is less than the best available estimates. Therefore, the authors concluded that choosing needle core biopsy instead of MRI both increased patients QALYs and lowered the average cost per patient.

Conclusion

We found that the summary sensitivity of MRI for all lesions is 91.7 percent (95% CI: 88.5 to 94.1%) and the summary specificity is 77.5 percent (95% CI: 71.0 to 82.9%) (Table 5). The data are inconsistent (namely, demonstrated significant heterogeneity in our statistical model), but the estimate of sensitivity is precise, therefore the strength of evidence supporting the estimate of the sensitivity of MRI is moderate. The estimate of specificity is imprecise, and therefore the strength of evidence supporting the estimate of specificity of MRI is low.

The only patient or lesion "factor" that was found to affect the accuracy of MRI and that had sufficient evidence to support a conclusion was the consistent finding that the sensitivity of MRI for evaluation of microcalcifications is considerably lower than the sensitivity of MRI for evaluation of any/all lesions. The strength of evidence supporting this conclusion was rated as high.

To aid in interpretation of these findings, we used Bayes' theorem and the summary likelihood ratios for MRI used to evaluate lesions in general and to evaluate lesions with microcalcifications (see Table 6 and Table 7). These calculations suggest that MRI examinations of women thought to have a higher than 12 percent pre-MRI probability of cancer will not be very clinically useful for diagnostic purposes because the input provided by the MRI examinations would probably not affect the suspicion of malignancy sufficiently to alter clinical decisions about management of the patient (e.g., recommendations for biopsy vs. followup). For many women an MRI examination will probably not result in a change in management or affect patient outcomes. In Figure 3, we illustrate models of theoretical changes in management that could be made after the use of MRI. Figure 3 demonstrates that the majority of women referred for biopsy after standard work-up (the left-most pathway) would probably experience no change in management after the addition of MRI to the work-up. The middle and right-most pathways in Figure 3 indicate that women with low (12% and 1%) suspicion of malignancy after standard work-up might have their risk of malignancy shift across the "change in management" thresholds after the addition of an MRI. Note that a "change in management" does not necessarily mean that the patient will benefit from the change. For example, a woman thought to have a 1 percent suspicion of malignancy may be referred for a biopsy instead of short-interval followup after an MRI; but in most cases this biopsy will return a "benign" finding, suggesting the primary clinical impact of the addition of an MRI exam to the work-up of this particular patient population may be to increase the rate of unnecessary biopsies.

A critical question for the application of this finding is whether it is feasible for clinicians to precisely estimate pretest probability in this range. Many of our expert reviewers did not think it is possible using currently available risk assessment methods.

Table 4. Included studies: magnetic resonance imaging (MRI)

Study	MRI Methods Studied	Design*	N Patients
Akita et al. 2009[11]	1.5T gadodiamide	Diagnostic cohort study	50
Baltzer et al. 2009[12]	1.5T gadopentetic acid CAD assistance vs. not	Prospective diagnostic cohort	329
Hara et al. 2009[13]	1.5T gadodiamide	Diagnostic cohort study	103
Kim et al. 2009[14]	1.5T gadopentetic acid	Diagnostic cohort study	249
Lo et al. 2009[15]	3T gadopentetic acid	Prospective diagnostic cohort	31
Imbracio et al. 2008[16]	1.5T gadopentetic acid	Prospective diagnostic cohort	44

Table 4. Included studies: magnetic resonance imaging (MRI) (continued)

Study	MRI Methods Studied	Design*	N Patients
Pediconi et al. 2008[17]	1.5T gadopentetic acid vs. gadobenic acid	Prospective diagnostic cohort	47
Vassiou et al. 2009[18]	1.5T gadopentetic acid	Prospective diagnostic cohort	69
Brem et al. 2007[19]	1.5T gadopentetic acid	Diagnostic cohort study	23
Cilotti et al. 2007[20]	1.5T gadoteridol	Retrospective	55
Pediconi et al. 2007[21]	1.5T gadobenic acid	Prospective diagnostic cohort	164
Zhu et al. 2007[22]	1.5T gadodiamide	Retrospective	52
Bazzocchi et al. 2006[23]	1.0 or 1.5 T gadoteridol	Prospective diagnostic cohort	174
Gokalp and Topal 2006[24]	1.5T gadopentetic acid	Prospective diagnostic cohort	43
Kneeshaw et al. 2006[25]	1.5T gadopentetic acid	Prospective diagnostic cohort	88
Ricci et al. 2006[26]	1.5T gadobenic acid	Prospective diagnostic cohort	48
Pediconi et al. 2005[27]	1.5T gadobenic acid	Prospective diagnostic cohort	36
Pediconi et al. 2005[28]	1.5T gadopentetic acid vs. gadobenic acid	Prospective diagnostic cohort	26
Wiener et al. 2005[29]	1.5 T gadopentetic acid	Prospective diagnostic cohort	65
Bluemke et al. 2004[30]	1.5T gadopentetic acid	Prospective diagnostic cohort	821
Huang et al. 2004[31]	1.5T gadodiamide	Prospective diagnostic cohort	50
Bone et al. 2003[32]	1.5T gadopentetic acid	Prospective diagnostic cohort	97
Daldrup-Link et al. 2003[33]	1.5T gadopentetic acid	Prospective diagnostic cohort	14
Heinisch et al. 2003[34]	1.0T gadopentetic acid	Prospective diagnostic cohort	36
Walter et al. 2003[35]	1.0T gadopentetic acid	Prospective diagnostic cohort	40
Guo et al. 2002[36]	1.5T gadopentetic acid	Retrospective diagnostic cohort	52
Kelcz et al. 2002[37]	1.5T gadodiamide	Prospective diagnostic cohort	62
Schedel et al. 2002[38]	1.5T gadopentetic acid	Diagnostic cohort study	65
Trecate et al. 2002[39]	1.5T gadopentetic acid	Prospective diagnostic cohort	28
Wiberg et al. 2002[40]	1.5T gadopentetic acid	Prospective diagnostic cohort	93
Brix et al. 2001[41]	1.5T gadopentetic acid	Prospective diagnostic cohort	14
Cecil et al. 2001[42]	1.5T gadopentetic acid	Diagnostic cohort study	37
Furman-Haran et al. 2001[43]	1.5T gadodiamide	Prospective diagnostic cohort	40
Imbriaco et al. 2001[44]	0.5T gadopentetic acid	Prospective diagnostic cohort	49
Malich et al. 2001[45]	1.5T gadopentetic acid	Diagnostic cohort study	94
Nakahara et al. 2001[46]	0.5T gadopentetic acid	Retrospective review of patients with microcalcifications on mammogram	40
Torheim et al. 2001[47]	1.5T gadodiamide	Prospective diagnostic cohort	127
Wedegartner et al. 2001[48]	1.0T gadopentetic acid	Prospective diagnostic cohort	53
Yeung et al. 2001[49]	1.5T gadopentetic acid	Diagnostic cohort study	30
Kvistad et al. 2000[50]	1.5T gadodiamide	Prospective diagnostic cohort	130
Van Goethem et al. 2000[51]	NR T gadopentetic acid	Retrospective review of patients with microcalcifications or a problem after clinical examination/mammogram/US	75

* At times it was difficult to determine if a study was prospective or retrospective, and in those cases we defaulted to simply calling it a "diagnostic cohort study."

Table 5. Magnetic resonance imaging (MRI) accuracy

	N Studies	N Lesions	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)	Strength of Evidence
MRI, overall	41	3,882	91.7% (88.5 to 94.1%)	77.5% (71.0 to 82.9%)	Moderate (sensitivity)/ Low (specificity)
MRI, lesions with microcalcifications	8	692	84.3% (79.5 to 88.3%)	79.4% (71.5 to 85.6%)	High (sensitivity), Moderate (specificity)
MRI, dense breasts vs. others	2	935	Results were inconsistent	Results were inconsistent	Insufficient
MRI, lesions classified as BIRADS 3 before MRI imaging	1	56	100.0% (20.8 to 99.2%)	96.4% (87.5 to 98.9%)	Insufficient
MRI, palpable lesions vs. non-nonpalpable lesions	1	821	MRI is more sensitive for palpable lesions	MRI is more specific for non-palpable lesions	Insufficient
MRI, small lesions vs. larger lesions	1	53	MRI is more sensitive for larger lesions	MRI is more specific for larger lesions	Insufficient
MRI, readers blinded vs. not	41	3,882	Sensitivity is lower if readers are blinded to patient clinical information	Specificity is not affected	Moderate
MRI, CAD assistance vs. not	1	451	Sensitivity is not affected	Specificity is not affected	Insufficient
MRI, patient age	2	874	Results were inconsistent	Specificity is not affected	Insufficient

Table 6. Clinical interpretations of magnetic resonance accuracy: benign finding on MRI

Pretest Probability of the Lesion Being Malignant	Post-test Probability of the Lesion Being Malignant Despite a Finding of "Benign" on the MRI Exam	
	Lesions in General[a]	Lesions with Microcalcifications
1%	0% (0 to 0%)	0% (0 to 0%)
5%	1% (0 to 1%)	1% (0% to 1%)
10%	1% (1 to 2%)	2% (2 to 3%)
12%	1% (1 to 2%)	Not calculated
20%	3% (2 to 4%)	5% (4 to 6%)
30%	5% (3 to 6%)	8% (6 to 10%)
40%	7% (5 to 9%)	12% (9 to 15%)
50%	10% (7 to 13%)	16% (13 to 21%)
60%	14% (11 to 18%)	23% (18 to 28%)
70%	20% (16 to 26%)	31% (26 to 38%)
80%	31% (24 to 38%)	44% (37 to 51%)
90%	50% (42 to 57%)	64% (57 to 70%)

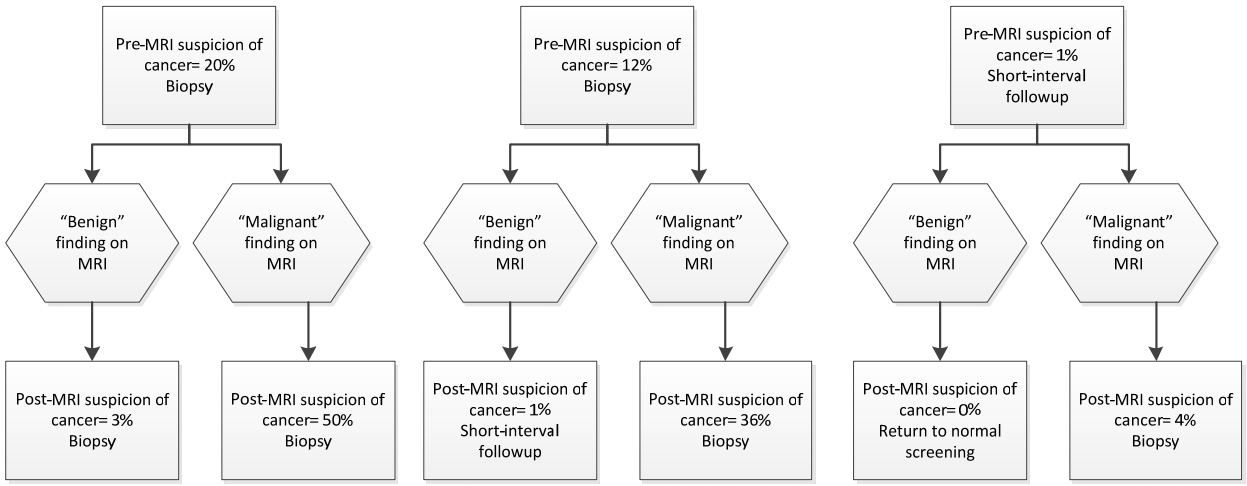
[a] The summary negative likelihood ratio is 0.11 (95% CI: 0.079 to 0.15).

Table 7. Clinical interpretations of MRI accuracy: malignant finding on MRI

Pretest Probability of the Lesion Being Malignant	Post-test Probability of the Lesion Being Malignant After a Finding of "Malignant" on the MRI Exam	
	Lesions in General[a]	Lesions with Microcalcifications
1%	4% (3 to 5%)	4% (3 to 5%)
5%	18% (14 to 22%)	18% (13 to 23%)
10%	31% (26 to 37%)	31% (25 to 39%)
20%	50% (44 to 57%)	51% (42 to 59%)
30%	64% (57 to 69%)	64% (56 to 71%)
40%	73% (67 to 78%)	73% (66 to 79%)
50%	80% (76 to 84%)	80% (75 to 85%)
60%	86% (82 to 89%)	86% (81 to 90%)
70%	90% (88 to 93%)	91% (87 to 93%)
80%	94% (93 to 95%)	94% (92 to 96%)
90%	97% (97 to 98%)	97% (96 to 98%)

[a] The summary positive likelihood ratio is 4.1 (95% CI: 3.1 to 5.3).

Figure 3. Possible clinical scenarios for MRI: theoretical changes in management



Positron Emission Tomography

Background

Technology

Positron emission tomography (PET) is a nuclear imaging modality that uses radioactive tracers to provide images of metabolic processes. Several different radiopharmaceuticals can be used in PET imaging. The tracer most commonly used is ^{18}F-fluorodeoxyglucose (FDG). Fluorine-18 (^{18}F) is a positron-emitting radionuclide, and this assessment will focus exclusively on PET scans that used FDG as a tracer. Fluorodeoxyglucose is a glucose analog that accumulates in tissue in proportion to the tissue's metabolic activity. Rapidly dividing tumor cells metabolize large amounts of glucose. The uptake of the radioactive tracer FDG can be monitored by PET and provide images of regional glucose metabolism. Areas of elevated metabolism, which may be tumor cells, can be visualized on the PET images.

When performing a PET scan, a small amount of FDG is injected into the bloodstream, and a gamma camera, dedicated breast scanner, or whole-body scanner is used to generate images that highlight areas of high tracer uptake. Whole-body scanners have a ring of detectors that surround the patient and image the entire body. Gamma cameras have only two detectors, one at each side of the patient, and image only a restricted portion of the body. Dedicated breast scanners have two detectors designed to image only the breasts. The performance of the different cameras may vary. However, it is not clear how clinically relevant these differences are with respect to the accuracy of breast imaging.[174]

Other factors may also affect the quality of the breast image acquired through a PET scan. In general, longer image acquisition times will improve the image quality of any PET scan.[174] However, other factors such as patient movement, comfort, and workflow suggest that acquisition times be kept to minimum. The optimum time depends on the characteristics of the detector, with dedicated breast cameras requiring the least amount of time (four to five minutes) and whole body scanners requiring the most time (45 to 60 minutes) to acquire the full image.[174]

In whole-body PET studies, it is standard practice to acquire a second set of images so that the reconstructed images can be corrected to account for differences in the attenuation of the gamma photons in different areas of the body ("attenuation correction"). In breast imaging some operators believe that attenuation correction is essential for tumor localization and quantification of uptake.[175]

The standardized uptake value (SUV), which is the mean tracer activity detected normalized for the injected dose of tracer and body weight, is dependent on the image reconstruction algorithm.[174] The reconstruction algorithm is manufacturer dependent. Therefore, diagnostic performance of breast PET imaging may vary across manufacturers. Diagnostic performance may also vary depending on study-specific factors such as FDG uptake time, patient motion, size of the lesion, histology of lesion, patient weight, blood glucose level, patient position, spatial resolution, and interpretation of the breast image.[175-177]

According to Rosen et al., stand-alone whole-body PET scanners for oncology indications are rapidly becoming obsolete.[178] Combined computed tomography (CT)/PET systems are increasingly available and currently account for almost all of the new whole-body PET installations. These systems allow images of metabolism and anatomy to be obtained at the same time. The combined machine uses x-rays to generate 3D anatomical images (CT scanning) upon which the PET images of metabolism can be overlaid on a computer workstation. In this report, whole-body scanners that combine PET with CT and stand-alone PET scanners will be considered as separate technologies.

Patient Safety and Comfort

Using a typical dose for a whole-body scan, the effective radiation dose delivered during a typical PET study is 19 μSv/MBq (the value depends on how often the patient voids). This translates to 7.6 mSv for a typical 400 MBq whole-body PET exam. The use of a combined CT/PET scanner also exposes the patient to x-rays. A typical abdominal CT scan exposes the body to approximately 10 mSv, for a total of around 18 mSv for a single PET/CT study.[179] For comparison, a typical x-ray mammogram exposes women to 0.36 mSV.[180] Studies of atomic-bomb survivors and radiation workers have found a significant increase in the risk of cancer after exposure to as little as 20 mSv.[179] Therefore, radiation dose from PET/CT scans may be a health concern. Following the exam, the short half-life of ^{18}F means that additional precautions, such as avoiding public transportation, are not necessary.[181]

The intravenous administration of any pharmaceutical could lead to an adverse reaction. In a retrospective analysis of 81,801 administrations of PET radiopharmaceuticals, the number of serious adverse reactions reported was zero.[182] Therefore, PET radiopharmaceuticals can be considered safe. All PET studies require the patient to relax for about an hour before image acquisition begins. In a whole-body PET camera, the patient must lie prone for 15 minutes to an hour, depending on the coverage of the study. No significant patient comfort issues have been reported.

Accreditation Factors

The Intersocietal Commission for the Accreditation of Nuclear Medicine Laboratories (ICANL) offers voluntary accreditation to facilities based on a peer review of their staff's qualifications, education, equipment, quality control, and volume of clinical procedures.[183]

All medical and technical staff are required to meet specific minimum experience and education requirements in order for their facility to be accredited by ICANL. Options available to a facility's medical staff range from board certification in nuclear medicine to board certification in a specialty area with a minimum number of years' practice and volume of studies interpreted.

The accreditation program requires the technical director and all technologists working in the facility to hold the RT(N) credential from the American Registry of Radiologic Technologists (ARRT) or the CNMT credential from the Nuclear Medicine Technology Certification Board (NMTCB). In all situations, the physician is ultimately responsible to see that the appropriate images are obtained.

Findings From 2006 Review

In the 2006 version of this CER, we included eight prospective diagnostic cohort studies of 226 breast lesions that were examined by whole-body PET scanning[34,35,41,55,184-187] and one study of 50 patients that compared whole-body PET scanning to PET imaging with a gamma camera.[188] We found that for suspicious lesions in general, at a fixed sensitivity of 95 percent, the specificity of whole-body PET scanning was only 46.7 percent. At the mean threshold of the included studies, the sensitivity of PET scanning was 82.2 percent and the specificity was 78.3 percent. There were no or insufficient data to come to any conclusions about the use of PET to evaluate any sub-populations of patients. Finally, we found that whole-body PET scanning was more accurate than gamma camera PET imaging for ruling out breast cancer. No studies of dedicated breast PET scanners met the inclusion criteria.

Evidence Base

Our literature searches identified seven diagnostic cohort studies of 18-fluorodeoxyglucose PET that met our inclusion criteria[34,35,41,52-55] and one study of the diagnostic value of dual-time point FDG-PET/CT.[16] All of the studies used a whole-body PET scanner. We did not identify any studies that used PEM devices and met the inclusion criteria.

The included studies enrolled 398 patients who were all women with suspicious lesions detected by physical exam, mammography, or ultrasound. Overall, a total of 403 lesions were detected. One of the studies excluded patients with lesions smaller than 1.0 cm (Brix et al.[41]). Patients ranged in age from 21 to 91, and reported mean ages ranged from 48.3 to 58.0, suggesting that the patient populations studied are younger than the typical breast cancer population. In all seven studies, final diagnosis was established through biopsy or surgery. One

study also clinically followed patients who were diagnosed as benign at biopsy (Kaida et al. 2008[52]). The included studies are listed in Table 8 at the end of this subsection on PET, and are described in detail in the Appendixes.

The single included study of PET/CT enrolled a total of 44 patients with 55 suspicious breast lesions detected by physical examination, mammography, or ultrasound.[16] No studies of dedicated breast PET scanners met the inclusion criteria.

Key Question 1. What is the accuracy of PET for diagnosis of breast cancer in women referred for further evaluation after identification of a possible breast abnormality on routine screening (mammography and/or clinical or self-detection of a palpable lesion)?

Seven studies reported results for 403 lesions in patients referred for further evaluation by whole-body PET scanning for suspicious breast lesions (abnormal mammogram and/or physical examination and/or ultrasound examination), summarized in Table 8. When combined in a mixed-effects bivariate model, the summary sensitivity of PET for all lesions was 83.0 percent (95% CI: 73.0 to 89.0%), and the summary specificity was 74.0 percent (95% CI: 58 to 86%), findings that are virtually identical to our estimates in the 2006 CER (Table 9). However, the data were found to contain significant heterogeneity ($I^2 = 64.0\%$), indicating substantial variability across the study results. The observed heterogeneity could not be explained through meta-regression using the following covariates: position (prone versus supine), enrolled mostly patients with palpable lesions (>75% vs. <75% or not reported), and blinded to patient clinical information (versus not blinded or not reported).

Because the PET data are inconsistent and imprecise, we rated the strength of evidence supporting the estimate of accuracy as "low."

The study of PET/CT was a single-center study that enrolled a total of 44 patients with 55 suspicious breast lesions detected by physical examination, mammography, or ultrasound.[16] PET scanning was performed at two time points. The first acquisition (Time 1) occurred immediately after an initial whole-body PET scan, and the second one (Time 2) occurred three hours after the first. At both time points, the images of the breast were acquired in the prone position. The CT data were used for attenuation correction, and images were reconstructed using a standard iterative algorithm.

The authors reported that dual-time point PET/CT (Time 2) demonstrated a sensitivity of 80 percent and specificity of 100 percent compared to a sensitivity of 62 percent and specificity of 100 percent for single time-point PET/CT. The authors concluded that malignant lesions showed a significant increase in FDG over time compared to benign lesions.

Key Question 2. Are there demographic (e.g., age) and clinical risk factors (e.g., morphologic characteristics of the lesion) that affect the accuracy of the tests considered in Key Question 1?

In three of the seven studies that addressed Key Question 1, the majority (>75.0%) of the women presented with palpable breast lesions— Kiada et al.[52]: 88.0 percent palpable, Schirrmeister et al.[54]: 76.0 percent, and Yutani et al.[55]: 93.0 percent palpable. Because there were only three studies, we could not fit the data in a bivariate model. Instead, we pooled the reported sensitivities and specificities in random-effects meta-analyses. However, the data were heterogeneous ($I^2 = 68.0\%$ and $I^2 = 54.6\%$ for sensitivity and specificity, respectively), indicating substantial variability among the study results. With only three studies, we did not attempt to

explore possible reason(s) for the heterogeneity. The overall sensitivity for primarily palpable lesions is higher than that for all seven studies considered under Key 1 (86.5% vs. 83.0%), but the specificity is lower (64.2% vs. 74.0%).

One study directly compared images acquired when patients were in prone position to images of the same patients in supine position.[52] In this study by Kaida et al. 2008, 118 women with 122 lesions suspected of having breast cancer underwent whole-body PET in the supine position immediately followed by prone breast PET imaging. According to the results reported in the study, the sensitivity and specificity of images in the supine position were 83.0 percent and 50.0 percent, respectively. The sensitivity and specificity of images in the prone position were 96.0 percent and 50.0 percent, respectively.

One study, Yutani et al. 2000, reported results separately for patients with BIRADS 5, lesions 1.5 cm or larger, and who were younger than 65.[55] The authors reported that PET was more sensitive for larger lesions, but the specificity was unchanged; and for the other factors, the accuracy of PET was virtually the same as for PET for all patients.

Key Question 3. Are there other factors and considerations that may affect the accuracy or acceptability of the tests considered in Key Questions 1 and 2?

None of the seven studies on stand-alone PET scanning or the one study on PET with CT reported information that addressed this question.

Previously Published Systematic Reviews

We identified two systematic reviews of PET for differential diagnosis of breast lesions. The review published by Sampson et al. in 2002 assessed the performance of PET in the differential diagnosis of benign and malignant lesions among patients with abnormal mammograms or a palpable breast mass.[189,190] The review included 13 articles published before March 2001. A more recent review was written by Escalona et al. and published in 2010.[191] This review included 16 studies of PET for diagnosis of breast lesions published before February 2007.

Sampson et al. performed a meta-analysis using a random-effects model, and selected a point on the summary ROC that reflected test performance, with a sensitivity of 89 percent and a specificity of 80 percent. When the prevalence of malignancy was 50 percent, 40 percent of all patients would benefit by avoiding the harm of a biopsy with negative biopsy results. However, the negative predictive value was found to only be 88 percent. For a patient with a negative PET scan, the authors concluded that a 12 percent chance of a missed or delayed diagnosis of breast cancer is too high to make it worth the 88 percent chance of avoiding biopsy of a benign lesion.[189,190]

Escalona et al. conducted a narrative discussion of the included studies and their findings. The authors concluded that "FDG-PET does not appear to be sufficiently accurate to be used in isolation for ruling out the presence of a primary tumour."[191]

Conclusion

We found that the summary sensitivity of PET for all lesions is 83.0 percent (95% CI: 73.0 to 89.0%) and the summary specificity is 74.0 percent (95% CI: 58.0 to 86.0%). The data are,

however, inconsistent and imprecise, therefore the strength of evidence supporting the estimate of the accuracy of PET is low.

There was insufficient data reported by the studies to conclude much about the impact of various factors on the accuracy of PET. PET may be equally accurate for evaluation of palpable lesions as for evaluation of lesions in general, but only three studies reported information about palpable lesions only.

To aid in interpretation of these findings, we used Bayes' theorem and the summary likelihood ratios for PET used to evaluate lesions in general (see Table 10 and Table 11). These calculations suggest that PET examinations of women thought to have a higher than 5 percent chance of malignancy will not be very clinically useful for diagnostic purposes because the input provided by the PET examination would probably not affect the suspicion of malignancy sufficiently to alter clinical decisions about management of the patient (e.g., recommendations for biopsy vs. followup). A critical question for the application of this finding is whether it is feasible for clinicians to precisely estimate pretest probability in this range. Several of our expert reviewers did not think it is possible using currently available risk assessment methods. For many women a PET examination will probably not result in a change in management or affect patient outcomes. This is further illustrated in Figure 4, where models of theoretical changes in management that could be made after the use of PET are shown graphically.

Table 8. Included studies: PET and PET/CT

Study	PET Methods Studied	Study Design*	Number of Patients
Imbriaco et al. 2008[16]	PET/CT	Diagnostic cohort study	44
Kaida et al. 2008[52]	Whole body PET	Prospective cohort study	118
Buchmann et al. 2007[53]	Whole body PET	Prospective cohort study	29
Hienisch et al. 2003[34]	Whole body PET	Prospective cohort study	36
Walter et al. 2003[35]	Whole body PET	Prospective cohort study	44
Brix et al. 2001[41]	Whole body PET	Prospective cohort study	14
Schirrmeister et al. 2001[54]	Whole body PET	Prospective cohort study	117
Yutani et al. 2000[55]	Whole body PET	Prospective cohort study	40

* At times it was difficult to determine if a study was prospective or retrospective, and in those cases we defaulted to simply calling it a "diagnostic cohort study."

Table 9. PET accuracy

Category	N Studies	N Lesions	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)	Strength of Evidence
PET	7	403	83.0% (73.0 to 89.0%)	74.0% (58.0 to 86%)	Low
PET/CT	1	55	80% (63 to 89%)	100% (63 to 100%)	Insufficient
PET, palpable lesions	3	275	86.5% (81.4 to 90.7%)	64.2% (49.8 to 76.9%)	Low
PET, prone vs. supine	1	122	PET performed in the prone position is more sensitive	Patient position did not affect specificity of PET	Insufficient
PET, BIRADS 5 lesions	1	26	93% (76.5% to 99.1%)	100.0% (15.7% to 84.3%)	Insufficient
PET, large lesions	1	27	79.4% (62.1% to 91.3%)	100.0% (2.5% to 100.0%)	Insufficient
PET, patients younger than age 65	1	25	78.1% (60.0% to 90.7%)	100.0% (15.8% to 100.0%)	Insufficient

Table 10. Clinical interpretations of PET accuracy: benign finding on PET

Pre-test Probability of the Lesion Being Malignant	Post-test Probability of the Lesion Being Malignant Despite a Finding of "Benign" on the PET Exam
	Lesions in General[a]
1%	0% (0 to 0%)
5%	1% (1 to 2%)
10%	3% (2 to 4%)
20%	6% (4 to 8%)
30%	9% (6 to 14%)
40%	14% (9 to 20%)
50%	19% (13 to 27%)
60%	26% (18 to 36%)
70%	36% (26 to 46%)
80%	49% (38 to 60%)
90%	68% (57 to 77%)

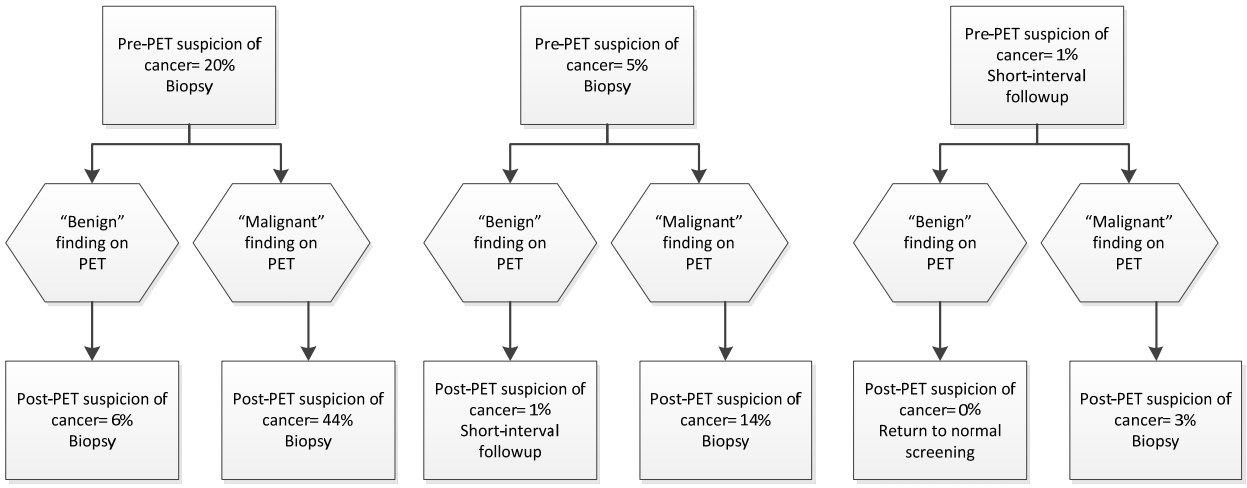
[a] The summary negative likelihood ratio is 0.24 (95% CI: 0.15 to 0.37).

Table 11. Clinical interpretations of PET accuracy: malignant finding on PET

Pre-test Probability of the Lesion Being Malignant	Post-test Probability of the Lesion Being Malignant After a Finding of "Malignant" on the PET Exam
	Lesions in General[a]
1%	3% (2 to 5%)
5%	14% (9 to 22%)
10%	26% (17 to 38%)
20%	44% (32 to 57%)
30%	58% (45 to 70%)
40%	68% (56 to 78%)
50%	76% (66 to 84%)
60%	83% (74 to 89%)
70%	88% (82 to 93%)
80%	93% (88 to 96%)
90%	97% (94 to 98%)

[a] The positive likelihood ratio is 3.2 (95% CI: 1.9 to 5.4).

Figure 4. Possible clinical scenarios for positron emission tomography (PET): theoretical changes in management



Scintimammography

Background

Technology

Scintimammography (SMM) is similar to PET scanning in that it detects tissues that accumulate higher levels of a radioactive tracer. The tracer most commonly used for breast examination is ^{99m}technetium-sestamibi (MIBI), and this assessment will only evaluate studies that used MIBI as the tracer. MIBI has a strong affinity for breast tumors, but may also accumulate in areas of inflammation or infection.[192] A method of improving visualization of tumor tissue specifically is "double phase" SMM, in which two sets of images, one acquired immediately after administration of the tracer, and one approximately 30 minutes later, are acquired and compared. Gamma cameras used for scintimammography are designed to perform either planar imaging or single photon emission tomography (SPECT). In planar imaging, each imaged point represents the superimposition of all materials in front and behind it over-laid into a two-dimensional image. This causes objects that are perpendicular to the image to appear shortened.[193] SPECT is a technique that uses multiple camera heads and computer processing to create a three-dimensional representation of the administered radiopharmaceutical taken up by tissue.

Scintimammography with MIBI may have limited spatial resolution for demonstrating cancers with diameters smaller than 10 mm.[194-196] The sensitivity of scintimammography has also been reported to be affected by type of tumor, size of tumor, and the phase of the menstrual cycle.[197] Scintimammography has been reported to be unaffected by the presence of a breast implant or by the density of the breast tissue.[197]

Breast specific gamma imaging (BSGI) is an offshoot of scintimammography. In 1999, Dilon Technologies received FDA 510(k) clearance for a BSGI camera. Their current product, the Dilon 6800®, is purported to overcome the obstacles of traditional scintimammography by providing a high resolution image with a small field of view. Specifically, the manufacturer claims it can identify very early stage cancers, about 1 mm in size; is not affected by breast

density; can differentiate benign from malignant lesions; and is smaller than traditional gamma imaging systems, allowing for easy portability from site to site.[198]

Patient Safety and Comfort

A typical scintimammography study exposes the patient to approximately 9 mSv.[199] For comparison, a typical x-ray mammogram exposes the patient to 0.36 mSv.[180]

Intravenous injection of MIBI has been associated with very few reported adverse reactions.[200] A case of a patient without a past history of allergies, who developed a rash following administration of MIBI, has been reported in the literature.[201] Another study reports, in addition to rash development, patients experiencing a strange taste following injection of MIBI.[202]

Other than removal of all clothing and jewelry above the waist, no special preparation is required of patients undergoing a scintimammography imaging study. Compared to other breast imaging procedures, scintimammography imaging takes longer to perform – forty minutes or more.[203] During a typical study, the patient is placed in a prone position with the breast to be imaged hanging down.[204] Although taut compression of the breast to be imaged is not required, prevention of cross-talk may require compression of the opposite breast.[195,205]

Accreditation Factors

The Intersocietal Commission for the Accreditation of Nuclear Medicine Laboratories (ICANL) offers voluntary accreditation to facilities based on a peer review of their staff's qualifications, education, equipment, quality control, and volume of clinical procedures.[183]

All medical and technical staff are required to meet specific minimum experience and education requirements in order for their facility to be accredited by ICANL. Options available to a facility's medical staff range from board certification in nuclear medicine to board certification in a specialty area with a minimum number of years' practice and volume of studies interpreted.

The accreditation program requires the technical director and all technologists working in the facility to hold the RT(N) credential from the American Registry of Radiologic Technologists (ARRT) or the CNMT credential from the Nuclear Medicine Technology Certification Board (NMTCB). In all situations, the physician is ultimately responsible to see that the appropriate images are obtained.

Findings From 2006 Review

Forty-four diagnostic cohort studies published in 45 manuscripts met our inclusion criteria.[32,36,44,55,85,163,166,167,185,206-241] Our analysis found that for non-palpable lesions, at a fixed 95 percent sensitivity, the specificity of scintimammography was only 39.2 percent. At the mean threshold of the included studies, the sensitivity was 68.7 percent and the specificity was 84.8 percent. For palpable lesions and suspicious breast lesions in general, there was unexplained heterogeneity in the data, and therefore summary diagnostic test characteristics were not calculated.

Evidence Base

Our literature searches identified a total of 11 studies of 1,064 patients that met the inclusion criteria for Key Question 1. One study evaluated BSGI;[19] another tested planar and SPECT imaging combined;[56] five studies assessed double-phase scintimammography;[14,57-60] and the

remaining four studies assessed planar imaging.[61-64] These studies are described in detail in the Appendixes, and are listed at the end of this subsection on scintimammography in Table 13.

Key Question 1. What is the accuracy of scintimammography for diagnosis of breast cancer in women referred for further evaluation after identification of a possible breast abnormality on routine screening (mammography and/or clinical or self-detection of a palpable lesion)?

When all 11 studies were combined in the analysis, regardless of imaging technique(s) used, the summary sensitivity of SMM for all lesions was 84.7 percent (78.0 to 89.7%) and the summary specificity was 77.0 percent (95% CI: 64.7 to 85.9%). We also meta-analyzed the data reported by the nine included studies that used standard SMM (planar and double-phase imaging) by fitting a bivariate mixed-effects model. The summary sensitivity of standard SMM for all lesions was 84 percent (95% CI: 76% to 89%) and the summary specificity was 79 percent (95% CI: 63% to 89%), approximately the same as for the full dataset. In 2006, we found that the sensitivity of scintimammography was 68.7 percent and the specificity was 84.8 percent. Improvements in technology and techniques since then, such as the development of double-phase imaging, may explain the improved accuracy in the more recent studies.

There was a great deal of heterogeneity ($I^2 = 93\%$) in the reported data. We were unable to identify with meta-regression any study- related characteristics that explained this heterogeneity, such as consecutive enrollment of patients, blinding of the diagnostic test reader to patient history/other clinical information, and use of the gold standard (biopsy) as the reference standard.

Key Question 2. Are there demographic (e.g., age) and clinical risk factors (e.g., morphologic characteristics of the lesion) that affect the accuracy of the tests considered in Key Question 1?

Two studies evaluated only patients with palpable breast masses,[57,62] one study evaluated only patients with non-palpable breast masses,[63] and one study evaluated only patients with microcalcifications detected on x-ray mammography.[61] With so few studies reporting on each category, evidence-based conclusions are difficult to support.

None of the studies reported outcomes by patient demographics or any other clinical risk factors that may have affected the accuracy of SMM.

Key Question 3. Are there other factors and considerations that may affect the accuracy or acceptability of the tests considered in Key Questions 1 and 2?

None were identified.

Previously Published Systematic Reviews

We identified two decision/cost effectiveness analyses and four systematic reviews of the use of scintimammography to evaluate women after a positive mammography exam. The majority of these analyses were published prior to publication of most of the studies included in the present report. The findings of these reports are briefly summarized in Table 12. The accuracy of scintimammography reported by all four systematic reviews is very similar to our findings—a summary sensitivity of approximately 85 percent. Most of the systematic reviews reported a

slightly higher (approximately 85%) specificity than our finding of approximately 80 percent specificity, but the confidence interval around our estimate of 80 percent is wide (imprecise estimate).

Table 12. Other published technology assessments of scintimammography

Study	Methods	Conclusions
Hussain and Buscombe 2006[242]	A meta-analysis of trials of scintimammography for diagnosis of breast cancer was performed. Studies that included more than 100 patients published since 1997 were identified and included.	The overall sensitivity was 85% and the specificity was 84%.
Liu et al. 2005[243]	A systematic review and meta-analysis intended to determine the value of scintimammography in diagnosing primary breast cancer. The authors of the review excluded the bulk of the published literature on the basis of "poor quality."	The overall sensitivity was 86% and specificity was 80% for diagnosis of breast cancer by scintimammography; these numbers dropped to 69% for diagnosis of non-palpable lesions
Medical Advisory Secretariat, Ontario Ministry of Health 2003[200]	A systematic review of the literature on the effectiveness of scintimammography in breast cancer detection. Studies published between 1992 and 2002 were eligible for inclusion. Seven studies directly comparing ultrasound to scintimammography, and 49 studies assessing the accuracy of scintimammography, were included. The data from the included studies were combined meta-analytically using the method of Littenburg and Moses.[173]	The authors concluded that scintimammography is an effective imaging technique that can improve the ability to classify patients correctly. Summary receiver operating curves were shown, but no summary test characteristics were derived.
Liberman et al. 2003[244]	A systematic review of the literature on the accuracy of scintimammography in the diagnosis of breast cancer. The review included 64 papers published between January 1967 and December 1999. The diagnostic test characteristics were individually combined meta-analytically in a fixed-effects model. Quality of the studies was formally assessed and used to weight the studies in the meta-analysis.	The aggregated summary test characteristics for scintimammography were 85.2% sensitivity and 86.6% specificity. For patients with a palpable mass, sensitivity was 87.8% and specificity was 87.5%. For patients without a palpable mass, lesions detected by mammography, sensitivity was 66.8% and specificity was 86.9%. The authors of the review concluded that scintimammography may be used effectively as an adjunct to mammography and physical examination in the diagnosis of breast cancer.

Table 12. Other published technology assessments of scintimammography (continued)

Study	Methods	Conclusions
Allen et al. 2000[245]	A decision tree sensitivity analysis comparing three patient management strategies: core needle biopsy after indeterminate or positive mammograms; core needle biopsy after positive mammograms, but patients with indeterminate mammograms were examined by scintimammography, and sent for core biopsy only if positive by scintimammography; all patients with indeterminate or positive mammograms were examined by scintimammography, and sent for core biopsy only if positive by scintimammography. Values used in the analysis were derived from the general literature.	The model predicted that the use of scintimammography would save money by reducing the number of biopsies, but at a cost of lost life expectancy. The use of scintimammography after indeterminate mammograms would save $189 million per year (assuming 21 million women undergo mammographic screening per year) at a cost of a loss of 0.000178 years of mean life expectancy. The use of scintimammography after positive and indeterminate mammograms would save $420 million per year, at a cost of a loss of 0.000222 years of life expectancy.
Hillner 1997[246]	A decision analysis model comparing scintimammography to core biopsy and open surgical biopsy for hypothetical cohorts of women with nonpalpable breast lesions detected by mammography. The performances of scintimammography and biopsy were estimated from the general literature.	The model predicted that per 1,000 women, core biopsy would miss seven invasive and 10 in situ cancers, as compared to open surgery. Scintimammography would miss an additional 16 invasive cancers and 12 in situ cancers, as compared to core biopsy. However, most missed cancers would be detected if all women with negative findings received a 6-month followup mammography, and 65% of women undergoing scintimammography would be able to avoid any type of biopsy. Compared to undergoing immediate surgery, costs would be reduced by 20% with core biopsy, and by 39% with scintimammography. For each cancer diagnosis that was delayed by six months, the authors concluded that scintimammography would save $77,500.

Conclusion

The estimates of the accuracy of various types of scintimammography, along with a rating of the strength of evidence supporting the accuracy estimate, are summarized in Table 14. We found that the summary sensitivity of scintimammography for all lesions was 84.7 percent (95% CI: 78.0 to 89.7%) and the summary specificity was 77.0 percent (64.7 to 85.9%). The data are, however, inconsistent and imprecise, therefore the strength of evidence supporting the estimate of the accuracy of scintimammography is low.

There was insufficient data reported by the studies to conclude much about the impact of patient demographics, clinical risk factors, lesion types, or other various factors on the accuracy of scintimammography.

To aid in interpretation of these findings, we used Bayes' theorem and the summary likelihood ratios for scintimammography used to evaluate lesions in general (see Table 15 and Table 16). These calculations suggest that SC examinations of women thought to have a higher

than 5 percent pre-SC probability of cancer will not be very clinically useful for diagnostic purposes because the input provided by the SC examinations would probably not affect the suspicion of malignancy sufficiently to alter clinical decisions about management of the patient (e.g., recommendations for biopsy vs. followup). Whether it is feasible for clinicians to estimate prior probability in this range is unclear; several of our expert reviewers did not think estimates could be this precise using currently available methods. For many women a SC examination will probably not result in a change in management or affect patient outcomes. In Figure 5 we illustrate models of theoretical changes in management that could be made after the use of scintimammography.

Table 13. Included studies: scintimammography

Study	Scintimammography Methods Studied	Design*	N Patients
Grosso et al. 2009[61]	Planar scintimammography with patient supine and prone	Prospective diagnostic cohort	283
Habib et al. 2009[57]	Double-phase scintimammography with patients supine and prone	Prospective diagnostic cohort	22
Kim et al. 2009[14]	Double-phase scintimammography	Prospective diagnostic cohort	249
Kim et al. 2008[58]	Double-phase scintimammography	Prospective diagnostic cohort	75
Wang et al. 2008[62]	Planar scintimammography	Prospective diagnostic cohort	55
Brem et al. 2007[19]	BSGI	Diagnostic cohort	33
Gommans et al. 2007[63]	Planar scintimammography	Prospective diagnostic cohort	101
Kim et al. 2007[59]	Double-phase scintimammography	Prospective diagnostic cohort	78
Schillaci et al. 2007[64]	Planar scintimammography	Prospective diagnostic cohort	53
Pinero et al. 2006[60]	Double phase scintimammography	Prospective diagnostic cohort	88
Mathieu et al. 2005[56]	SPECT	Retrospective chart review	37

* At times it was difficult to determine if a study was prospective or retrospective, and in those cases we defaulted to simply calling it a "diagnostic cohort study."

Table 14. Scintimammography accuracy

Category	N Studies	N Lesions	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)	Strength of Evidence
Scintimammography, any	11	1,064	84.7% (78.0 to 89.7%)	77.0% (64.7 to 85.9%)	Low
Scintimammography, double-phase planar	5	502	84.6% (73.2 to 91.7%)	72.8% (59.2 to 83.1%)	Low
Scintimammography, planar	4	492	81.5% (74.3 to 87.3%)	82.1% (77.6 to 86.0%)	Low
Scintimammography, BSGI	1	33	88.9% (51.8 to 99.7%)	70.8% (48.9 to 87.4%)	Insufficient
Scintimammography, SPECT	1	37	95.0% (75.1 to 99.9%)	70.6% (44.0 to 89.7%)	Insufficient
Scintimammography, palpable lesions	2	77	85.0% (73.4 to 92.9%)	90.5% (80.4 to 96.4%)	Insufficient
Scintimammography, nonpalpable lesions	1	101	82.2% (67.9 to 92.0%)	92.9% (82.7 to 98.0%)	Insufficient
Scintimammography, microcalcifications	1	283	78.1% (60.0 to 90.7%)	82.5% (77.2 to 87.0%)	Insufficient

Table 15. Clinical interpretations of scintimammography accuracy: benign finding on scintimammography

Pre-test Probability of the Lesion Being Malignant	Post-test Probability of the Lesion Being Malignant Despite a Finding of "Benign" on the SC Exam
	Lesions in General[a]
1%	0% (0 to 0%)
5%	1% (1 to 2%)
10%	2% (2 to 3%)
20%	5% (3 to 6%)
30%	8% (6 to 11%)
40%	12% (9 to 16%)
50%	17% (13 to 22%)
60%	23% (18 to 29%)
70%	32% (25 to 39%)
80%	44% (36 to 52%)
90%	64% (56 to 71%)

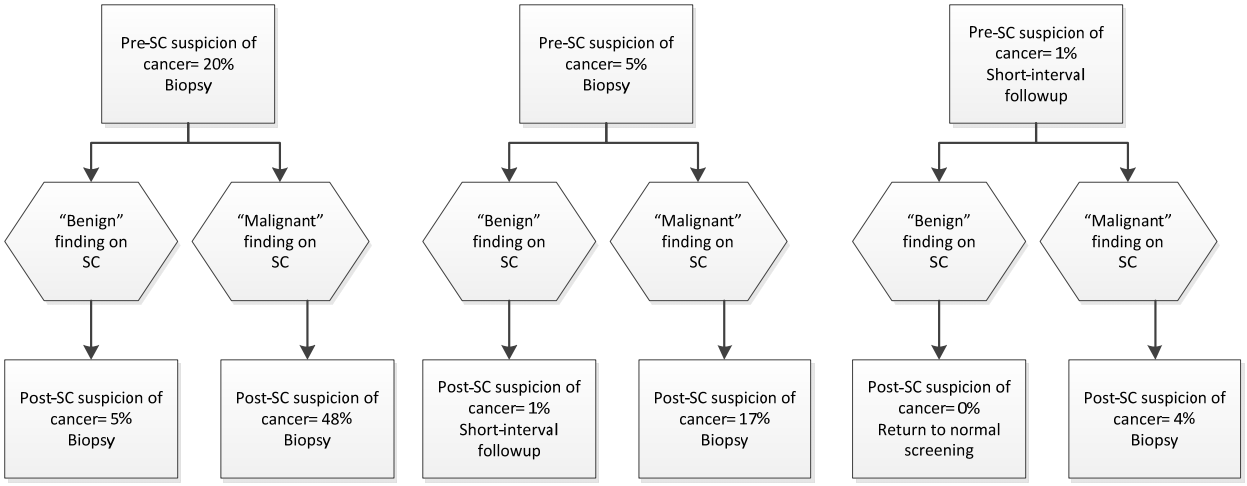
[a] The summary negative likelihood ratio is 0.21 (95% CI: 0.15 to 0.29).

Table 16. Clinical interpretations of scintimammography accuracy: malignant finding on scintimammography

Pre-test Probability of the Lesion Being Malignant	Post-test Probability of the Lesion Being Malignant After a Finding of "Malignant" on the Scintimammography Exam
	Lesions in General[a]
1%	4% (2 to 5%)
5%	17% (10 to 26%)
10%	29% (21 to 39%)
20%	48% (37 to 59%)
30%	61% (51 to 71%)
40%	71% (61 to 79%)
50%	79% (71 to 85%)
60%	85% (78 to 89%)
70%	90% (85 to 93%)
80%	94% (91 to 96%)
90%	97% (96 to 98%)

[a] The summary positive likelihood ratio is 3.9 (95% CI: 2.2 to 6.8).

Figure 5. Possible clinical scenarios for scintimammography (SC): theoretical changes in management



SC = scintimammography

Ultrasound

Background

Technology

Ultrasound waves are high-frequency sound waves that reflect at boundaries between tissues with different acoustic properties. Ultrasound is commonly used to distinguish between solid breast lesions and cysts, and to guide biopsy needles.[247]

The most commonly used type of ultrasound (conventional, or regular, ultrasound) may be referred to as B-mode gray-scale ultrasound.[248] The contrast resolution of conventional ultrasound depends on the transducer's frequency. All modern breast imaging applications employ high frequency transducers (7 MHz or higher). Ultrasound images obtained by B-mode gray-scale imaging use differences in the brightness of the image (caused by different ways the ultrasound waves reflect and absorb off tissue interfaces) to examine the internal anatomy of the breast.[248] The echoes of the sound waves are combined to form two-dimensional images of the structure of the interior of the breast. Malignant breast lesions generally appear darker on the images than the surrounding normal tissues, and often have ill-defined borders.[249-251]

One of the known problems with B-mode ultrasound is that interpretation of the images is primarily done by visually inspecting the image. Differences in human perception and utilization of different features for use in diagnosis cause variability in diagnosis and reader-dependent variations in the accuracy of diagnosis.[249] Computer-aided diagnosis (CAD) systems are under development to address this problem. CAD systems are designed to detect patterns in images that are suggestive of malignancy, and to draw the readers' attention to the areas of suspicion.

Compound imaging is a variant on B-mode imaging that is intended to reduce the "noise" in the image and thus improve the image quality.[249] Compound imaging takes multiple ultrasound views from different angles and combines the many views into a single two-dimensional image.

Another variant on B-mode ultrasound is harmonic imaging. B-mode ultrasound waves develop harmonics (multiples of the transmission frequency) as they pass through breast tissue. Digital encoding can be used by computers to construct images from the harmonic frequencies.[248] Harmonic images generally have improved resolution and fewer artifacts than regular B-mode ultrasound.[249]

Doppler ultrasound uses ultrasound to evaluate blood flow through vessels. The speed of blood flow can be evaluated by observing changes in the pitch of the reflected sound waves (the Doppler effect). Malignant masses often exhibit increased rates and amounts of blood flow (increased vascularity) in comparison to benign tissues.[249] Doppler imaging can also be performed with microbubble contrast agents that enhance imaging of blood vessels.[249] Two primary types of Doppler imaging exist, color and power. Color Doppler imaging encodes the mean Doppler frequency shifts at particular locations in various colors, whereas power Doppler imaging encodes the power of the signal (extent of the Doppler effect) at particular locations in various colors.[252] Color Doppler therefore detects the velocity of the blood cells while power Doppler detects the amount of blood present.[252]

Ultrasound tomography uses ultrasound to acquire multiple images of the breast from different angles, and uses a computer to develop a 3D image of the structure of the interior of the breast. We intended to include ultrasound tomography in this systematic review, but did not identify any studies that met the inclusion criteria.

Patient Safety and Comfort

Ultrasound is generally considered to be extremely safe. Ultrasound examinations that use microbubble contrast agents have the potential for patients to react to the agents, but most reactions appear to be transient and mild, and consist of alteration of taste, facial flushing, and pain at the injection site.[253]

During a typical ultrasound breast imaging study, the patient is placed in a supine oblique position, with a pillow under the shoulder and the arm extended behind the head.[254] Because taut compression is not required, ultrasound is generally painless. As long as routine practices are followed, ultrasound breast imaging can be considered a safe exam for most patients.

Accreditation Factors

The American College of Radiology (ACR) has instituted a voluntary breast ultrasound accreditation program that offers facilities the opportunity for peer review of their staff's qualifications, equipment, and quality control and quality assurance programs.[255]

A physician supervising and interpreting breast ultrasound examinations is required to meet specific minimum experience and education requirements in order for their facility to be accredited by the ACR.

The accreditation program requires sonographers/mammographers to be certified by the American Registry of Diagnostic Medical Sonography (ARDMS), or post-primary certification ("advanced registry") in breast sonography by the American Registry of Radiologic Technologists (ARRT), or certification by the ARRT or unrestricted state license and qualified to do mammography under Mammography Quality Standards Act (MQSA). The physician is not required to be present during breast ultrasound examinations performed by ARDMS sonographers or ARRT technologists with certification in breast sonography. However, the physician must be in the department during breast ultrasound examinations performed by ARRT

technologists without an advanced registry in breast sonography. In all situations, the physician is ultimately responsible to see that the appropriate images are obtained.

Findings From 2006 Review

In the 2006 version of this CER, we included eight prospective diagnostic cohort studies of 5,348 breast lesions that were examined by B-mode gray-scale ultrasound.[45,73,79,83,162,256-258] We found that for suspicious lesions in general, the sensitivity of ultrasound examination was 86.1 percent, the specificity was 66.4 percent, and the negative predictive value was 93.3 percent (for a population with a prevalence of disease of 25.7%). The stability of these estimates was judged to be moderate, indicating a small chance that publication of new evidence could substantially change these estimates.

Evidence Base

Our literature searches identified 31 diagnostic cohort studies of various types of ultrasound published between 1994 and 2009.[18,26,45,60,65-91] These studies included a total of 8,642 patients with 9,044 breast lesions. The included studies are listed in Table 17 at the end of this subsection on ultrasound, and are described in detail in the Appendixes. A complexity in interpreting the evidence base is that some of the women enrolled in the included studies may have undergone a prior B-mode grayscale ultrasound examination before being enrolled in the study. In many cases, the studies reported that only women with "solid" lesions were included in the study, suggesting that women found to have simple cysts by ultrasound were not part of the study population. Other studies reported that women found to "clearly benign" (probably fibroadenomas and simple cysts) lesions on ultrasound were not included in the study. We believe the use of these study inclusion criteria improves the applicability of the evidence base. In standard clinical practice a woman recalled for further evaluation would, under most circumstances, undergo an ultrasound examination to rule out cysts and obviously benign lesions before being examined more thoroughly for signs of malignancy (although in standard practice the diagnostic portion of the US exam and identification of simple cysts with US would probably be conducted during the same ultrasound session).

Key Question 1. What is the accuracy of ultrasound for diagnosis of breast cancer in women referred for further evaluation after identification of a possible breast abnormality on routine screening (mammography and/or clinical or self-detection of a palpable lesion)?

B-mode 2D Grayscale

Twenty-one studies of 8,199 lesions addressed the accuracy of B-mode 2D grayscale.[18,26,65-83] We combined the reported data in a bivariate binomial model. The summary sensitivity of B-mode 2D grayscale ultrasound for all lesions was 92.4 percent (95% CI: 84.6 to 96.4%) and the summary specificity was 75.8 percent (60.8 to 86.3%); there was, however, considerable heterogeneity in the data ($I^2 = 99.6\%$). In our 2006 assessment, we found that for suspicious lesions in general, the sensitivity of B-mode ultrasound examination was 86.1 percent, considerably lower than the findings of the current update; and we also found in 2006 that the specificity was 66.4 percent, lower than the 75.8 percent specificity of the current update. The

2006 version of the report included only a small subset of the evidence base included in the current update.

We conducted meta-regressions to explore the heterogeneity in the data. The variables we investigated were: whether the studies accounted for inter-reader differences; whether the studies blinded image readers to clinical information or not; whether all diagnoses were verified by histopathology or not; whether a prospective design was used; whether the study was funded by a source without a financial interest in the results or not; whether the study enrolled consecutive/ all patients; the geographical location of the study; what type(s) of breast lesions were enrolled in the study; and the prevalence of disease in the study. Two of these variables, whether the studies accounted for inter-reader differences, and whether the studies blinded image readers to clinical information or not, were statistically significantly associated with the results ($p = 0.01$ and 0.03, respectively). Subgroup analyses found that studies that had blinded image readers to clinical information had a higher sensitivity (96.6% vs. 87.0%) but a much lower specificity (59.5% vs. 85.1%) than unblinded studies. Studies that had accounted for inter-reader differences had a similar sensitivity (93.4% vs. 93.0%) but a much lower specificity (52.7% vs. 90.1%) than studies that did not account for inter-reader differences.

B-mode 2D Grayscale, Contrast Enhanced

Only two studies of a total of 154 breast lesions reported on the accuracy of B-mode 2D grayscale contrast-enhanced ultrasound compared to non-contrast enhanced.[26,66] Contrast enhancement was reported to increase the sensitivity (97.5% vs. 82.7%) but to not dramatically affect the specificity (76.7% vs. 74.0%).

B-mode 3D Grayscale

Only one study of 150 breast lesions, Cho et al., reported on the accuracy of B-mode 3D grayscale ultrasound.[71]

Color Doppler Ultrasound

Six studies of a total of 718 lesions reported on the accuracy of color Doppler ultrasound.[78,80,84-87] We combined the data reported by these studies in a bivariate binomial model. The summary sensitivity of color Doppler ultrasound for all lesions was 88.5 percent (95% CI: 74.4 to 95.4%) and the summary specificity was 76.4 percent (95% CI: 61.7 to 86.7%). There was considerable heterogeneity in the data ($I^2 = 95.2\%$). Exclusion of data from two studies that enrolled only patients with palpable lesions[80,85] from the bivariate model did not affect the results. There were too few studies of color Doppler to perform full meta-regressions.

Color Doppler Ultrasound, Contrast Enhanced

Two studies of 146 lesions compared the accuracy of contrast-enhanced color Doppler to non-enhanced color Doppler.[84,86] Contrast-enhancement was found to slightly increase the sensitivity (97.8% vs. 95.7%) and to dramatically increase the specificity (90.7% vs. 55.6%).

Color Doppler Ultrasound Directly Compared With B-mode Grayscale Ultrasound

Two studies directly compared the accuracy of color Doppler ultrasound to B-mode grayscale ultrasound.[78,80] Color Doppler was found to have a higher sensitivity (74.0% vs. 53.1%) but a lower specificity than B-mode ultrasound (84.0% vs. 96.3%).

Power Doppler Ultrasound

Nine studies of a total of 614 lesions reported on the accuracy of power Doppler ultrasound.[65,72,75,77,86,88-91] We combined the data in a bivariate binomial model. The summary sensitivity of power Doppler ultrasound for all lesions was 70.8 percent (95% CI: 47.5 to 86.6%) and the summary specificity was 72.6 percent (95% CI: 59.9 to 82.5%). There was considerable heterogeneity in the data (I^2 = 97.4%).

Power Doppler Ultrasound, Contrast Enhanced

Seven studies of 403 lesions reported on the accuracy of contrast-enhanced power Doppler ultrasound.[72,75,77,86,88,90,91] When we combined the data in a bivariate binomial model, the summary sensitivity for all lesions was 89.3 percent (95% CI: 52.4 to 98.4%) and the summary specificity was 70.4 percent (95% CI: 55.4 to 82.0%). There was considerable heterogeneity in the data (I^2 = 87.5%).

Power Doppler Ultrasound Directly Compared With B-mode Grayscale Ultrasound

Four studies of 248 lesions directly compared the accuracy of power Doppler ultrasound to B-mode grayscale ultrasound.[65,72,75,77] Power Doppler was found to have a lower sensitivity (54.7% vs. 87.7%) but a higher specificity (79.4% vs. 50.7%) than B-mode grayscale ultrasound in these four direct comparisons.

Power Doppler Ultrasound Directly Compared With Color Doppler Ultrasound

One study directly compared the accuracy of power Doppler, with and without contrast-enhancement, to color Doppler, with and without contrast-enhancement.[86] This study reported that all four methods had a 100 percent sensitivity, but specificity for contrast-enhanced methods was much higher than for non-contrast-enhanced methods.

Tissue Harmonics

Only one study of 91 lesions reported on the accuracy of tissue harmonic ultrasound methods.[68]

Key Question 2. Are there demographic (e.g., age) and clinical risk factors (e.g., morphologic characteristics of the lesion) that affect the accuracy of the tests considered in Key Question 1?

None were identified.

Key Question 3. Are there other factors and considerations that may affect the accuracy or acceptability of the tests considered in Key Questions 1 and 2?

None were identified.

Previously Published Systematic Reviews

Flobbe et al. published a decision analysis model comparing different strategies for managing patients presenting with palpable breast masses in 2004.[259] Their decision model was based

entirely on data from a single clinical study they previously authored (Flobbe et al.[260]). This particular clinical study by Flobbe et al. was excluded from the current report because it was confounded. Findings from the ultrasound exams influenced the way each patient was managed, including whether the patient was evaluated by biopsy. Therefore the data from Flobbe et al. cannot be used to accurately estimate the diagnostic characteristics of ultrasound because the study is strongly affected by verification bias. Because the decision model developed by Flobbe et al. was based entirely upon this confounded study, the results of the decision model are also suspect and will not be discussed here.

Conclusion

The estimates of the accuracy of the various types of ultrasound, along with a rating of the strength of evidence supporting the accuracy estimate, are summarized in Table 18. We intended to evaluate ultrasound tomography, but did not identify any relevant studies that met the inclusion criteria.

Qualitative indirect and direct comparisons between different types of ultrasound imaging were also performed. B-mode grayscale ultrasound was found to be more sensitive than either power or color Doppler imaging (conclusion supported by a Low strength of evidence). Color Doppler imaging was more accurate (both more sensitive and more specific) than power Doppler imaging (conclusion supported by a Low strength of evidence). In general, contrast-enhancement was found to improve the accuracy of all types of ultrasound imaging (conclusion supported by a Low strength of evidence). However, in actual clinical practice, it is unlikely that Doppler imaging would be used in isolation; most likely Doppler imaging and B-mode imaging would be performed by the same operator during the same procedure, and the image reader would incorporate information from all of the types of imaging into the diagnosis. There is insufficient data available to reach conclusions about the accuracy of combined ultrasound modalities.

We were unable to identify any patient demographics, clinical risk factors, or other factors that affected the accuracy of the various types of ultrasound imaging. Most of the studies did not enroll women found to have obvious cysts, and therefore our findings do not apply to women who clearly have cystic lesions on ultrasound imaging.

To aid in interpretation of these findings, we used Bayes' theorem and the summary likelihood ratios for the three primary types of ultrasound imaging (see Table 19 and Table 20). These calculations suggest that diagnostic ultrasound examinations of women thought to have a higher than 10 percent pre-ultrasound probability of cancer will not be very clinically useful for diagnostic purposes because the input provided by the ultrasound examinations would probably not affect the suspicion of malignancy sufficiently to alter clinical decisions about management of the patient (e.g., recommendations for biopsy vs. followup). These calculations suggest that ultrasound examinations may be clinically useful for diagnostic purposes for only a small subgroup of women, but clinicians would need to be able to identify women with a >0 percent but <10 percent suspicion of malignancy following standard workup. Several of our expert reviewers did not think this was currently feasible. For many women an ultrasound examination will probably not result in a change in management or affect patient outcomes. This is further illustrated in Figure 6, where models of theoretical changes in management that could be made afterthe use of diagnostic grayscale B-mode ultrasound are shown graphically.

Because most of the included studies did not enroll women found to have simple cysts or obviously benign lesions, our results did not measure the accuracy of ultrasound for identification of cysts or obviously benign lesions, and should not be applied to the use of

ultrasound for these purposes. Ultrasound is generally accepted to have been well-established for accurately identifying simple cysts and certain types of "obviously benign" lesions.

Table 17. Included studies: ultrasound

Study	US Methods Studied	Design*	N Patients
Gokalp et al. 2009[65]	B-mode 2D grayscale, power Doppler, and combination of both methods	Prospective diagnostic cohort	49
Vassiou et al. 2009[18]	B-mode 2D grayscale	Prospective diagnostic cohort	69
Liu et al. 2008[66]	B-mode 2D grayscale, with and without contrast (with Sono Vue [Bracco, Italy]), and combination of both methods	Diagnostic cohort study	108
Vade et al. 2008[67]	B-mode 2D grayscale	Retrospective chart review	20
Cha et al. 2007[68]	B-mode 2D grayscale and tissue harmonic imaging	Prospective diagnostic cohort	88
Chala et al. 2007[69]	B-mode 2D grayscale	Retrospective chart review	203
Zhi et al. 2007[70]	B-mode 2D grayscale	Diagnostic cohort study	232
Cho et al. 2006[71]	B-mode 2D and 3D grayscale	Prospective diagnostic cohort	141
Pinero et al. 2006[60]	Combination power Doppler and color Doppler using a contrast agent (Levovist [Schering AG, Berlin, Germany])	Prospective diagnostic cohort	88
Ricci et al. 2006[26]	B-mode grayscale with and without contrast (with Sono Vue [Bracco, Italy]); also compared US to MRI	Prospective diagnostic cohort	48
Forsberg et al. 2004[72]	B-mode 2D grayscale and power Doppler, with and without contrast (Levovist or Optison)	Diagnostic cohort study	55
Meyberg-Solomayer et al. 2004[73]	B-mode 2D gray-scale	Prospective diagnostic cohort	65
Ozdemir et al. 2004[88]	Power Doppler, with or without contrast (Levovist)	Prospective diagnostic cohort	80
Chen et al. 2003[74]	B-mode 2D gray scale	Prospective diagnostic cohort	32
Kook and Kwag 2003[75]	B-mode US and power Doppler, with and without contrast (Levovist)	Prospective diagnostic cohort	36
Marini et al. 2003[76]	B-mode 2D grayscale	Diagnostic cohort study	238
Caruso et al. 2002[84]	Color Doppler with and without contrast (Levovist)	Prospective diagnostic cohort	36
Koukouraki et al. 2001[85]	Color Doppler	Prospective diagnostic cohort	116
Malich et al. 2001[45]	Combination of B-mode, power Doppler, and color Doppler; also compared US to MRI	Diagnostic cohort study	94
Milz et al. 2001[89]	Power Doppler	Prospective diagnostic cohort	102
Reinikainen et al. 2001[77]	B-mode US and power Doppler, with and without contrast (Levovist)	Prospective diagnostic cohort	63

Table 17. Included studies: ultrasound (continued)

Study	US Methods Studied	Design*	N Patients
Moon et al. 2000[90]	Power Doppler, with and without contrast (Levovist)	Prospective diagnostic cohort	69
Blohmer et al. 1999[78]	B-mode 2D gray-scale and color Doppler	Prospective diagnostic cohort	200
Chao et al. 1999[79]	B-mode 2D gray-scale	Prospective diagnostic cohort	3,050
Schroeder et al. 1999[86]	Power and color Doppler, with and without contrast (Levovist)	Prospective diagnostic cohort	92
Albrecht et al. 1998[91]	Power Doppler, with or without contrast (EchoGen)	Prospective diagnostic cohort	20
Wilkens et al. 1998[80]	B-mode 2D gray-scale and color Doppler	Diagnostic cohort study	53
Buadu et al. 1997[87]	Color Doppler	Diagnostic cohort study	114
Stavros et al. 1995[81]	B-mode 2D gray-scale	Prospective diagnostic cohort	622
Ciatto et al. 1994[82]	B-mode 2D gray scale	Prospective diagnostic cohort	2,079
Perre et al. 1994[83]	B-mode 2D gray-scale	Prospective diagnostic cohort	380

* At times it was difficult to determine if a study was prospective or retrospective, and in those cases we defaulted to simply calling it a "diagnostic cohort study."

Table 18. Ultrasound accuracy: accuracy of different types of ultrasound

Type of Ultrasound	N Studies	N Lesions	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)	Strength of Evidence
B-mode grayscale 2D	21	8,199	92.4% (84.6 to 96.4%)	75.8% (60.8 to 86.3%)	Low
B-mode grayscale 2D contrast enhanced	2	154	97.5% (91.4 to 99.7%)	76.7% (65.4 to 85.8%)	Low
B-mode grayscale 3D	1	150	98.3% (91.1 to 100.0%)	70.0% (59.4 to 79.2%)	Insufficient
Color Doppler	6	718	88.5% (74.4 to 95.4%)	76.4% (61.7 to 86.7%)	Low
Color Doppler contrast enhanced	2	146	97.8% (92.4 to 99.7%)	90.7% (79.7 to 96.9%)	Low
Power Doppler	9	614	70.8% (47.5 to 86.6%)	72.6% (59.9 to 82.5%)	Low
Power Doppler contrast enhanced	7	403	89.3% (52.4 to 98.4%)	70.4% (55.4 to 82.0%)	Low
Tissue harmonics	1	91	96.7% (82.8 to 99.9%)	62.3% (49.0 to 74.4%)	Insufficient

Table 19. Clinical interpretations of ultrasound accuracy: benign finding on ultrasound

Pre-test Probability of the Lesion Being Malignant	Post-test Probability of the Lesion Being Malignant Despite a Finding of "Benign" on the Ultrasound Exam		
	B-mode Grayscale 2D Ultrasound[a]	Power Doppler Ultrasound	Color Doppler Ultrasound
1%	0% (0 to 0%)	0% (0 to 1%)	0% (0 to 0%)
5%	1% (0 to 1%)	2% (1 to 4%)	1% (0 to 2%)
10%	1% (1 to 2%)	4% (2 to 8%)	2% (1 to 3%)
20%	2% (1 to 5%)	9% (5 to 16%)	4% (2 to 7%)
30%	4% (2 to 8%)	15% (9 to 24%)	6% (3 to 12%)
40%	6% (3 to 12%)	21% (13 to 33%)	9% (5 to 17%)
50%	9% (5 to 17%)	29% (18 to 43%)	13% (7 to 24%)
60%	13% (7 to 23%)	38% (25 to 53%)	18% (10 to 32%)
70%	19% (10 to 32%)	48% (34 to 63%)	26% (14 to 42%)
80%	29% (16 to 45%)	62% (47 to 75%)	38% (22 to 56%)
90%	47% (31 to 65%)	78% (66 to 87%)	57% (39 to 74%)

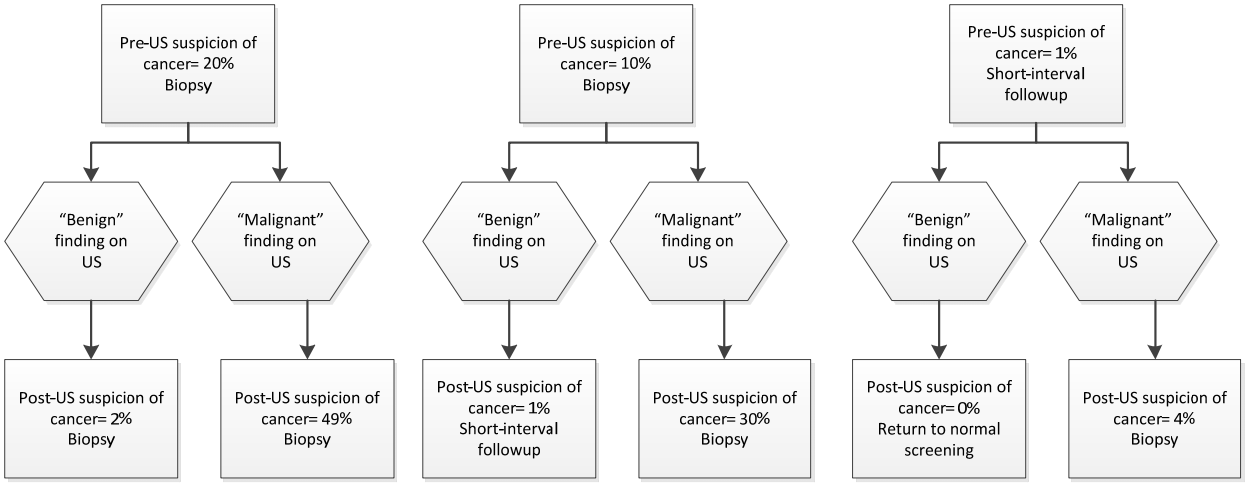
[a] The summary negative likelihood ratio is 0.10 (95% CI: 0.049 to 0.20).

Table 20. Clinical interpretations of ultrasound accuracy: malignant finding on ultrasound

Pre-test Probability of the Lesion Being Malignant	Post-test Probability of the Lesion Being Malignant After a Finding of "Malignant" on the Ultrasound Exam		
	B-mode Grayscale 2D Ultrasound[a]	Power Doppler Ultrasound	Color Doppler Ultrasound
1%	4% (2 to 7%)	3% (2 to 4%)	4% (2 to 6%)
5%	17% (5 to 11%)	12% (9 to 16%)	17% (11 to 24%)
10%	30% (20 to 42%)	22% (17 to 29%)	29% (21 to 40%)
20%	49% (36 to 62%)	39% (32 to 47%)	48% (38 to 62%)
30%	62% (49 to 73%)	53% (45 to 61%)	62% (51 to 72%)
40%	72% (60 to 81%)	63% (56 to 71%)	71% (62 to 80%)
50%	79% (69 to 86%)	72% (66 to 78%)	79% (71 to 86%)
60%	85% (77 to 91%)	80% (74 to 84%)	85% (78 to 90%)
70%	90% (84 to 94%)	86% (82 to 89%)	90% (85 to 93%)
80%	94% (90 to 96%)	91% (88 to 94%)	94% (91 to 96%)
90%	97% (95 to 98%)	96% (94 to 97%)	97% (96 to 98%)

[a] The summary positive likelihood ratio is 3.8 (95% CI: 2.3 to 0.96).

Figure 6. Possible clinical scenarios for B-mode grayscale ultrasound (US): theoretical changes in management



Comparative Accuracy and Safety

We identified three studies that directly compared PET and MRI[34,35,41] and one study that directly compared PET/CT and MRI.[16] There was no consistent pattern of relative accuracy across the three studies that directly compared PET and MRI. Imbracio et al. directly compared the diagnostic accuracy of PET/CT and MRI in the same set of patients.[16] MRI was more sensitive but less specific than PET/CT in diagnosing breast lesions in this study.[16] A qualitative indirect comparison of the summary accuracy estimates from the other sections of this report suggests that MRI is more sensitive than PET, but the two imaging methods have approximately the same specificity. Indirect comparisons may be inaccurate and should be used with extreme caution.

We identified two studies that directly compared B-mode grayscale ultrasound to MRI,[18,26] and one study that compared a combination of several Doppler ultrasound methods to MRI.[45] All three studies found that MRI was more sensitive than ultrasound for diagnosing breast lesions (results for specificity were inconsistent across studies). A qualitative indirect comparison of the summary accuracy estimates from the other sections of this report suggest that the two imaging methods are of approximately equal accuracy. As mentioned above, indirect comparisons should only be used with extreme skepticism about their accuracy.

We identified one study that directly compared scintimammography to a combination of several Doppler ultrasound methods[60] that found the two methods were approximately equally accurate, with a slightly higher sensitivity for scintimammography. Qualitative indirect comparisons of the summary accuracy estimates from the other sections of this report suggest that ultrasound may be slightly more sensitive than scintimammography, but this finding should not be considered to be supported by solid evidence (see comments above about indirect comparisons).

We identified one study[14] that directly compared scintimammography and MRI, and found MRI to be more sensitive but less specific than scintimammography. A qualitative indirect comparison of the summary accuracy estimates from the other sections of this report concurs with the direct comparison conclusion. We also identified one study[19] that directly compared

MRI to a variant of scintimammography (BSGI) with similar findings (MRI more sensitive but less specific than BSGI).

The summary estimates of accuracy of each modality are shown in Table 21, and comparative safety concerns are shown in Table 22. The data suggest, but do not prove, that ultrasound and MRI are more accurate than PET or scintimammography for evaluation of suspicious breast lesions. Because the evidence supporting these comparisons is, for the most part, indirect in nature, and not reported in sufficient detail to support statistical testing, we have refrained from drawing any solid evidence-based conclusions about comparisons across technologies.

Table 21. Summary accuracy results

Technology	N Studies	N Lesions	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)	Post-test Probability of "Malignancy"[a]	Strength of Evidence
B-mode grayscale 2D	21	8,199	92.4% (84.6 to 96.4%)	75.8% (60.8 to 86.3%)	2% (1 to 5%)	Low
MRI	41	3,882	91.7% (88.5 to 94.1%)	77.5% (71.0 to 82.9%)	3% (2 to 4%)	Moderate (sensitivity)/ Low (specificity)
Scintimammography	11	1,064	84.7% (78.0 to 89.7%)	77.0% (64.7 to 85.9%)	5% (3 to 6%)	Low
PET	7	403	83.0% (73.0 to 89.0%)	74.0% (58.0 to 86%)	6% (4 to 8%)	Low

[a] Post-test probability of a lesion being "malignant" after a benign finding on the test for a typical woman with an estimated 20% chance of having a malignant lesion.

Table 22. Comparative safety concerns

Technology	Radiation Exposure	Possible Contrast Agent Reactions	Other Concerns
B-mode grayscale 2D	None	None	None
MRI	None	Rare cases of nephrotoxicity and rare cases of severe allergic reactions	Accidental injury from the magnetic field
Scintimammography	9.0 mSv	Rare cases of severe allergic reactions	None
PET	7.6 mSv	Rare cases of severe allergic reactions	None
X-ray mammography[a]	0.36 mSv	None	None

[a] Provided for comparison purposes.

Summary and Discussion

After identification of a possible abnormality on screening mammography or physical examination, women typically undergo additional imaging studies (diagnostic mammography) and a physical examination. If these studies suggest the abnormality may be malignant, a biopsy of the suspicious area may be recommended. This evidence review focuses on the noninvasive imaging studies conducted after the discovery of a possible abnormality on screening mammography or physical examination - studies intended to guide patient management decisions. In other words, these studies are not intended to provide a final diagnosis as to the nature of the breast lesion; rather, they are intended to provide additional information about the nature of the lesion such that women can be appropriately triaged into "biopsy," "watchful waiting," or "return to normal screening intervals" care pathways.

According to the American College of Radiology, the threshold of suspicion at which management of women changes is 2 percent.[92] After recall and workup, women with a suspicion of malignancy greater than 2 percent are generally advised to undergo tissue sampling of some kind (i.e., biopsy), and women with a lower suspicion of malignancy are triaged into imaging pathways. We used the 2 percent threshold to explore the clinical usefulness of the various noninvasive imaging technologies as add-ons to the current standard of care, namely, if a woman was recalled for evaluation after a screening mammography, and received standard of care workup vs. standard of care workup plus the noninvasive imaging technology, would the use of the noninvasive imaging technology be likely to alter the recommendations for care after the workup?

For all of the technologies evaluated in this assessment, only women with a low suspicion of malignancy after standard of care workup might be expected to experience a change in management decisions as a result of additional noninvasive imaging. A woman with a ≤12 percent suspicion of malignancy who has benign findings on MRI could have her suspicion of malignancy drop below the 2 percent threshold, and therefore she might be assigned to short-interval imaging followup management rather than tissue sampling management; a woman with a 1 percent suspicion of malignancy who has benign findings on MRI could have her suspicion of malignancy drop to near 0 percent and therefore she might be assigned to return to normal screening rather than short-interval followup imaging; a woman with a 1 percent suspicion of malignancy who has malignant findings on MRI could have her suspicion of malignancy increase to 4 percent and therefore she might be assigned to tissue sampling management rather than short-interval followup. The equivalent thresholds of pretest suspicion of malignancy at which additional imaging may change management are: for B-mode grayscale ultrasound, 1 to 10 percent; for scintimammography, 1 to 5 percent; and for PET, 1 to 5 percent.

Only women with a low suspicion of malignancy on standard of care workup might be expected to experience a change in management decisions as a result of additional noninvasive imaging. Clinicians can estimate the risk of malignancy by using patient age, family and personal history details, details of the mammographic images, and results of physical examination.[261,262] Current standard practice already requires clinicians to estimate patient risk of malignancy. BI-RADS scores, for example, are estimates of patient risk of malignancy. Information is available that can be used to generate more precise estimates. For example, Wiratkapun et al. recently reported that a large cohort of women classified as BI-RADS 4 after diagnostic mammography were subsequently found to have a 20 percent prevalence of breast cancer, indicating that the methods used by this center to assign women as BI-RADS 4 were estimating that these women

had a 20 percent probability of malignancy. Wiratkapun et al. performed a retrospective analysis of clinical risk factors and details of the mammographic images and found that these women could be classified into sub-categories that had cancer prevalences that ranged from as low as 9 percent to as high as 57 percent.[261]

Therefore, if the 2 percent threshold is chosen, the use of noninvasive imaging in addition to standard workup may be clinically useful for diagnostic purposes only for women with a low (generally, less than 12%) suspicion of malignancy. When choosing which noninvasive imaging technology to use for this purpose, diagnostic B-mode grayscale ultrasound and MRI appear to more accurate than PET, scintimammography, or the other types of ultrasound (Doppler) that were evaluated in this comparative effectiveness review.

Noninvasive imaging appears to be an acceptable option for many women. Liang et al. invited a series of women referred for breast biopsy to undergo an additional mammographic exam, MRI, and scintimammography before the biopsy.[263] The women reported that MRI and scintimammography were much more comfortable than mammography, and that they would rather have additional noninvasive tests, even if they had to pay extra money out of pocket, instead of proceeding to immediate biopsy (assuming the results of the noninvasive tests were very accurate).

Several of our expert peer reviewers did not think that it is currently feasible for clinicians to estimate pre-test probability with sufficient precision to identify women with >0 but <5, 10 or 12 percent suspicion of malignancy after standard work-up. If it is not possible, then it is unlikely that these findings can be applied in practice. Furthermore, there are possible harms from noninvasive imaging, such as radiation exposure, that also need to be considered during decision-making.

Changes Since 2006

This CER is an update of a CER finalized in 2006. The updated results are, in general, very similar to the findings of the 2006 report. For MRI, in 2006 we found that the sensitivity was 92.5 percent and the specificity was 75.5 percent; the updated evidence base supported estimates of 91.7 percent sensitivity and 77.5 percent specificity. In both reports, MRI was found to be less sensitive (approximately 85%) for evaluation of microcalcifications than for evaluation of lesions in general. For PET, in 2006 we found that the sensitivity was 82.2 percent and the specificity was 78.3 percent; the updated evidence base supported estimates of 83.0 percent sensitivity and 74.0 percent specificity. In the updated report we attempted to evaluate the accuracy of PET/CT, but only one study that met the inclusion criteria was identified.

For scintimammography, the updated evidence base identified a sensitivity of 84.7 percent, much higher than the sensitivity estimate from 2006 of 68.7 percent. Specificity was estimated at 84.8 percent in 2006, and at 77.0 percent in the update; however, the confidence intervals around the updated estimate of specificity are wide. It is possible that improvements in the technology in the last few years improved the sensitivity of the technique.

For ultrasound, in 2006 we only evaluated a relatively small subset of studies of B-mode grayscale ultrasound, and estimated a sensitivity of 86.1 percent and a specificity of 66.4 percent. The update included a significantly expanded evidence base on B-mode grayscale ultrasound, and identified a sensitivity of 92.4 percent and specificity of 75.8 percent. In the update we included numerous other types of ultrasound, including power and color Doppler ultrasound, that were not studied in the 2006 report.

Limitations of the Evidence Base

The majority of conclusions about accuracy were rated as supported by "Low" strength of evidence. The evidence bases were rated as Low rather than Moderate or High due primarily to the heterogeneity of the results (inconsistency). All of the evidence bases were found to contain significant heterogeneity, and exploratory meta-regressions did not identify satisfactory explanations for the heterogeneity.

Another limitation of the evidence base is that most of the studies included only patients who had been referred for biopsy or surgery. Therefore the patient population under study does not contain a good representation of patients thought to be at sufficiently low risk of malignancy that additional imaging would be considered rather than immediate biopsy. The studies also did not distinguish between patients diagnosed with DCIS vs. invasive cancer; this point is important in addressing the consequences of delayed diagnoses of cancer, because a delay in diagnosis of DCIS may not be as harmful as a delay in diagnosis of invasive cancer. In addition, little information was reported about different patient subgroups, making it difficult to address Key Questions 2 and 3.

Applicability

We used inclusion criteria intended to restrict the evidence base to only those studies that included the population of interest: women of average baseline risk after discovery of a suspicious lesion on routine screening who had already undergone standard recall and workup (diagnostic x-ray mammography). "Women of average baseline risk" refers to women who do not have a strong family history of breast cancer, do not carry a known genetic susceptibility mutation, do not have a prior personal history of breast cancer, and are not presenting for examination because of an overt symptom such as nipple discharge. However, the patient populations studied had much higher prevalences of cancers than would be expected if the populations were actually representative of the patient population of interest. The prevalence of cancers in the general population sent for breast biopsy (in the U.S.) has been reported to be approximately 20 to 30 percent percent.[103] The population of interest includes not only those women who will be referred for biopsy, but should also include women who will be referred for short interval followup, and therefore the expected prevalence of cancers in the population of interest should be lower than 20 percent. However, the prevalence of cancers in the included studies was 25.8 percent for ultrasound, 54.5 percent for MRI, 56 percent for scintimammography, and 75.9 percent for PET. One reason for the elevated prevalence is that the studies generally attempted to use the "gold standard" reference to verify diagnoses (histopathology), and therefore many of the studies only enrolled patients who subsequently underwent biopsy or surgery. An additional possible reason for the elevated prevalence of disease is the fact that many of the studies were conducted in non-U.S. locations, where the prevalence of cancers in populations sent for biopsy has been reported to be 60 to 70 percent.[264]

The patient populations studied are therefore not truly representative of the patient population of interest. It is possible that the accuracy estimates we derived from these studies do not apply to women thought to be at sufficiently low risk of malignancy that additional imaging would be considered rather than immediate biopsy.

Possible Impact of Key Assumptions on the Conclusions

The key assumption made was that the "reference standard," a combination of biopsy, open surgery, and patient followup, was 100 percent accurate. Open surgery has been reported to have a false-negative rate of approximately 1 to 2 percent.[265] Biopsy and patient followup have error rates higher than open surgery. Therefore some of the reference standard diagnoses were almost certainly incorrect. However, the errors should consist of a low rate of both false-negatives and false-positives, which should not systematically bias the results in any one direction. It seems unlikely that our estimates of diagnostic accuracy are significantly different from the "true" accuracy solely due to errors made by the reference standard diagnoses.

In addition, we have assumed the ACR's suggested threshold of "change of management" of 2 percent is applicable and valid. It is possible that some patients or physicians may wish to use a different threshold. For example, a patient who has a strong desire to avoid biopsy may prefer the use of a higher threshold, whereas a patient who has a strong desire to avoid any uncertainty about breast cancer at all may prefer the use of a lower threshold. However, our results can be directly applied to such situations. Our post-test probability calculations can simply have a different threshold of "change in management" applied in order to derive theoretical models of the impact of the use of the different threshold on management decisions.

Future Research

The strength of the evidence supporting the conclusions about accuracy in this assessment was in general rated as "low" primarily due to imprecise estimates of accuracy (wide confidence intervals) and/or inconsistencies across studies (heterogeneity). While further studies on the diagnostic accuracy of the noninvasive technologies evaluated are unlikely to substantially change the conclusions, the publication of additional diagnostic accuracy studies may increase the precision of the estimates of accuracy, and provide enough additional information to allow productive exploration into the causes of the heterogeneity. An additional limitation of the evidence base that could be explored in future research is inclusion of women thought to be at low risk of malignancy - the majority of the published studies only included women thought to be at moderate to high risk of malignancy.

One primary shortcoming in the current evidence base is the lack of evidence for specific subgroups of lesion types. For example, while we were able to determine the accuracy of MRI for patients presenting with microcalcifications, we were unable to determine the accuracy of PET, ultrasound, or scintimammography for patients presenting with microcalcifications due to lack of evidence. We had also hoped to be able to study the impact of variations in MRI methodology on the accuracy, but the many variations of imaging methods in use and the inconsistency in reporting across studies precluded any such analysis. Also, due to lack of evidence we were unable to determine the impact of patient characteristics such as age on the accuracy of the various imaging methods. Future diagnostic accuracy studies that report data for specific subgroups of patients or directly compare different imaging methods would be helpful in addressing these unanswered questions.

Studies of new technologies, and improvements in current technologies, are of course essential. For example, the use of computer-aided diagnosis software (CADx) to help interpret MRI images is a technology that appears to be rapidly diffusing, yet there is little clinical evidence available at this time on the impact of CADx on MRI accuracy.

A number of expert reviewers of this report commented that, based on the current state of knowledge, it is impossible to predict the pre-test probability of malignancy with sufficient accuracy to allow the findings of this technology report to be directly used in clinical practice. Therefore, continued research to improve clinicians' ability to accurately estimate a woman's probability of malignancy prior to diagnostic tests could also help to avoid missing cancers and to avoid unnecessary biopsies.

Future research efforts should also be turned to studies that report the impact of the use of noninvasive imaging on management decisions and patient-oriented outcomes. The ideal design for such a study would be a randomized controlled trial in which one group undergoes noninvasive imaging and one does not; the noninvasive imaging results are then used in management decisions; and the patients are followed up for long periods of time to determine the downstream impact of the use of noninvasive imaging on survival and quality of life. Admittedly such studies may be logistically difficult to conduct. When randomized trials are difficult to perform for logistical reasons, modeling studies are often considered acceptable methods of providing information about links between diagnostic testing strategies and patient outcomes.

The diagnostic thresholds that trigger invasive diagnostic testing should also be studied in the context of the addition of noninvasive imaging to standard protocols. Current standard of care results in large numbers of healthy women undergoing invasive diagnostic procedures, and many women may be undergoing treatment for small early-stage breast cancers that will never become clinically relevant even if not diagnosed and treated.[5,103,266,267] The diagnostic thresholds in current use are intended to reduce the rate of missed cancers, which by necessity causes a loss of specificity. The low thresholds are also intended to partially compensate for diagnostic inaccuracy of tests in current use. The hope is that the addition of new kinds of noninvasive imaging to standard protocols may be able to reduce the number of false-positives without increasing the number of false-negatives. The thresholds used in clinical practice to trigger implementation of invasive diagnostic testing and treatment should be based on solid evidence about patient benefit-to-harm ratios derived from controlled trials and modeling studies.

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Acronyms and Abbreviations

ADH	Atypical ductal hyperplasia
AHRQ	Agency for Healthcare Research and Quality
ALH	Atypical lobular hyperplasia
BI-RADS®	Breast Imaging Reporting and Data System
BSGI	Breast specific gamma imaging
CER	Comparative Effectiveness Review
CI	Confidence interval
CT	Computed tomography
2D	Two dimensional
3D	Three dimensional
DCIS	Ductal carcinoma in situ
FDG	fluorodeoxyglucose
FN	False negative
FP	False positive
LCIS	Lobular carcinoma in situ
MIBI	Sestamibi
MRI	Magnetic resonance imaging
NA	Not applicable
NR	Not reported
PET	Positron emission tomography
SMM	Scintimammography
SPECT	Single photon emission computed tomography
TEP	Technical expert panel
TN	True negative
TP	True positive
UK	United Kingdom
US	Ultrasound
USA	United States of America

Glossary

Atypical ductal hyperplasia (ADH). A condition in which the cells that line the milk ducts of the breast experience abnormal growth. The lesion itself is not malignant but may sometimes contain foci of malignant cells and women with ADH have an elevated risk of developing a malignant lesion.

Doppler ultrasound. A method of using ultrasound to evaluate blood flow through vessels. The speed of blood flow is evaluated by observing changes in the pitch of the reflected sound waves.

Ductal carcinoma in situ (DCIS). A type of early stage breast cancer that is confined to the breast duct in which it arose.

Harmonic ultrasound. Ultrasound waves develop harmonics as they pass through breast tissue. Digital encoding can be used by computers to construct images from the harmonic frequencies.

High-risk lesion. Any of a number of different types of non-cancerous lesions of the breast that have been observed to sometimes contain foci of malignant cells, and women diagnosed with these types of lesions have an elevated risk of developing a malignant lesion. Some common types of high-risk lesions include atypical ductal hyperplasia (ADH), radial scars, papillary lesions, atypical lobular hyperplasia (ALH), and lobular carcinoma in situ (LCIS).Magnetic resonance imaging: A method of imaging internal anatomy by using strong magnetic fields and radiofrequency energy.

Microcalcification. A tiny deposit of calcium visible as a bright spot on a mammogram. Tight clusters of microcalcifications may be a sign of a malignant lesion.

Negative likelihood ratio. The ability of the diagnostic test to accurately "rule out" the presence of breast cancer.

Negative predictive value. The probability of a woman actually not having breast cancer after testing negative for breast cancer. Negative predictive value = (true negatives)/(false negatives + true negatives).

Palpable lesion. A breast lesion that can be felt by manual manipulation.

Positive likelihood ratio. The ability of the diagnostic test to accurately predict the presence of breast cancer.

Positive predictive value. The probability of a woman actually having breast cancer after testing positive for breast cancer. Positive predictive value = (true positives)/(true positives + false positives).

Positron emission tomography. A method of imaging tissues by tracking the metabolism of a positron-emitting radioactive tracer.

Scintimammography. A method of imaging tissues by tracking the metabolism of a radioactive tracer.

Sensitivity. The proportion of women with breast cancer who test positive for breast cancer. Sensitivity = (true positives)/(true positives + false negatives).

Specificity. The proportion of women with benign lesions who test negative for breast cancer. Specificity = (true negatives)/(false positives + true negatives).

Tomography ultrasound. Multiple ultrasound images from different angles are acquired and a computer used the information to develop a three-dimensional image of the interior anatomy of the breast.

Ultrasound. A method of imaging anatomy by observing the reflections of high-frequency sound waves off of tissues with different acoustic properties. Conventional ultrasound is often referred to as B-mode ultrasound.

Appendix A. Search Strategy and Exact Search Strings

Table A1. Electronic database searches

Name	Date Limits	Platform/Provider
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through September 9, 2010	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through September 9, 2010	www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through September 9, 2010	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through September 9, 2010	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	Through September 9, 2010	OVID
Health Technology Assessment Database (HTA)	Through September 9, 2010	www.thecochranelibrary.com
Healthcare Standards	Through September 9, 2010	www.ecri.org
MEDLINE	Through September 9, 2010	OVID
U.K. National Health Service Economic Evaluation Database (NHS EED)	Through 2009, Issue 4	www.thecochranelibrary.com
U.S. National Guideline Clearinghouse™ (NGC)	Searched December 1, 2009	www.ngc.gov

Search Strategies

The search strategies employed combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across Embase, MEDLINE, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

Medical Subject Headings (MeSH), EMTREE, PsycINFO and Keywords

Conventions:

OVID

$ = truncation character (wildcard)

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = publication type

[sb] = subset of PubMed database (PreMEDLINE, Systematic, OldMEDLINE)

[sh] = MeSH subheading (qualifiers used in conjunction with MeSH headings)

[tiab] = keyword in title or abstract

[tw] = text word

Table A2. Topic specific search terms

Concept	Controlled Vocabulary	Keywords
Breast diseases	breast cancer breast carcinoma breast diseases breast neoplasms	breast cancer breast carcinoma breast lesions breast lumps breast neoplasms breast tumors breast tumours
Diagnosis	diagnosis diagnostic accuracy diagnostic imaging diagnostic procedure diagnostic value early diagnosis sensitivity and specificity tumor diagnosis	accuracy diagnosis false negative false positive gold standard likelihood precision predictive value receiver operating characteristic ROC sensitivity specificity true negative true positive
Non-invasive technique		noninvasive non-invasive
Ultrasonography	echomammography ultrasonography ultrasonography, mammary ultrasound	echography echomammography sonography sonomammography ultrasonic ultrasonography ultrasound
Magnetic resonance imaging	magnetic resonance imaging nuclear magnetic resonance imaging	magnet strength magnetic resonance MR MRI NMR nuclear magnetic resonance pulse sequence

Table A2. Topic specific search terms (continued)

Concept	Controlled Vocabulary	Keywords
Positron emission tomography	fluorodeoxyglucose F 18 positron emission tomography tomography,emission-computed	computed tomography F18 F-18 FDG f-fluorodeoxyglucose PET positron emission tomography
Scintimammography	gamma cameras gamma spectrometry methoxy isobutyl isonitrile technetium tc-99 nuclear medicine organotechnetium compounds [diagnostic use] radionuclide imaging radiopharmaceuticals scintillation camera scintimammography spectrometry, gamma technetium Tc 99m Sestamibi [diagnostic use]	BSGI gamma camera gammagraphy gammagraphy MIBI miraluma nuclear medicine pem tetrofosomin radionuclide radiotracers scintimammography sestamibi technetium tetrofosmin
SPECT	single photon emission computer tomography spectrometry, x-ray emission	SPECT SPET
Tomosynthesis	three dimensional imaging	3D 3-D three dimensional tomosynthesis
Computer-aided detection	computer assisted diagnosis diagnosis, computer-assisted digital mammography image analysis image interpretation, computer-assisted image processing, computer-assisted radiographic image interpretation, computer-assisted	CAD computer aided detection computer aided diagnosis computer assisted detection computer assisted diagnosis digital mammography
Doppler ultrasound	doppler echography ultrasonography, Doppler ultrasonography, doppler, color ultrasonography, doppler, duplex	doppler echography doppler ultrasonography

Table A2. Topic specific search terms (continued)

Concept	Controlled Vocabulary	Keywords
Combined PET/CT	computer assisted tomography positron-emission tomography tomography, emission-computed tomography, x-ray computed	PET/CT positron emission tomography and computed tomography

Table A3. CINAHL/EMBASE/MEDLINE

Set N	Concept	Search Statement
1	Breast diseases	exp Breast neoplasms/ or exp breast diseases/ or exp breast cancer/ or breast carcinoma/ or ((breast or mammary) and (cancer$ or neoplasm$ or carcinoma$ or tumor$ or tumour$ or lump$ or lesion$)).mp.
2	Diagnosis	"sensitivity and specificity"/ or early diagnosis/ or diagnostic imaging/ or diagnostic value/ or diagnostic accuracy/ or diagnostic procedure/ or tumor diagnosis/ or diagnos$.mp. or di.xs. or "gold standard".mp. or ROC.mp. or "receiver operating characteristic".mp. or likelihood.mp. or ((false or true) adj (positive or negative)).tw. or "predictive value".mp. or accuracy.mp. or precision.mp. or sensitivity.mp. or specificity.mp.
3	Combine sets	1 and 2
4	Non-invasive technique (2005-2009)	3 and (noninvasive or non-invasive).mp.
5	Ultrasonography (2005-2009)	3 and (ultrasonography.fs. or ultrasonography, mammary/ or echogra$.mp. or echomammog$.mp. or sonogra$.mp. or sonomammogr$.mp. or ultrasound.mp. or ultrason$.mp. or echomammography/ or ultrasound/)
6	Magnetic resonance imaging (2000-2009)	3 and (exp magnetic resonance imaging/ or "magnet strength".mp. or pulse sequence.mp. or MR.mp. or MRI.mp. or nuclear magnetic resonance.mp. or NMR.mp. or nuclear magnetic resonance imaging/ or magnetic resonance.mp.)
7	Positron emission tomography (2000-2009)	3 and ((FDG$ or f-fluorodeoxyglucose or f18 or f-18).mp. or fluorodeoxyglucose F 18/ or PET.ti. or positron emission tomography.mp. or exp tomography,emission-computed/ or (comput$ ADJ tomograph$).tw. or positron emission tomography/)
8	Scintimammography (2005-2009)	3 and ((gamma camera$ or gammagraph$ or nuclear medicine or radionuclide$).mp. or radionuclide imaging.fs. or radiotracer$.mp. or radiopharmaceuticals/ or sestamibi.mp. or technetium Tc 99m Sestamibi/du or gammagraph$.mp. or pem tetrofosomin.mp. or technetium.mp. or miraluma.mp. or tetrofosmin.mp. or scintimammogr$.mp. or spectrometry, gamma/ or methoxy isobutyl isonitrile technetium tc-99/ or nuclear medicine/ or scintillation camera/ or scintimammography/ or gamma spectrometry/ or exp organotechnetium compounds/du or MIBI.mp. or BSGI.mp. or gamma cameras/)
9	SPECT (2005-2009)	3 and (exp spectrometry, x-ray emission/ or SPET.mp. or SPECT.mp. or single photon emission computer tomography/)
10	Tomosynthesis 2007-2009)	3 and (tomosynthesis.mp. or three dimensional imaging/ or 3-D.mp. or 3D.mp. or imaging, three dimensional/ or ((three or 3) ADJ dimension$)).tw.

Table A3. CINAHL/EMBASE/MEDLINE (continued)

Set N	Concept	Search Statement
11	Computer-aided detection (2001-2009)	3 and (diagnosis, computer-assisted/ or image interpretation, computer-assisted/ or radiographic image interpretation, computer-assisted/ or computer assisted diagnosis/ or digital mammography/ or (comput$ ADJ (aided or assisted) ADJ (detection or diagnos$)).tw. or digital mammogra$.mp. or CAD.mp. or exp image processing, computer-assisted/ or image analysis/)
12	Doppler ultrasound (1997-2009)	3 and (ultrasonography, doppler/ or ultrasonography, doppler, duplex/ or ultrasonography, doppler, color/ or doppler echography/ or (doppler ADJ2 (ultraso$ or echograph$)).tw.)
13	Combined PET/CT (2000-2009)	3 and (((positron-emission tomography/ or tomography, emission-computed/) and (tomography, x-ray computed/ or computer assisted tomography.mp.)) or (pet ADJ ct).tw. or pet/ct or (positron emission tomograph$ and comput$ tomograph$).mp.)
14	Combine sets	or/4-13
15	Limit by publication type	15 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)

Appendix B. Sample Data Abstraction Forms

Abstract Screening Form

1. Is the topic of the article "diagnosis of breast cancer"?
2. Is the article a full-length published journal article?
3. Is the article written in English?
4. Is the article describing a clinical study?
5. Does the study use one of the technologies being considered in the report?
6. Does the study appear to address at least one of the Key Questions?
7. Is the study about diagnosis and not about screening asymptomatic individuals?
8. Did the study enroll at least 10 female humans?

Inclusion/Exclusion Screening Form

2. Did the study directly compare the test of interest to an acceptable reference standard- core-needle biopsy, open surgery, or patient followup- in the same group of patients?
3. Were at least 85% of the originally enrolled patients evaluated by both the non-invasive imaging technology and an acceptable reference standard?
4. If the study is retrospective in design, did it enroll all patients, consecutive patients, or a randomized sample of patients? Retrospective case-control and case studies are excluded.
5. The studies must have used current generation scanners and protocols of the selected technologies only, as defined in the following list of technologies and cut-off publication dates (to present):
    - Ultrasound (B-mode grayscale, tissue harmonics, power Doppler, color Doppler, tomography): 1994+
    - Magnetic resonance imaging (MRI), without computer aided-detection (CADx), using breast-specific coils and gadolinium-based contrast agents: 2000+
    - Magnetic resonance imaging (MRI), with computer aided-detection (CADx) (breast-specific coils and gadolinium-based contrast agents, CAD package FDA approved): 2000+
    - Positron emission imaging (PET), with or without computed tomography (PET/CT), using 18-flurodeoxyglucose (FDG) as the tracer: 2000+
    - Scintimammography, including breast specific gamma imaging (BSG1) and single photon emission computed tomography (SPECT), using technetium-99m sestamibi (sestamibi or MIBI) as the tracer: 2005+

6. Did the study enrolled female human subjects? If male subjects were enrolled, the majority (90%+) of the patients must have been female.

7. Did the study enroll patients referred for the purpose of primary diagnosis of a breast abnormality detected by routine screening (mammography and/or physical examination)? Studies that enrolled subjects that were undergoing evaluation for any of the following purposes were excluded as being out of scope of the report: screening of asymptomatic women; breast cancer staging; evaluation for a possible recurrence of breast cancer; monitoring response to treatment; evaluation of the axillary lymph nodes; evaluation of metastatic or suspected metastatic disease; or diagnosis of types of cancer other than primary breast cancer. Studies that enrolled patients from high-risk populations such as BRCA1/2 mutation carriers, or patients with a strong family history of breast cancer, are also out of scope. If a study enrolled a mixed patient population and did not report data separately, it was excluded if more than 15% of the subjects did not fall into the "primary diagnosis of women at average risk presenting with an abnormality detected on routine screening" category.

8. Did the study report test sensitivity, specificity, or sufficient data to calculate these measures of diagnostic test performance; or (for Key Question 3) reported factors that affected the accuracy of the non-invasive test being evaluated.

9. Was a complete set of data reported for at least 50% or more of the originally enrolled patients? Studies with extremely high rates of attrition are prone to bias and were excluded.

10. Was the study published in English?

11. Study must be published as a peer-reviewed full article. Meeting abstracts were not included.

12. Did the study enroll 10 or more individuals per arm?

13. Does the study include data that was also published in a different manuscript?

Quality Assessment (Risk of Bias) Form

1. Was patient recruitment either consecutive or random?

2. Was the study prospective in design?

3. Were more than 85% of the patients approached for recruitment enrolled in the study?

4. Were the patient inclusion/ exclusion criteria consistently applied to all patients?

5. Was the study free from obvious spectrum bias? Obvious spectrum bias was defined as more than 40% or less than 10% of the breast lesions were diagnosed as malignant; and/or the mean or median age of the enrolled population was less than 50 or greater than 70.

6. Did the study account for inter-reader/scorer differences?

7. Were the reader(s) of the biopsies blinded to the results of the reference standard?

8. Were readers of the reference standard blinded to the results of the biopsy?

9. Were the readers of the biopsy blinded to all other clinical information?
10. Were readers of the reference standard blinded to all other clinical information?
11. Were patients assessed by a reference standard regardless of the biopsy results?
12. Were the patients assessed by the gold standard (open surgical procedure) regardless of the initial biopsy results?
13. Was a diagnostic threshold chosen *a priori* by the study?
14. Were there no intervening treatments or interventions conducted between the time the diagnostic test was performed and the reference standard was performed?
15. Was a complete set of data reported for at least 85% of enrolled lesions?
16. Was funding for this study provided by a source that doesn't have an obvious financial interest in the findings of the study?
17. Was the report of the study free from unresolvable discrepancies?

Study Design and Patients Data Abstraction Form

Study design:
Multi-center:
Country set in:
Source of funding:
Patient recruitment methods:
Patient enrollment criteria:
N patients enrolled:
N lesions enrolled:
N lesions completing study:
Patient age, mean or median, range:
Describe imaging methods:
Describe imaging operators/readers:
Care setting:
Reference standard:
% lesions malignant:
% lesions palpable:
Tumor size:
Other lesion descriptors:

Data Abstraction Form

Category/type/descriptors:

Number TP	Number FP
Number FN	Number TN

Appendix C. Evidence Tables

Magnetic Resonance Imaging (MRI)

Total of 41 studies

Total of 3,882 patients; 4,202 lesions

1 study of 3.0T; 2 studies of 0.5T; 3 studies of 1.0T; 33 studies of 1.5T; 1 study of mixed 1.0T and 1.5T; and 1 study NR

1 study comparing CAD assistance to not

26 studies of gadopentetic acid; 8 studies of gadodiamide; 3 studies of gadobenic acid; 2 studies of gadoteridol; 2 studies mixed or not reported; 2 studies compared gadopentetic acid to gadobenic acid.

Table C1. Included studies of MRI

Study	MRI Methods Studied	Design	N Patients	N Lesions	Geographical Location	Funded by
Akita et al. 2009[1]	1.5T gadodiamide	Diagnostic cohort study	50	50	Japan	NR
Baltzer et al. 2009[2]	1.5T gadopentetic acid CAD assistance vs. not	Prospective diagnostic cohort study	329	469	Germany	NR
Hara et al. 2009[3]	1.5T gadodiamide	Diagnostic cohort study	103	93	Japan	NR
Kim et al. 2009[4]	1.5T gadopentetic acid	Diagnostic cohort study	249	249	South Korea	Pusan National University Research Grant
Lo et al. 2009[5]	3T gadopentetic acid	Prospective diagnostic cohort study	31	31	Hong Kong	NR
Imbracio et al. 2008[6]	1.5T gadopentetic acid	Prospective diagnostic cohort study	44	55	Italy	NR
Pediconi et al. 2008[7]	1.5T gadopentetic acid vs. gadobenic acid	Prospective diagnostic cohort study	47	78	Italy	NR

Table C1. Included studies of MRI (continued)

Study	MRI Methods Studied	Design	N Patients	N Lesions	Geographical Location	Funded by
Vassiou et al. 2009[8]	1.5T gadopentetic acid	Prospective diagnostic cohort study	69	78	Greece	NR
Brem et al. 2007[9]	1.5T gadopentetic acid	Diagnostic cohort study	23	33	U.S.	NR
Cilotti et al. 2007[10]	1.5T gadoteridol	Retrospective diagnostic cohort study	55	55	Italy	NR
Pediconi et al. 2007[11]	1.5T gadobenic acid	Prospective diagnostic cohort	164	230	Italy	NR
Zhu et al. 2007[12]	1.5T gadodiamide	Retrospective diagnostic cohort study	52	52	Japan	NR
Bazzocchi et al. 2006[13]	1.0 or 1.5 T gadoteridol	Prospective diagnostic cohort study	174	112	Italy; multi-centered	Supported by Bracco Imaging Spa
Gokalp and Topal 2006[14]	1.5T gadopentetic acid	Prospective diagnostic cohort study	43	56	Turkey	NR
Kneeshaw et al. 2006[15]	1.5T gadopentetic acid	Prospective diagnostic cohort study	88	88	U.K.	Yorkshire Cancer Research
Ricci et al. 2006[16]	1.5T gadobenic acid	Prospective diagnostic cohort study	48	50	Italy	NR
Pediconi et al. 2005[17]	1.5T gadobenic acid	Prospective diagnostic cohort study	36	68	Italy	NR
Pediconi et al. 2005[18]	1.5T gadopentetic acid vs. gadobenic acid	Prospective diagnostic cohort study	26	46	Italy	States it was not industry funded
Wiener et al. 2005[19]	1.5 T gadopentetic acid	Prospective diagnostic cohort study	65	119	U.S.	NR
Bluemke et al. 2004[20]	1.5T gadopentetic acid	Prospective diagnostic cohort study	821	960	Many; multi-centered	National Cancer Institute

Table C1. Included studies of MRI (continued)

Study	MRI Methods Studied	Design	N Patients	N Lesions	Geographical Location	Funded by
Huang et al. 2004[21]	1.5T gadodiamide	Prospective diagnostic cohort study	50	50	U.S.	Susan G. Komen Breast Cancer Foundation
Bone et al. 2003[22]	1.5T gadopentetic acid	Prospective diagnostic cohort study	97	111	Hungary	NR
Daldrup-Link et al. 2003[23]	1.5T gadopentetic acid	Prospective diagnostic cohort study	14	19	Germany	NR
Heinisch et al. 2003[24]	1.0T gadopentetic acid	Prospective diagnostic cohort study	36	40	Austria	NR
Walter et al. 2003[25]	1.0T gadopentetic acid	Prospective diagnostic cohort study	40	42	Germany	NR
Guo et al. 2002[26]	1.5T gadopentetic acid	Retrospective diagnostic cohort study	52	47	China	NR
Kelcz et al. 2002[27]	1.5T gadodiamide	Prospective diagnostic cohort study	62	68	U.S.	Weizman Institute of Science, Rehovot, Israel and the Israel Binational Science Foundation in the United States
Schedel et al. 2002[28]	1.5T gadopentetic acid	Diagnostic cohort study	65	34	Germany	NR
Trecate et al. 2002[29]	1.5T gadopentetic acid	Prospective diagnostic cohort study	28	28	Italy	NR
Wiberg et al. 2002[30]	1.5T gadopentetic acid	Prospective diagnostic cohort study	93	114	Sweden	NR

Table C1. Included studies of MRI (continued)

Study	MRI Methods Studied	Design	N Patients	N Lesions	Geographical Location	Funded by
Brix et al. 2001[31]	1.5T gadopentetic acid	Prospective diagnostic cohort study	14	14	Germany	Wilhelm Sanders-Stifttung grant
Cecil et al. 2001[32]	1.5T gadopentetic acid	Diagnostic cohort study	37	23	U.S.	Grant funding through the National Institute of Health and U.S. Army
Furman-Haran et al. 2001[33]	1.5T gadodiamide	Prospective diagnostic cohort study	40	48	U.S.	U.S.-Israel Binational Foundation
Imbriaco et al. 2001[34]	0.5T gadopentetic acid	Prospective diagnostic cohort study	49	49	Italy	Associazione Italiana Ricerca Cancro
Malich et al. 2001[35]	1.5T gadopentetic acid	Diagnostic cohort study	94	100	Germany	NR
Nakahara et al. 2001[36]	0.5T gadopentetic acid	Retrospectivediagnostic cohort study	40	40	Japan	NR
Torheim et al. 2001[37]	1.5T gadodiamide	Prospective diagnostic cohort study	127	127	Norway	Norwegian Research Council
Wedegartner et al. 2001[38]	1.0T gadopentetic acid	Prospective diagnostic cohort study	53	62	Germany	NR
Yeung et al. 2001[39]	1.5T gadopentetic acid	Diagnostic cohort study	30	23	China	NR
Kvistad et al. 2000[40]	1.5T gadodiamide	Prospective diagnostic cohort study	130	130	Norway	Norwegian Cancer Society

Table C1. Included studies of MRI (continued)

Study	MRI Methods Studied	Design	N Patients	N Lesions	Geographical Location	Funded by
Van Goethem et al. 2000[41]	NR T gadopentetic acid	Retrospective diagnostic cohort study	75	75	Belgium; multi-centered	NR

NR Not reported
T Tesla
U.K. United Kingdom
U.S. United States

Table C2. MRI studies: patient and lesion details

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable
Akita et al. 2009[1]	Patients with mammographically detected microcalcifications classified as BI-RADS 3 or higher	50	50	50	Mean: 50.6	28 to 80	26.0% (13/50)	NR
Baltzer et al. 2009[2]	Consecutive female patients with unclear or suspect findings on mammography who underwent surgery; patients who underwent preoperative chemotherapy were excluded.	329	469	469	55.3	15 to 83	59.5% (279/469)	NR
Hara et al. 2009[3]	Patients with suspected malignancy in routine examination.	103	93	93	49.1	21 to 75	23.6% (22/93)	NR
Kim et al. 2009[4]	Consecutive patients with palpable breast masses on physical examination and/or suspicious mammographic findings	249	249	249	47	37 to 57	85.3% (205/249)	59%
Lo et al. 2009[5]	Patients with suspicious lesions on mammography/US	31	31	31	46	34 to 69	64.5% (20/31)	NR

Table C2. MRI studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable
Imbracio et al. 2008[6]	Consecutive patients with lesions detected on physical exam or mammography/US; excluded were pregnant, lactating, under 18 years, prior history of breast cancer	44	55	44	54	NR	81.8% (45/55)	NR
Pediconi et al. 2008[7]	Women with suspicious lesions diagnosed by physical examination or mammography, referred for biopsy; excluded were under 18 years; pregnant or lactating; had received any other contrast agent during 48 hours before MRI undergoing radiation therapy, chemotherapy, or anticancer hormonal therapy, or had any medical conditions or other circumstances that would decrease chances of obtaining reliable data, or were sensitive to gadolinium chelates.	47	78	47	50.8	30 to 75	64.0% (50/78)	NR
Vassiou et al. 2009[8]	Women with suspicious lesions diagnosed by physical examination or mammography, referred for biopsy	69	78	69	53	39 to 68	68% (53/78)	NR

Table C2. MRI studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable
Brem et al. 2007[9]	Indeterminate breast findings that required a biopsy	23	33	33	53	33 to 70	27.3% (9/33)	NR
Cilotti et al. 2007[10]	Patients with BIRADS 3-5 microcalcifications from mammography that were not opaque or distorted	55	55	55	56	37 to 76	47.3% (26/55)	0%
Pediconi et al. 2007[11]	Consecutive patients with suspicious clinical exam, mammogram and or US; excluded were patients contraindicated for MRI or with mammogram BIRADS 2 or 3	164	230	164	NR	NR	93.3% (211/226)	NR
Zhu et al. 2007[12]	consecutive patients with microcalcifications suspicious of DCIS; patients with palpable lesions	52	52	52	NR	30 to 74	50% (26/52)	0%
Bazzocchi et al. 2006[13]	Patients with mammographically detected microcalcifications (BIRADS 4-5); any race; associated or not with an opacity; excluded were younger than 18 years, contraindications to MRI, pregnant/breastfeeding, severe renal failure, sensitivity to gadolinium.	174	112	112	NR	NR	67.0% (75/112)	0%

Table C2. MRI studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable
Gokalp and Topal 2006[14]	Nonpalpable lesions defined as BIRADS category 3 on screening mammography	43	56	43	49.7	37 to 68	1.8% (1/56)	0.00%
Kneeshaw et al. 2006[15]	Patients with microcalcifications on mammography	88	88	88	58	50 to75	22.7% (20/88)	0%
Ricci et al. 2006[16]	Consecutive patients with lesions detected on mammography	48	50	50	58	40 to 81	76% (38/50)	NR
Pediconi et al. 2005[17]	Consecutive patients with suspected breast cancer based on mammogram/US; Excluded under 18 years of age; pregnant/lactating; undergoing cancer treatment; or had another contrast agent in the last 48 hours	36	68	36	NR	31 to 78	79.4% (54/68)	NR
Pediconi et al. 2005[18]	Consecutive patients with suspected breast cancer based on mammogram/US; Excluded under 18 years of age; pregnant/lactating; undergoing cancer treatment; or had another contrast agent in the last 48 hours	26	46	25	47.8	32 to 67	82.6% (38/46)	NR

Table C2. MRI studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable
Wiener et al. 2005[19]	Women 18 to 80 years of age with suspicious lesions diagnosed by physical examination or mammography, referred for biopsy; Excluded if: a prior invasive breast procedure had been performed within 6 months of the surgery; contraindication to MRI (pacemaker, metallic implant, etc.); history of prior breast cancer in the affected breast; pregnancy	960	960	821	53.2	42 to 65	49.2% (404/821)	39%
Bluemke et al. 2004[20]	Patients with a BIRADS 4 or 5 at mammography scheduled for CNB/surgery	50	50	50	50.2	34 to 71	36.0% (18/50)	NR
Huang et al. 2004[21]	Patients with indeterminate lesions on mammogram, US, or both; MRI done during the first 2 weeks of menstrual cycle, who were candidates for surgery; excluded were lesions larger than 5 cm, thought to have multicentric disease, not a candidate for radiation, small breast to lesion ratio	65	119	65	NR	NR	58.0% (69/119)	72.3% (47/65)

Table C2. MRI studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable
Bone et al. 2003[22]	Consecutive patients scheduled for surgery after detection of lesions by palpation or mammography	97	111	90	54	33 to 81	71.2% (79/111)	NR
Daldrup-Link et al. 2003[23]	Women with suspicious lesions diagnosed by physical examination, mammography, or ultrasound, scheduled for surgery; Excluded were: women less than 18 years of age, with implanted metal devices, claustrophobia, pregnant, lactating, or had been administered iron oxides with 7 days before the study, participation in antoher study, serious liver dysfunction, or a history of serious allergies or reactions to any drugs particularly contrast agents.	14	19	19	55	35 to 77	47% (9/19)	NR
Heinisch et al. 2003[24]	Women with suspicious breast lesions detected by physical exam, mammography, and/or ultrasound, scheduled for biopsy, referred when there happened to be time on the scanners	36	40	40	48.3	25 to 77	62.5% (25/40)	NR

Table C2. MRI studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable
Walter et al. 2003[25]	A subset of patients were randomly selected from a consecutive series who were referred for biopsy due to findings on mammography, ultrasound, or physical examination	40	42	42	52	21 to 77	45.2% (19/42)	NR
Guo et al. 2002[26]	No specific criteria reported	52	47	47	58	25 to 75	56.4% (31/55)	NR
Kelcz et al. 2002[27]	Women with palpable masses, or who had mammographic or sonographic abnormalities thought to require biopsy. Women with prebiopsy studies indicating a high likelihood of a cyst were excluded	62	68	57	50	31 to 80	46.0% (31/68)	NR

Table C2. MRI studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable
Schedel et al. 2002[28]	Women with suspicious lesions diagnosed by physical examination or mammography, referred for biopsy; Excluded were women who had undergone tumor therapy or had diagnostic puncture of the breast to be evaluated within 3 months of the study, women who had undergone any kind of breast surgery within 6 months, or women who had irradiation treatment of the breast within 18 months.	65	34	57	52	21 to 78	59.6% (34/57)	NR
Trecate et al. 2002[29]	Patients with mammographically suspicious clustered or diffuse microcalcifications	28	28	28	NR	33 to 65	53.6% (15/28)	NR
Wiberg et al. 2002[30]	Consecutive patients scheduled for surgery between January 1996 to June 1997 after detection of lesions by palpation or mammography and after undergoing diagnostic triple assessment (diagnostic mammography, physical exam, and fine needle aspiration) who had no contraindications to MRI	93	114	114	54	33 to 81	72% (82/114)	54%

Table C2. MRI studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable
Brix et al. 2001[31]	Patients with suspicious lesions detected on mammography or physical examination who were scheduled for a biopsy.	14	14	14	49	35 to 66	64.2% (9/14)	NR
Cecil et al. 2001[32]	Women with a palpable or suspicious mass detected by mammography that was at least 1 cm in diameter but did not appear to be a focal mass.	37	23	37	47	18 to 85	60.5% (23/38)	NR
Furman-Haran et al. 2001[33]	Patients had lesions at mammography/US and biopsy was recommended	40	48	40	NR	NR	52.1% (25/48)	71%
Imbriaco et al. 2001[34]	Consecutive patients with a suspicious breast lesion detected either by physical examination or mammography and US; Patients were excluded if they were pregnant, lactating, under 18 years of age, had a personal history of breast cancer or had undergone fine-needle aspiration before the MRI could be performed	49	49	49	49	30 to 60	51% (25/49)	37%
Malich et al. 2001[35]	Consecutive patients with equivocal mammographic abnormalities referred for biopsy	94	100	90	NR	NR	67% (60/90)	NR

Table C2. MRI studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable
Nakahara et al. 2001[36]	Only patients who proceeded to biopsy were included	40	40	40	49.5	27 to 76	50.0% (20/40)	0%
Torheim et al. 2001[37]	Patients with solid breast tumors	127	127	126	53	NR	55.1% (70/127)	NR
Wedegartner et al. 2001[38]	Patients with palpable or mamographically suspicious lesions scheduled for excisional biopsy	53	62	53	49	18 to 82	71.0% (44/62)	NR
Yeung et al. 2001[39]	Women that showed non-specific lesions larger than 1.5 cm on mammography or ultrasound.	30	23	30	50	20 to 80	77.0% (23/30)	NR
Kvistad et al. 2000[40]	Patients with recently discovered solid breast tumors (palpable masses or mammographic screening) scheduled to undergo biopsy were invited; patients with cysts and microcalcifications but no solid mass were excluded, as were patients unable to undergo MRI due to old age, poor physical condition, claustrophobia, or lack of available time on the MRI schedule.	130	130	130	59	37 to 82	55.4% (72/130)	74%

Table C2. MRI studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable
Van Goethem et al. 2000[41]	Consecutive patients from 9 hospitals having MRI for any indication.	75	75	74	NR	NR	36.5% (27/74)	NR

MRI Magnetic resonance imaging
NR Not reported
US Ultrasound

Table C3. Details of MRI methodology

Study	Tesla	Machine Used	Precontrast Sequence	Contrast Agent	Post-contrast Sequence	Other/Final Sequence	Readers	Reference Standard
Akita et al. 2009[1]	1.5T	Signa HD (General Electric, Milwaukee, WI)	T2 weighted FSE with fat suppression, and T1 weighted SPGR	Gadodiamide hydrate (Omniscan) 0.1 mmol/kg	Dynamic 3D fat-suppressed	Fat-suppressed delayed-phase sagittal	Consensus of two radiologists	All patients underwent stereotactic vacuum-assisted breast biopsy
Baltzer et al. 2009[2]	1.5T	Magnetom Symphony or Sonata (Siemens, Erlangen, Germany)	T1 weighted SPGR	Gd-DTPA 0.1 mmol/kg	Dynamic FLASH	T2 weighted TSE	Consensus of two blinded reviewers vs. CAD	Open surgery
Hara et al. 2009[3]	1.5T	Magnetom Symphony (Siemens, Erlangen, Germany)	T2 and T1 weighted fat suppressed	Gadodiamide hydrate (Omniscan) 0.15 mmol/kg	Dynamic	None reported	One blinded radiologist	Fine needle biopsy and follw-up every 3 or 6 months (median follow-up 309 days)
Kim et al. 2009[4]	1.5T	Somatom Vision (Siemens, Erlangen, Germany)	T1 weighted FLASH	Gd-DTPA 0.16 mmol/kg	Dynamic T1 weighted 3D FLASH	None reported	Consensus of two radiologists	Open surgical biopsy (n = 215) or core needle biopsy (n = 24)
Lo et al. 2009[5]	3T	Magnetom Tim Trio (Siemens, Erlangen, Germany)	Diffusion-weighted single-shot followed by T1 and T2-weighted fat saturated	Gd-DTPA 0.1 mmol/kg	Dynamic 3D	T1 weighted fat-saturated	Consensus of two radiologists	Needle or excisional biopsy

Table C3. Details of MRI methodology (continued)

Study	Tesla	Machine Used	Precontrast Sequence	Contrast Agent	Post-contrast Sequence	Other/Final Sequence	Readers	Reference Standard
Imbracio et al. 2008[6]	1.5T	Gyroscan Intera (Philips Healthcare)	FFE	Gd-DTPA 0.1 mmol/kg	Dynamic T1-weighted 3D FFE	None reported	One radiologist	Excisional or core needle biopsy
Pediconi et al. 2008[7]	1.5T	Visions Plus (Siemens)	T1 weighted gradient echo	Gd-DTPA or gadobenate dimeglumine, 0.1 mmol/kg	Dynamic T1-weighted 3D gradient echo	None reported	Consensus of two blinded radiologists	Surgery, excisional biopsy, or core biopsy in all patients 24 hours to 1 month after MRI
Vassiou et al. 2009[8]	1.5T	Magnetom Vision (Siemens, Erlangen, Germany)	T2 weighted TSE	Gd-DTPA 0.2 mmol/kg	Dynamic T1 weighted SPGR	None reported	Not reported	Surgery, excisional biopsy, or core biopsy in all patients within 2 months after MRI
Brem et al. 2007[9]	1.5T	General Electric Healthcare, Milwaukee, WI	T1 and T2 weighted fat saturated	Gd-DTPA 0.1 mmol/kg	Dynamic T1 weighted	T1 fat saturated	Two experienced non-blinded breast imagers	MRI-guided biopsy and follow-up if needed
Cilotti et al. 2007[10]	1.5T	Symphony (Seimens)	T1 weighted, then T2 weighted fat saturated, then T1 3D FLASH	Gadoteridol (Prohance, Bracco) 0.1 mmol/kg	Dynamic	None reported	Not reported	Vaccumm assisted steotactic core needle biopsy or surgery

Table C3. Details of MRI methodology (continued)

Study	Tesla	Machine Used	Precontrast Sequence	Contrast Agent	Post-contrast Sequence	Other/Final Sequence	Readers	Reference Standard
Pediconi et al. 2007[11]	1.5T	Seimens Vision Plus (Seimens, Erlangen, Germany)	T1 weighted gradient echo	Gadobenate dimeglumine (MultiHance; Bracco Imaging, Milan, Italy) 0.1 mmol/kg	Dynamic 3D T1 weighted gradient echo	None reported	Two radiologists in consensus	Open surgery or core needle biopsy or followup
Zhu et al. 2007[12]	1.5T	Intera Master (Phillips Medical Systems, Cleveland, OH)	T2 weighted TSE and T1 weighted FFE fat saturated	Gadodiamide hydrate (Omniscan; Daiichi Pharma-ceuticals) 0.1 mmol/kg	Dynamic T1 weighted	None reported	One radiologist	Vacuum assisted core needle biopsy or surgery
Bazzocchi et al. 2006[13]	1.0 or 1.5 T	Various	3D gradient echo	Gadoteridol (ProHance, Bracco Imaging) 0.1 mmol/kg	Dynamic	None reported	Consensus of two blinded radiologists	Surgical biopsy after preoperative localization with a hook wire technique
Gokalp and Topal 2006[14]	1.5T	Magnetom Vision (Siemens, Erlangen, Germany)	T2 weighted TSE fat suppressed then T1 weighted 3D FLASH	Gd-DTPA 0.1 mmol/kg	Dynamic T1 weighted 3D FLASH	None reported	One radiologist	Follow up or biopsy
Kneeshaw et al. 2006[15]	1.5T	Signa Echospeed (General Electric, Milwaukee, WI)	T1 weighted 3D	Gd-DTPA 0.1 mmol/kg	Dynamic T1 weighted SPGR	T1 weighted 3D fat suppressed	One radiologist	Open surgery or follow-up

Table C3. Details of MRI methodology (continued)

Study	Tesla	Machine Used	Precontrast Sequence	Contrast Agent	Post-contrast Sequence	Other/Final Sequence	Readers	Reference Standard
Ricci et al. 2006[16]	1.5T	Magnetom Vision Plus (Seimens, Elrangen, Germany)	T2 weighted and T1 weighted 3D FLASH	Gadobenate dimeglumine 0.1 mmol/kg	Dynamic T1 weighted 3D SPGR	None reported	Not reported	Open surgical biopsy
Pediconi et al. 2005[17]	1.5T	Vision Plus (Siemens, Erhlangen, Germany)	T1 weighted	Gadobenate dimeglumine 0.1 mmol/kg	Dynamic 3D T1 weighted	None reported	Two blinded radiologists in consensus	Surgery, biopsy, or follow-up
Pediconi et al. 2005[18]	1.5T	Vision Plus (Siemens, Erhlangen, Germany)	T1 weighted	Gd-DTPA or gadobenate dimeglumine, 0.1 mmol/kg	Dynamic 3D T1 weighted	None reported	Two blinded radiologists in consensus	Surgery, biopsy, or follow-up
Wiener et al. 2005[19]	1.5 T	Symphony (Seimens)	T1 and T2 weighted	Gd-DTPA 0.1 mmol/kg	Dynamic 3D FLASH T1 weighted SPGR	None reported	One radiologist	Open surgery or core-needle biopsy; all core-needle biopsies were followed by either surgical excision or at least 1 year of clinical and mammo-graphic followup

Table C3. Details of MRI methodology (continued)

Study	Tesla	Machine Used	Precontrast Sequence	Contrast Agent	Post-contrast Sequence	Other/Final Sequence	Readers	Reference Standard
Bluemke et al. 2004[20]	1.5T	Various	T2 weighted, then 3D T1-weighted	Gd-DTPA 0.1 mmol/kg	3D T1 weighted fat suppressed; women with enhancing lesions also underwent 2D dynamic T1 weighted	None reported	One reader per center	Excisional or core needle biopsy
Huang et al. 2004[21]	1.5T	Edge (Marconi Medical Systems, Cleveland, OH)	None reported	Gadodiamide hydrate (Omniscan; Daiichi Pharma-ceuticals) 0.1 mmol/kg	Dynamic 3D T1 weighted SPGR	T2 weighted FLASH perfusion imaging	Not reported	Excisional biopsy or image guided core needle biopsy
Bone et al. 2003[22]	1.5T	Magentom SP63 (Seimens)	3D T1 weighted FLASH	Gd-DTPA 0.2 mmol/kg	Dynamic 3D T1 weighted FLASH	None reported	One radiologist	Surgical biopsy
Daldrup-Link et al. 2003[23]	1.5T	Philips ACS NT (BEST, the Nether-lands)	2D T2 weighted TSE	Gd-DTPA 0.2 mmol/kg	Dynamic 3D T1 weighted FLASH	None reported	Two radiologists	Open surgery
Heinisch et al. 2003[24]	1.0T	Not reported	T2 weighted TSE	Gd-DTPA 0.2 mmol/kg	Conventional dynamic	High-resolution 3D FFE with fat suppression including an additional contrast media injection	One radiologist	Open surgery

Table C3. Details of MRI methodology (continued)

Study	Tesla	Machine Used	Precontrast Sequence	Contrast Agent	Post-contrast Sequence	Other/Final Sequence	Readers	Reference Standard
Walter et al. 2003[25]	1.0T	Gyroscan T10 NT (Philips, Eindhoven, the Nether-lands)	T2 weighted TSE	Gd-DTPA 0.1 mmol/kg	Dynamic T1 weighted 3D FFE	None reported	Two radiologists in consensus	Biopsy
Guo et al. 2002[26]	1.5T	Signa Horizon (General Electric, Milwaukee, WI)	T2 weighted FSE with fat suppression and diffusion weighted spin echo	Gd-DTPA 0.1 mmol/kg	Fast gradient echo	None reported	Not reported	Excisional surgery
Kelcz et al. 2002[27]	1.5T	Sigma (General Electric, Milwaukee, WI)	3D gradient echo	Gadodiamide hydrate (Omniscan; Daiichi Pharma-ceuticals) 0.1 mmol/kg	3D gradient echo	None reported	One radiologist	57 excisional biopsy and 11 fine needle biopsy
Schedel et al. 2002[28]	1.5T	Magnetom 63 SP (Seimens, Erhlangen, Germany)	3D T1 weighted FLASH	Gd-DTPA 0.2 mmol/kg	3D T1 weighted FLASH	None reported	Not reported	Open biopsy or mastectomy
Trecate et al. 2002[29]	1.5T	Seimens Vision	3D T1 weighted FLASH	Gd-DTPA 0.1 mmol/kg	3D T1 weighted FLASH	None reported	Not reported	Surgical biopsy after preoperative localization with a hook wire technique
Wiberg et al. 2002[30]	1.5T	Magnetom SP 63 (Seimens)	3D T1 weighted FLASH	Gd-DTPA 0.2 mmol/kg	Dynamic 3D T1 weighted FLASH	None reported	One blinded radiologist	Open surgery

Table C3. Details of MRI methodology (continued)

Study	Tesla	Machine Used	Precontrast Sequence	Contrast Agent	Post-contrast Sequence	Other/Final Sequence	Readers	Reference Standard
Brix et al. 2001[31]	1.5T	Magnetom SP 4000 (Seimens, Erhlangen, Germany)	3D FLASH	Gd-DTPA 0.1 mmol/kg	Dynamic specially optimized saturation-recovery turbo FLASH	Static 3D FLASH	Not reported	Biopsy
Cecil et al. 2001[32]	1.5T	Signa (General Electric, Milwaukee, WI)	T1 weighted spin echo then fat saturated T2 weighted FSE	Gd-DTPA 0.1 mmol/kg	3D fat-saturated SPGR	None reported	Two radiologists and one blinded radiologist	Excisional or needle biopsy
Furman-Haran et al. 2001[33]	1.5T	Signa (General Electric, Milwaukee, WI)	Fast gradient echo	Gadodiamide hydrate (Omniscan; Daiichi Pharma-ceuticals) 0.1 mmol/kg	Dynamic fast gradient echo	None reported	One radiologist	Biopsy
Imbriaco et al. 2001[34]	0.5T	General Electric, Milwaukee, WI	T1 weighted spin echo	Gd-DTPA 0.1 mmol/kg	3D gradient echo	None reported	One radiologist	Open surgery or 1 year of followup (n = 6)
Malich et al. 2001[35]	1.5T	Gyroscan ACSII (Phillips, Hamburg, Germany)	T1 weighted FFE	Gd-DTPA 0.1 mmol/kg	Dynamic 2D T1 weighted FFE	T1 weighted FFE and then T2 weighted TSE	Not reported	Open surgical biopsy
Nakahara et al. 2001[36]	0.5T	Signa (General Electric)	T2 weighted	Gd-DTPA 0.1 mmol/kg	Fat-saturated SPRG	T1 weighted	Not reported	Biopsy after preop localization by hook wire

Table C3. Details of MRI methodology (continued)

Study	Tesla	Machine Used	Precontrast Sequence	Contrast Agent	Post-contrast Sequence	Other/Final Sequence	Readers	Reference Standard
Torheim et al. 2001[37]	1.5T	Picker Edge II (Picker, Cleveland, OH)	None reported	Gadodiamide hydrate (Omniscan; Daiichi Pharma-ceuticals) 0.1 mmol/kg	Dynamic 3D SPRG	T2 weighted perfusion imaging	Not reported	Excisional biopsy or FNA plus imaging follow up
Wedegartner et al. 2001[38]	1.0T	Magentom 63 SP or Magnetom Impact (Seimens)	None reported	Gd-DTPA 0.2 mmol/kg	Dynamic 3D or 2D FLASH	None reported	Panel of five blinded radiologists	Excisional biopsy, image guided biopsy
Yeung et al. 2001[39]	1.5T	Gyroscan ACS NT (Philips, Best, the Netherlands)	T1 weighted spin echo fat saturation	Gd-DTPA 0.2 mmol/kg	T1 weighted spin echo fat saturation and T2 weighted TSE	None reported	Not reported	15 mastectomy; 1 hook-wire guided excision; 16 core biopsy; and 5 fine-needle aspiration
Kvistad et al. 2000[40]	1.5T	Picker Edge II (Picker, Cleveland, OH)	3D T1 weighted SPGR	Gadodiamide hydrate (Omniscan; Daiichi Pharma-ceuticals) 0.1 mmol/kg	Dynamic 3D T1 weighted SPGR	T2 weighted perfusion imaging	Not reported	Open surgery (n = 100) or a mean of 18 months followup (n = 30)
Van Goethem et al. 2000[41]	NR	Various	None reported	Gd-DTPA 0.1 mmol/kg	3D FLASH	None reported	Not reported	Biopsy and follow-up

3D Three dimensional
FFE Fast field echo
FLASH Fast low-angle shot
FSE Fast spin echo
Gd-DTPA Magnevist, also called gadolinium diethylenetriamine penta-acetic acid dimeglumine, also called gadopentetic acid
NR Not reported

Table C3. Details of MRI methodology (continued)

SPGR	Spoiled gradient echo
T	Tesla
TSE	Turbo spin echo

Table C4. MRI studies: Information for meta-regressions

Study	Magnet	Tracer[a]	Consecutive or All Enrollment (1 = Yes)	Prospective Design (1 = Yes)	Probably Affected by Spectrum Bias[b] (1 = Yes)	Accounted for Inter-reader Differences (1 = Yes)	Readers Blinded to Clinical Information (1 = Yes)	All Diagnoses Confirmed by Histopathology (1 = Yes)	Multi-centered (1 = Yes)	Funded by (1 = Declared No Financial Conflicts of Interest)	Geographic Region[c]	Proportion Malignant
Akita et al. 2009[1]	1.5	2	1	0	1	0	0	1	0	0	1	0.26
Baltzer et al. 2009[2]	1.5	1	1	1	0	1	1	1	0	0	3	0.60
Hara et al. 2009[3]	1.5	2	1	0	1	0	0	0	0	0	1	0.24
Kim et al. 2009[4]	1.5	1	1	0	0	0	0	0	0	1	1	0.85
Lo et al. 2009[5]	3.0	1	0	1	0	0	1	0	0	0	0	0.65
Imbracio et al. 2008[6]	1.5	1	1	1	0	0	0	0	0	0	2	0.82
Pediconi et al. 2008[7]	1.5	1	0	1	0	0	1	1	0	0	2	0.64
Vassiou et al. 2009[8]	1.5	1	0	1	0	0	0	1	0	0	2	0.68
Brem et al. 2007[9]	1.5	1	0	0	1	0	0	0	0	0	4	0.27
Cilotti et al. 2007[10]	1.5	4	0	0	0	0	0	0	0	0	2	0.47

Table C4. MRI studies: Information for meta-regressions (continued)

Study	Magnet	Tracer[a]	Consecutive or All Enrollment (1 = Yes)	Prospective Design (1 = Yes)	Probably Affected by Spectrum Bias[b] (1 = Yes)	Accounted for Inter-reader Differences (1 = Yes)	Readers Blinded to Clinical Information (1 = Yes)	All Diagnoses Confirmed by Histopathology (1 = Yes)	Multi-centered (1 = Yes)	Funded by (1 = Declared No Financial Conflicts of Interest)	Geographic Region[c]	Proportion Malignant
Pediconi et al. 2007[11]	1.5	3	1	1	0	1	0	0	0	0	2	0.93
Zhu et al. 2007[12]	1.5	2	1	0	0	0	0	0	0	0	1	0.50
Bazzocchi et al. 2006[13]	1.2	4	0	1	0	1	1	1	1	1	2	0.67
Gokalp and Topal 2006[14]	1.5	1	1	1	0	0	0	0	0	0	2	0.02
Kneeshaw et al. 2006[15]	1.5	1	0	1	1	0	0	0	0	1	3	0.23
Ricci et al. 2006[16]	1.5	3	1	1	0	0	0	1	0	0	2	0.67
Pediconi et al. 2005[17]	1.5	3	1	1	0	1	1	0	0	0	2	0.79
Pediconi et al. 2005[18]	1.5	1	1	1	0	1	1	0	0	1	2	0.83
Wiener et al. 2005[19]	1.5	1	0	1	0	0	0	0	0	0	4	0.49
Bluemke et al. 2004[20]	1.5	1	0	1	0	0	0	0	1	1	6	0.36
Huang et al. 2004[21]	1.5	2	0	1	1	0	0	0	0	1	4	0.58

Table C4. MRI studies: Information for meta-regressions (continued)

Study	Magnet	Tracer[a]	Consecutive or All Enrollment (1 = Yes)	Prospective Design (1 = Yes)	Probably Affected by Spectrum Bias[b] (1 = Yes)	Accounted for Inter-reader Differences (1 = Yes)	Readers Blinded to Clinical Information (1 = Yes)	All Diagnoses Confirmed by Histopathology (1 = Yes)	Multi-centered (1 = Yes)	Funded by (1 = Declared No Financial Conflicts of Interest)	Geographic Region[c]	Proportion Malignant
Bone et al. 2003[22]	1.5	1	1	1	0	0	1	1	0	0	3	0.71
Daldrup-Link et al. 2003[23]	1.5	1	0	1	0	0	0	1	0	0	3	0.47
Heinisch et al. 2003[24]	1.0	1	0	1	0	0	0	1	0	0	3	0.63
Walter et al. 2003[25]	1.0	1	1	1	0	0	0	1	0	0	3	0.45
Guo et al. 2002[26]	1.5	1	0	0	0	0	0	1	0	0	0	0.56
Kelcz et al. 2002[27]	1.5	2	1	1	0	0	0	0	0	1	4	0.46
Schedel et al. 2002[28]	1.5	1	0	0	0	0	0	1	0	0	3	0.60
Trecate et al. 2002[29]	1.5	1	0	1	0	0	0	1	0	0	2	0.54
Wiberg et al. 2002[30]	1.5	1	1	1	0	0	1	1	0	0	3	0.72
Brix et al. 2001[31]	1.5	1	1	1	0	0	1	1	0	1	3	0.70
Cecil et al. 2001[32]	1.5	1	1	0	0	0	0	0	0	1	4	0.60

Table C4. MRI studies: Information for meta-regressions (continued)

Study	Magnet	Tracer[a]	Consecutive or All Enrollment (1 = Yes)	Prospective Design (1 = Yes)	Probably Affected by Spectrum Bias[b] (1 = Yes)	Accounted for Inter-reader Differences (1 = Yes)	Readers Blinded to Clinical Information (1 = Yes)	All Diagnoses Confirmed by Histopathology (1 = Yes)	Multi-centered (1 = Yes)	Funded by (1 = Declared No Financial Conflicts of Interest)	Geographic Region[c]	Proportion Malignant
Furman-Haran et al. 2001[33]	1.5	2	0	1	0	0	1	1	0	1	4	0.52
Imbriaco et al. 2001[34]	0.5	1	1	1	0	0	1	0	0	1	2	0.51
Malich et al. 2001[35]	1.5	1	1	0	0	0	0	1	0	0	3	0.67
Nakahara et al. 2001[36]	0.5	1	0	0	0	0	0	1	0	0	1	0.50
Torheim et al. 2001[37]	1.5	2	0	1	0	0	0	0	0	1	3	0.55
Wedegartner et al. 2001[38]	1.0	1	0	1	0	0	1	1	0	0	3	0.71
Yeung et al. 2001[39]	1.5	1	1	0	0	0	0	0	0	0	0	0.77
Kvistad et al. 2000[40]	1.5	2	0	1	0	1	1	0	0	1	3	0.55
Van Goethem et al. 2000[41]	1.2	1	1	0	1	0	0	0	1	0	3	0.37

[a] For Tracer, 1 = gadopentetic acid; 2 = gadodiamide; 3 = gadobenic acid; 4 = gadoteridol; 0 = mixed or not reported. For the studies directly comparing tracers, data for gadopentetic acid was used in the primary meta-regression.

[b] Spectrum bias defined as median/mean age greater than 50 and/or % lesions malignant less than 10% or greater than 40%

[c] China = 0; Asia = 1; Turkey, Greece, Italy = 2; Europe and United Kingdom = 3; North America = 4; South America = 5; multiple = 6

Positron Emission Tomography (PET)

Total of 8 studies

Total of 438 patients, 459 lesions

7 studies of PET; 1 study of PET/CT

Table C5. Included studies of PET

Study	PET Methods Studied	Design	N Patients	N Lesions	Geographical Location	Funded by
Imbriaco et al. 2008[6]	PET/CT	Diagnostic cohort study	44	55	Italy	Not reported
Kaida et al. 2008[42]	PET	Prospective diagnostic cohort	118	122	Japan	Not reported
Buchmann et al. 2007[43]	PET	Prospective diagnostic cohort	29	29	Germany	Not reported
Hienisch et al. 2003[24]	PET	Prospective diagnostic cohort	36	40	Austria	Not reported
Walter et al. 2003[25]	PET	Prospective diagnostic cohort	40	42	Germany	Not reported
Brix et al. 2001[31]	PET	Prospective diagnostic cohort	14	14	Germany	Wilhelm Sanders-Stiftung
Schirrmeister et al. 2001[44]	PET	Prospective diagnostic cohort	117	117	Germany	Not reported
Yutani et al. 2000[45]	PET	Prospective diagnostic cohort	40	40	Japan	Not reported

Table C6. PET studies: patient and lesion details

Study	Inclusion/Exclusion Criteria	N Patients	Mean or Median Age and Range (Years)	% 65 or Older	% Post-menopausal	% Palpable	Tumor Size Mean (Range)
Imbriaco et al. 2008[6]	Patients with suspicious breast lesions (detected by mammography, sonography, or physical examination) confirmed on the basis of histopathologic results. Patients who were pregnant or lactating, younger than 18, had a personal history of breast cancer, or who underwent fine needle aspiration biopsy prior to MRI or PET/CT were excluded.	45	Mean: 54 Standard deviation: 12	NR	NR	NR	17mm (7 to 30 mm)
Kaida et al. 2008[42]	Women for whom breast cancer was suggested based on clinical examination and mammography. Exclusion criteria not reported.	118	Mean: 58 Range: 28 to 91	NR	NR	88.0%	Not reported for all tumors
Buchmann et al. 2007[43]	Women suspected of having breast cancer on mammography and/or ultrasound. Patients were excluded if they were younger than 18, pregnant or lactating, had a second malignancy, or had been treated for drug/alcohol abuse.	29	Mean: 50.5 Standard deviation: 11.5	10%	NR	NR	26.9 mm (10 to 80 mm)

Table C6. PET studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	Mean or Median Age and Range (Years)	% 65 or Older	% Post-menopausal	% Palpable	Tumor Size Mean (Range)
Hienisch et al. 2003[24]	Women with suspicious breast lesions detected by physical exam, mammography, and/or ultrasound, scheduled for biopsy, referred when there was time on the scanners. Pregnant women were excluded.	36	Mean: 48.3 Range: 25 to 77	NR	NR	NR	16.7 mm (5 to 45 mm)
Walter et al. 2003[25]	Patients referred to the clinic for biopsy of suspicious lesions on the basis of mammography, ultrasound, or physical examination. Referred patients were chosen randomly from 550 possible patients to fill restricted scanner time.	44	Mean: 52 Range: 21 to 77	NR	NR	NR	Mean NR (0.5 to 6.0 cm)
Brix et al. 2001[31]	Women with suspicious breast lesions detected by physical exam, mammography, and/or ultrasound, scheduled for biopsy, referred when there was time on the scanners. Women with lesions smaller than 10 mm, elevated blood glucose, younger than age 18, pregnant, or had metal implants were excluded.	14	Mean: 49 Range: 35 to 66	NR	NR	NR	Excluded lesions <10 mm Mean and range NR

Table C6. PET studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	Mean or Median Age and Range (Years)	% 65 or Older	% Post-menopausal	% Palpable	Tumor Size Mean (Range)
Schirrmeister et al. 2001[44]	Women with palpable breast tumors or suspicious lesions on mammography and/or ultrasound. Pregnant women and women younger than 18 were excluded from the study.	117	Mean: 56.8 Range: 28 to 86	NR	51.3%	76%	Not reported for all tumors
Yutani et al. 2000[45]	Patients with suspicious lesions (detected by mammography, ultrasound, or physical exam) scheduled for excisional biopsy.	40	Mean: 51 Range: 25 to 86	15%	NR	93%	21 mm (4 to 45 mm)

CT Computer tomography
FDG 18-fluorodeoxyglucose
NR Not reported
PET Positron emission tomography

Table C7. Details of PET methodology

Study	Type of Scanner	PET Parameters	Tracer FDG Parameters	Reference Standard
Imbriaco et al. 2008[6]	Whole body PET/CT	Prone position, 60 minutes after injection (Time 1) and 3 hours after injection (Time 2) CT images were reconstructed using standard iterative algorithm	5.2 MBq/kg of body weight, fast of 6 to 8 hours	Biopsy or surgery
Kaida et al. 2008[42]	Whole body	Supine position, 60 minutes after tracer followed by prone imaging 85 minutes after tracer	263 MBq, fast of at least 4 hours	Biopsy or surgery Benign patients followed for up to 2 years
Buchmann et al. 2007[43]	Whole body	Supine position, 60 minutes after tracer followed by prone imaging 135 minutes after tracer.	263 (±15) MBq, injected in fasting state (total fast time not reported)	All surgery
Hienisch et al. 2003[24]	Whole body	Prone position, 70 minutes after tracer	120 to 180 MBq, fast of 12 hours or longer	All surgery
Walter et al. 2003[25]	Whole body	Prone position, 40 to 60 minutes after tracer	300 to 370 MBq, fast of 12 hours or longer	All surgery
Brix et al. 2001[31]	Whole body	Prone position, 60 minutes after tracer	138 to 248 MBq, fast of 6 hours or longer	Biopsy or surgery
Schirrmeister et al. 2001[44]	Whole body	Prone position, 45 to 60 minutes after tracer	370 MBq, fast of 8 hours	Biopsy or surgery
Yutani et al. 2000[45]	Whole body	Supine position, 60 minutes after tracer	370 MBq, fast of 4 hours or longer	All surgery

CT Computed tomography
FDG 18-fluorodeoxyglucose
MBq Mega becquerel
NR Not reported
PET Positron emission tomography

Table C8. PET Studies: information for meta-regressions

Study	Patient Position (1 = Prone)	Palpable Lesions Only (1 = All Palpable)	Readers Blinded to Clinical Information (1 = Yes)	All Diagnoses Confirmed by Histopathology (1 = Yes)
Kaida et al. 2008[42]	1	1	1	1
Buchmann et al. 2007[43]	1	0	0	0
Hienisch et al. 2003[24]	1	0	0	0
Walter et al. 2003[25]	1	0	0	0
Brix et al. 2001[31]	1	0	0	0
Schirrmeister et al. 2001[44]	1	1	1	0
Yutani et al. 2000[45]	0	1	1	0

Scintimammography (SMM)

Total of 11 studies

Total of 1,074 patients, 1,074 lesions

10 studies of conventional SMM, 1 study of BSG1

Table C9. Included studies of scintimammography

Study	SMM Methods Studied	Design	N Patients	N Lesions	Geographical Location	Funding Source
Grosso et al. 2009[46]	SMM at 5 minutes after administration of 99m Tc sestamibi, planar images with patient supine and prone.	Prospective diagnostic cohort	283	283	Italy	NR
Habib et al. 2009[47]	Double-phase SMM images were acquired 5-10 minutes and one hour after administration of with 99m Tc sestamibi, planar images patients prone and supine	Prospective diagnostic cohort	22	22	Karachi	NR
Kim et al. 2009[4]	Double-phase SMM at 10 minutes and 3 hours after 99m Tc sestamibi administration, planar images in prone and lateral positions.	Prospective diagnostic cohort	249	249	Republic of Korea	Pusan National University Research Grant
Kim et al. 2008[48]	Double-phase SMM images after 10 minutes and three hours after IV administration of 99m Tc sestamibi; planar images with patient in the lateral and prone positions and planar anterior chest image with patient in supine position	Prospective diagnostic cohort	75	75	Republic of Korea	NR
Wang et al. 2008[49]	SMM with 99mTc-MIBI; planar images with patient supine (anterior and oblique views) and prone (lateral views)	Prospective diagnostic cohort	55	55	China	Jiangsu Government Science Grant and Nanjing Health Bureau Grant, China

Table C9. Included studies of scintimammography (continued)

Study	SMM Methods Studied	Design	N Patients	N Lesions	Geographical Location	Funding Source
Brem et al. 2007[9]	BSGI 10 minutes after 99mTc-sestamibi injection, images were obtained in the cranial caudal and medial lateral oblique projections	NR	33	33	U.S.	NR
Gommans et al. 2007[50]	SMM mages were taken 5 minutes after injection of 99m Tc sestamibi; anterior, left and right lateral images (10 minute acquisition, 256x256), patient supine and prone	Prospective diagnostic cohort	101	101	Netherlands	NR
Kim et al. 2007[51]	Double-phase SMM performed 10 minutes and 3 hrs after IV 99m Tc sestamibi; Planar images, patient prone and lateral and anterior chest images in the supine position.	Prospective diagnostic cohort	78	78	South Korea	Pusan National University Research Grant
Schillaci et al. 2007[52]	99m Tc sestamibi; planar images were acquired (left and right lateral images with patient prone and an anterior chest image, with patient supine)	Prospective diagnostic cohort	53	53	Italy	NR
Pinero et al. 2006[53]	Double-phase Sestamibi gammagraphy; planar images 5 minutes and one hour after injection of 99m Tc sestamibi, patient prone and supine	Prospective diagnostic cohort	88	88	Spain	NR
Mathieu et al. 2005[54]	Patient supine 10 minutes after 99mTc-MIBI, and prone position, 256x256 matrix, SPECT and planar images	Retrospective chart review	37	37	Belgium	NR

U.S. United States

Table C10. Scintimammography studies: patient and lesion details

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable	Lesion Size
Grosso et al. 2009[46]	Patients with non-palpable breast lesions (microcalcifications) detected on screening mammography. Other inclusion criteria: SMM within 2 weeks after conventional mammography, breast lesion operated upon within 1 month after SMM; a minimum follow-up of 5 years after SMM; mental capacity and age above 18 years. Exclusion criteria: a palpable lesion suspicious of malignancy; palpable nodes in the axillary region; a history of prior carcinoma; prior FNA or CNB within one week prior to SMM, pregnancy and lactation.	283	283	283	53 ±8.2	32-79	11.3%	0%	NR

Table C10. Scintimammography studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable	Lesion Size
Habib et al. 2009[47]	Women with a palpable mass or lump or with positive or indeterminate findings on mammography. Exclusion criteria: medically unstable patients; lactating or pregnant women; patients with a history of surgery within the past week.	22	22	22	Mean: 36.5 Median: 40.0	17 to 80	68.2%	90.9%	NR
Kim et al. 2009[4]	Patients with palpable masses on physical examination and/or suspicious mammographic findings. No exclusion criteria presented.	249	239	239	47 ±9.7	NR	85.3%	85.3%	Malignant: 0.3 to 3.5 cm, Mean: 1.61 ±0.69 cm Benign: 0.7 to 3.5, Mean: 1.87 ±0.67 cm
Kim et al. 2008[48]	Patients with palpable breast masses on physical examination and/or suspicious mammograms. No exclusion criteria presented.	75	75	75	46.9 ±9.5	NR	65.3%	54.7%	NR
Wang et al. 2008[49]	Patients with palpable breast lesions. No exclusion criteria presented.	55	55	55	48 ±14.7	7 to 77	67.3%	100%	NR

Table C10. Scintimammography studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable	Lesion Size
Brem et al. 2007[9]	Indeterminate breast findings that required BSGI and MRI follow-up as determined by the patient's clinician. No exclusion criteria presented.	33	33	33	53 ±10	33 to 70	27.3%	NR	Malignant lesions ranged from 8 mm to extensive and multifocal
Gommans et al. 2007[50]	Patients with non-palpable lesions on mammography suspicious for malignancy, over 18 years of age and with the mental capacity to participate in the study. Exclusion criteria included a palpable lesion suspicious for malignancy, palpable nodes in the axillary region, a history of prior carcinoma, prior thin needle biopsy, pregnancy and lactation.	101	101	101	61 ±7.3	50 to 75	44.6%	0%	NR
Kim et al. 2007[51]	Women with indeterminate US findings. No exclusion criteria presented.	78	78	78	49.6 ±6.8	NR	84.6%	NR	0.8 to 7.5 cm

Table C10. Scintimammography studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable	Lesion Size
Schillaci et al. 2007[52]	Patients with suspicious lesions on mammography. No exclusion criteria presented.	53	53	53	NR	27 to 78	69.8%	60.4%	NR
Pinero et al. 2006[53]	Palpable or non-palpable lesions with a BIRADS score of either 4 or 5 on mammography. Excluded were men and pregnant women.	88	88	88	57.65	33 to 87	77.3%	64.8%	NR
Mathieu et al. 2005[54]	Patients with inconclusive/ contradictory triple screen (mammography, US, FNA) result. Retrospective chart review. No exclusion criteria presented.	37	37	37	NR	NR	54.1%	NR	NR

FNA Fine-needle aspiration
NR Not reported
US Ultrasound

Table C11. Details of scintimammography methods

Study	Tracer	Imager Specifications	Brand	Type of Imaging	Matrix	Method
Grosso et al. 2009[46]	740 MBq ^{99m}Tc-sestamibi	A dual head large fied of view gamma camera equipped with low energy, high resolution collaminators	GE Medical Systems Millennium MG, Milwaukee, WI, USA	Planar images with patient supine and prone.	256 x 256 pixels	Not specified
Habib et al. 2009[47]	740 MBq (20 mCi) Tc-99m sestamibi	Single headed gamma camera equipped with a low energy all purpose collimator	NR	Planar images with patients prone and supine	NR	Double-phase SMM at 10 mins and 60-90 mins
Kim et al. 2009[4]	925 MBq Tc-99m MIBI	Dual headed gamma camera equipped with low energy high resolution collimators	Vertex™, ADAC, Milpitas, CA, USA)	Planar images in prone and lateral positions.	128 x 128 pixels	Double-phase SMM at 10 minutes and 3 hours
Kim et al. 2008[48]	925 MBq Tc-99m MIBI	Dual headed gamma camera equipped with low energy high resolution collimators	Vertex™, ADAC, Milpitas, CA, USA)	Planar images with patient in the lateral and prone positions and planar anterior chest image with patient in supine position	128 x 128 pixels	Double-phase SMM images after 10 minutes and three hours
Wang et al. 2008[49]	740 MBq (20mCi) ^{99m} Tc-MIBI	Dual headed gamma camera equipped with a high resolution parallel hole collimator	Millennium VG, Hawkeye; General Electric Medical Systems	Planar images with patient supine (anterior and oblique views) and prone (lateral views)	256 x 256	Not specified

Table C11. Details of scintimammography methods (continued)

Study	Tracer	Imager Specifications	Brand	Type of Imaging	Matrix	Method
Brem et al. 2007[9]	25.0-30.0 mCi ^{99m}Tc-sestamibi (925-1110 MBq)	High resolution breast specific gamma camera	Dilon 6800, Dilon Technologies, Inc., Newport News, VA	Images were obtained in the cranial caudal and medial lateral oblique projections	Not reported	BSGI
Gommans et al. 2007[50]	700 MBq 99mTc-sestamibi	One head used; Low energy high resolution collimator	GE-Millenium VG	To label 99mTc sestamibi, 99mTc pertechnetate in saline was added to Cardiolite; SMM mages were taken 5 minutes after injection; anterior, left and right lateral images (10 minute acquisition, 256x256), patient supine and prone	256 x 256	Not spcified
Kim et al. 2007[51]	925 MBq of Tc-99m MIBI	Dual headed gamma camera equipped with low energy high resolution collimators	Vertex, ADAC, Milpitas, CA, USA	Planar images, patient prone and lateral and anterior chest images in the supine position.	128 x 128	Double-phase SMM performed 10 minutes and 3 hrs

Table C11. Details of scintimammography methods (continued)

Study	Tracer	Imager Specifications	Brand	Type of Imaging	Matrix	Method
Schillaci et al. 2007[52]	740 MBq Tc-99m sestamibi	Combined SPECT/CT system composed of a dual head variable angle gamma camera. This system allowed for sequential interchangeable acquisition of nuclear medicine and CT images	Millenium VG and Hawkeye;General Electric Medical Systems, Milwaukee, WI, USA	99m Tc sestamibi; planar images were acquired (left and right lateral images with patient prone and an anterior chest image, with patient supine)	256 x 256	SMM
Pinero et al. 2006[53]	740 MBq (20 mCi) Cardiolite	gamma camera equipped with a high resolution collimator	Elscint SP6	Planar images twith patient prone and supine	NR	Double-phase Sestamibi gamma-graphy
Mathieu et al. 2005[54]	740 MBq (20 mCi) ^{99m}Tc-MIBI	Triple head system using a high resolution lowenergy collimator	Multispect; Siemens	Patients in the supine and prone position	256 x 256	SPECT and planar images

NR Not reported

Table C12. Scintimammography studies: information for meta-regression

Study	Consecutive or All Enrollment (1 = Yes)	Readers Blinded to Clinical Information (1 = Yes)	All Diagnoses Confirmed by Histopathology (1 = Yes)	Percent Malignant
Grosso et al. 2009[46]	1	1	0	11.3%
Habib et al. 2009[47]	0	1	0	68.2%
Kim et al. 2009[4]	1	0	0	85.3%
Kim et al. 2008[48]	0	1	0	65.3%
Wang et al. 2008[49]	1	1	1	67.3%
Gommans et al. 2007[50]	1	1	0	44.6%
Kim et al. 2007[51]	1	1	0	84.6%
Schillaci et al. 2007[52]	0	0	1	69.8%
Pinero et al. 2006[53]	1	0	1	77.3%

Ultrasound

Included Studies of Ultrasound

Total of 31 studies

Total of 8,642 patients; 9,044 lesions

Types of Ultrasound Studied: (many articles studied more than one type of ultrasound)

B-mode 2D grayscale: 21 studies

B-mode 2D grayscale contrast enhanced: 2 studies

B-mode 3D grayscale: 1 study

Color Doppler: 6 studies

Color Doppler, contrast enhanced: 2 studies

Combination of methods: 4 studies

Power Doppler: 9 studies

Power Doppler, contrast enhanced: 7 studies

Tissue harmonics: 1 study

Table C13. Included studies of ultrasound

Study	US Methods Studied	Design	N Patients	N Lesions	Geographical Location	Funding Source
Gokalp et al. 2009[55]	B-mode 2D grayscale, power Doppler, and combination of both methods	Prospective diagnostic cohort	49	94	Turkey	NR
Vassiou et al. 2009[8]	B-mode 2D grayscale	Prospective diagnostic cohort	69	78	Greece	NR

Table C13. Included studies of ultrasound (continued)

Study	US Methods Studied	Design	N Patients	N Lesions	Geographical Location	Funding Source
Liu et al. 2008[56]	B-mode 2D grayscale, with and without contrast (with Sono Vue [Bracco, Italy]), and combination of both methods	Diagnostic cohort study	108	108	China	Authors report no financial conflicts of interest
Vade et al. 2008[57]	B-mode 2D grayscale	Retrospective chart review	20	21	USA	NR
Cha et al. 2007[58]	B-mode 2D grayscale and tissue harmonic imaging	Prospective diagnostic cohort	88	91	Korea	NR
Chala et al. 2007[59]	B-mode 2D grayscale	Retrospective chart review	203	229	Brazil	NR
Zhi et al. 2007[60]	B-mode 2D grayscale	Diagnostic cohort study	232	296	China	NR
Cho et al. 2006[61]	B-mode 2D and 3D grayscale	Prospective diagnostic cohort	141	150	Korea	NR
Pinero et al. 2006[53]	Combination power Doppler and color Doppler using a contrast agent (Levovist [Schering AG, Berlin, Germany])	Prospective diagnostic cohort	88	88	Spain	NR
Ricci et al. 2006[16]	B-mode grayscale with and without contrast (with Sono Vue [Bracco, Italy]); also compared US to MRI	Prospective diagnostic cohort	48	50	Italy	NR
Forsberg et al. 2004[62]	B-mode 2D grayscale and power Doppler, with and without contrast (Levovist or Optison)	Diagnostic cohort study	55	55	USA	U.S. Army Medical Research and Material Command and National Institutes of Health
Meyberg-Solomayer et al. 2004[63]	B-mode 2D gray-scale	Prospective diagnostic cohort	65	65	Germany	NR

Table C13. Included studies of ultrasound (continued)

Study	US Methods Studied	Design	N Patients	N Lesions	Geographical Location	Funding Source
Ozdemir et al. 2004[64]	Power Doppler, with or without contrast (Levovist)	Prospective diagnostic cohort	80	81	Turkey	NR
Chen et al. 2003[65]	B-mode 2D gray scale	Prospective diagnostic cohort	32	32	China	NR
Kook and Kwag 2003[66]	B-mode US and power Doppler, with and without contrast (Levovist)	Prospective diagnostic cohort	36	36	South Korea	NR
Marini et al. 2003[67]	B-mode 2D grayscale	Diagnostic cohort study	238	238	Italy	NR
Caruso et al. 2002[68]	Color Doppler with and without contrast (Levovist)	Prospective diagnostic cohort	36	36	Italy	NR
Koukouraki et al. 2001[69]	Color Doppler	Prospective diagnostic cohort	116	116	Greece	NR
Malich et al. 2001[35]	Combination of B-mode, power Doppler, and color Doppler; also compared US to MRI	Diagnostic cohort study	94	100	Sweden	NR
Milz et al. 2001[70]	Power Doppler	Prospective diagnostic cohort	102	118	Germany	NR
Reinikainen et al. 2001[71]	B-mode US and power Doppler, with and without contrast (Levovist)	Prospective diagnostic cohort	63	69	Finland	Finnish Breast Cancer Group and Cancer Society of Northern Finland
Moon et al. 2000[72]	Power Doppler, with and without contrast (Levovist)	Prospective diagnostic cohort	69	69	South Korea	Seoul National University Hospital Research Fund

Table C13. Included studies of ultrasound (continued)

Study	US Methods Studied	Design	N Patients	N Lesions	Geographical Location	Funding Source
Blohmer et al. 1999[73]	B-mode 2D gray-scale and color Doppler	Prospective diagnostic cohort	200	200	Germany	NR
Chao et al. 1999[74]	B-mode 2D gray-scale	Prospective diagnostic cohort	3050	3093	Taiwan	NR
Schroeder et al. 1999[75]	Power and color Doppler, with and without contrast (Levovist)	Prospective diagnostic cohort	92	110	Germany	NR
Albrecht et al. 1998[76]	Power Doppler, with or without contrast (EchoGen)	Prospective diagnostic cohort	20	20	United Kingdom	NR
Wilkens et al. 1998[77]	B-mode 2D gray-scale and color Doppler	Diagnostic cohort study	53	55	USA	NR
Buadu et al. 1997[78]	Color Doppler	Diagnostic cohort study	114	117	Japan	NR
Stavros et al. 1995[79]	B-mode 2D gray-scale	Prospective diagnostic cohort	622	750	USA	NR
Ciatto et al. 1994[80]	B-mode 2D gray scale	Prospective diagnostic cohort	2079	2079	Italy	NR
Perre et al. 1994[81]	B-mode 2D gray-scale	Prospective diagnostic cohort	380	400	Netherlands	NR

NR Not reported
US Ultrasound
USA United States of America

Table C14. Ultrasound studies: patient and lesion details

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable	Lesion Size Mean (Range)
Gokalp et al. 2009[55]	Patients with solid breast lesions referred for US-guided core needle biopsy	49	94	49	53.6	27 to 89	41.5% (39/94)	NR	16.35 mm (5 to 35 mm)
Vassiou et al. 2009[8]	Women with suspicious lesions diagnosed by physical examination or mammography, referred for biopsy	69	78	69	53	39 to 68	68% (53/78)	NR	NR
Liu et al. 2008[56]	Consecutive patients with US-visible breast lesions who were referred for open surgical biopsy	108	108	104	44	19 to 86	41.3% (43/104)	NR	2.4 cm (0.5 to 7.6 cm)
Vade et al. 2008[57]	Consecutive patients under the age of 20 with palpable breast masses	20	21	21	14.8	13 to 19	0%	100%	NR
Cha et al. 2007[58]	Consecutive patients with solid breast lesions that were visible on US who were scheduled to undergo biopsy due to findings on mammography and/or physical exam	88	91	91	45	25 to 67	33% (30/91)	32%	13 mm (4 to 28 mm)

Table C14. Ultrasound studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable	Lesion Size Mean (Range)
Chala et al. 2007[59]	Consecutive female patients with solid breast lesions who were referred for biopsy due to findings on mammography and/or physical exam	203	229	229	56	30 to 77	22.7% (52/229)	56.3% (129/229)	19 mm (5 to 62 mm)
Zhi et al. 2007[60]	Consecutive patients with solid breast lesions	232	296	296	42	17 to 87	29.4% (87/296)	NR	15.5 mm (3.1 to 100.6 mm)
Cho et al. 2006[61]	Consecutive patients with solid breast lesions that were visible on US who were scheduled to undergo biopsy due to findings on mammography and/or physical exam	141	150	150	46	25 to 71	40% (60/150)	38.70%	4 to 36 mm (range NR)
Pinero et al. 2006[53]	Consecutive patients who were scheduled to undergo biopsy due to findings on mammography and/or physical exam, who were not pregnant	88	88	88	57.7	33 to 87	77% (68/88)	65%	NR
Ricci et al. 2006[16]	Consecutive patients with breast lesions detected on mammography	48	50	50	58	40 to 81	76% (38/50)	NR	NR

Table C14. Ultrasound studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable	Lesion Size Mean (Range)
Forsberg et al. 2004[62]	Patients with solid breast lesions detected on mammography and/or physical exam, who were mentally stable, not pregnant, and not breast-feeding	55	55	50	52	26 to 72	29% (16/55)	NR	NR
Meyberg-Solomayer et al. 2004[63]	Female patients with breast lesions	65	65	65	54	16 to 96	64.6% (42/65)	NR	21.5 mm (2 to 70 mm)
Ozdemir et al. 2004[64]	Patients with breast lesions that were not clearly cystic or benign, that were visible on US, who were likely to have followup data due to living near the study center, who were scheduled to undergo biopsy due to findings on mammography and/or physical exam	80	81	69	47.3	19 to 75	40.5% (28/69)	32%	16.1 mm (6 to 44 mm)
Chen et al. 2003[65]	Patients with palpable lesions that had indeterminate mammographic results due to dense breasts	32	32	32	44.6	34 to 55	75% (24/32)	100%	NR

Table C14. Ultrasound studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable	Lesion Size Mean (Range)
Kook and Kwag 2003[66]	Patients referred for diagnostic US after discovery of a palpable mass or mammographic abnormality that was 2 cm or smaller in diameter	36	36	36	43.5	18 to 69	47% (17/36)	NR	2 cm or less Mean and range NR
Marini et al. 2003[67]	Consecutive patients with microcalcifications detected on mammography who were older than 27 years of age, and who had an US exam followed by either a biopsy or at least three years of clinical followup	238	238	238	55	31 to 98	39% (94/238)	NR	NR
Caruso et al. 2002[68]	Patients with a single breast lesion 1 to 2 cm in diameter with no microcalcifications that was detected on mammography	36	36	36	55	42 to 63	56% (20/36)	NR	1 to 2 cm Mean and range NR

Table C14. Ultrasound studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable	Lesion Size Mean (Range)
Koukouraki et al. 2001[69]	Women with abnormal findings on screening mammography who were scheduled for an open surgical biopsy	116	116	116	NR	25 to 78	74% (86/116)	32.70%	NR
Malich et al. 2001[35]	Consecutive patients with equivocal mammographic abnormalities	94	100	100	NR	NR	62% (62/100)	NR	NR
Milz et al. 2001[70]	Patients with indeterminate findings after mammography and examination who were referred for diagnostic US	102	118	118	51	15 to 77	47% (55/118)	NR	NR
Reinikainen et al. 2001[71]	Patients with an US-visible breast lesion detected by palpation or mammography that was suggestive of malignancy or not conclusively benign	63	69	65	51	20 to 81	52.3% (34/65)	81.50%	NR

Table C14. Ultrasound studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable	Lesion Size Mean (Range)
Moon et al. 2000[72]	Consecutive patients with suspicious non-palpable lesions detected on mammography who were scheduled to undergo surgical biopsy	69	69	50	52	30 to 67	44% (22/50)	0%	NR
Blohmer et al. 1999[73]	Patients referred for biopsy because of a suspicious breast lesion	200	200	168 (regular US), 150 (Doppler US)	NR	NR	49.5% (99/200)	NR	NR
Chao et al. 1999[74]	Patients with solid breast masses	3,050	3,093	3,093	38.7	14 to 86	24% (733/3093)	NR	2.1 cm (0.5 to 24 cm)
Schroeder et al. 1999[75]	Patients with clinically suspected breast tumors after mammography and examination	92	110	110	46.1	17 to 79	65.5% (72/110)	NR	NR
Albrecht et al. 1998[76]	Patients with breast lesions	20	20	20	47	22 to 74	55% (11/20)	NR	NR
Wilkens et al. 1998[77]	Patients with palpable masses; those with obvious simple cysts were excluded	53	55	55	NR	13 to 81	40% (22/55)	100%	NR
Buadu et al. 1997[78]	Consecutive patients referred for surgery due to breast masses or suspicious mammograms	114	117	116	49	15 to 78	72.4% (84/116)	NR	NR

Table C14. Ultrasound studies: patient and lesion details (continued)

Study	Inclusion/Exclusion Criteria	N Patients	N Lesions	N Completed Study	Median or Mean Age (Years)	Age Range (Years)	% Lesions (n/N) Malignant	% Lesions Palpable	Lesion Size Mean (Range)
Stavros et al. 1995[79]	Patients with indeterminate mammographic findings of solid lesions; obviously malignant lesions were excluded	622	750	750	47	18 to 88	16.7% (125/750)	NR	most were 1.5 cm or smaller Mean and range NR
Ciatto et al. 1994[80]	Consecutive women with clinical or mammographic abnormalities who were referred for diagnostic US	2,079	2,079	2,079	48	14 to 93	12.5% (259/2079)	NR	NR
Perre et al. 1994[81]	Female patients with palpable breast lesions	380	400	400	49.3	13.7 to 98.9	43.5% (174/400)	100%	NR

NR Not reported
US Ultrasound

Table C15. Ultrasound studies: details of methods

Study	US Method	US Device	US MHz	US Operators	Reference Standard
Gokalp et al. 2009[55]	B-mode 2D grayscale, power Doppler, and combination of both methods	ATL HDI 5000 (Philips-ATL Medical Systems, Bothell, WA)	5 to 12 MHZ	One radiologist	Core needle biopsy followed by surgery or 2 years followup
Vassiou et al. 2009[8]	B-mode 2D grayscale	Technos, Esaote	7 to 12 MHz	One radiologist	Core needle biopsy or surgery
Liu et al. 2008[56]	B-mode 2D grayscale, with and without contrast (with Sono Vue [Bracco, Italy]), and combination of both methods	HDI 5000 or iU22 (Phillips Medical Systems, Bothell, WA)	4 to 7 or 8 MHZ	Two radiologists in consensus	Open surgical biopsy
Vade et al. 2008[57]	B-mode 2D gray-scale	Sequoia (Siemens Medical Solutions)	7 to 15 MHz	NR	14 had open biopsy, 3 had FNA, and 4 had 3 to 6 months of followup
Cha et al. 2007[58]	B-mode 2D gray-scale and tissue harmonic imaging	LIGIQ 700 (GE Medical Systems, Milwaukee, WI)	5 to 13 MHz	One operator obtained all of the image, and then four other radiologists evaluated all images	Open sugery (n = 30) or core-needle biopsy and followup (n = 61)
Chala et al. 2007[59]	B-mode 2D gray-scale	HDI 3000 or 5000 (Phillips Ultrasound, Bothell, WA) or Logiq 700 (GE medical Systems, Milwaukee, WI)	5 to 12 MHZ	One of three operators	Core-needle biopsy except 20 cases had FNA followed by 28 to 30 months of followup
Zhi et al. 2007[60]	B-mode 2D gray-scale	EUB-8500 (Hitachi Medical Corp., Tokyo, Japan)	7.5 to 13.0 MHZ	2 operators in consensus	Open surgical biopsy

Table C15. Ultrasound studies: details of methods (continued)

Study	US Method	US Device	US MHz	US Operators	Reference Standard
Cho et al. 2006[61]	B-mode 2D and 3D gray-scale	Voluson 530D (GE Kretz, Zipf, Austria)	5 to 10 MHz	One operator obtained all of the image, and then three other radiologists evaluated all images	Open surgery (n = 78) or core-needle biopsy and followup (n = 72)
Pinero et al. 2006[53]	Combination power Doppler and color Doppler using a contrast agent (Levovist [Schering AG, Berlin, Germany])	SSA-370 A Power Vision 6000 (Toshiba Corp.)	6 to 11 MHz	One radiologist	Open surgery
Ricci et al. 2006[16]	B-mode grayscale with and without contrast (with Sono Vue [Bracco, Italy]); also compared US to MRI	Esatune (Esaote, Genova, Italy)	5 to 10 MHz	Two radiologists in consensus	Open surgical biopsy
Forsberg et al. 2004[62]	B-mode 2D grayscale and power Doppler, with and without contrast (Levovist or Optison)	HDI 3000 (Philips Medical Systems, Bothell, WA), for 3D a LIS 6000A (Life Imaging Systems Inc., London, Ontario, Canada)	5 to 10 MHz	One of two radiologists	Open surgical biopsy
Meyberg-Solomayer et al. 2004[63]	B-mode 2D gray-scale	HDI 3000 (ATL, Zipf, Austria) or Voluson 730 (General Electric, Bothell, WA)	5 to 12 or 5 to 10 MHz	One operator, entire study	Core biopsy or lumpectomy
Ozdemir et al. 2004[64]	Power Doppler, with or without contrast (Levovist)	HDI 5000 (Phillips Medical Systems, Bothwell, WA)	5 to 12 MHZ	One radiologist	Open surgical biopsy, core needle biopsy, or patient followup for at least 2 years
Chen et al. 2003[65]	B-mode 2D gray scale	Aloka 650 (Aloka, Tokyo, Japan)	7.5 MHz	Two radiologists in consensus	Open surgical biopsy or excision
Kook and Kwag 2003[66]	B-mode US and power Doppler, with and without contrast (Levovist)	Logiq 700 (GE Medical Systems, Milwaukee, WI)	9 to 12 MHz	Two radiologists in consensus	Open surgical or core needle biopsy

Table C15. Ultrasound studies: details of methods (continued)

Study	US Method	US Device	US MHz	US Operators	Reference Standard
Marini et al. 2003[67]	B-mode 2D grayscale	AU530 (Esaote, Genoa, Italy)	10 to 13 MHz	Two radiologists in consensus	Core biopsy or at least three years followup
Caruso et al. 2002[68]	Color Doppler with and without contrast (Levovist)	ATL HDI 5000 (Philips-ATL Medical Systems, Bothell, WA)	5 to 10 MHz	NR	Open surgical biopsy
Koukouraki et al. 2001[69]	color Doppler	Accuson 128XP/10	7.5 MHz	NR	Open surgery
Malich et al. 2001[35]	Combination of B-mode, power Doppler, and color Doppler; also compared US to MRI	HDI 5000 (ATL, Bothwell, WA) or SONOLINE Versa Pro (Siemens, Solna, Sweden)	7.5 to 10 MHz	One of several operators	Histological examination
Milz et al. 2001[70]	Power Doppler	AU 4 Esaote (Biomedica, Milan, Italy)	4.7 MHz	One of two radiologists	Open surgical biopsy or fine needle (n = 2) aspiration
Reinikainen et al. 2001[71]	B-mode US and power Doppler, with and without contrast (Levovist)	Power Vision (Toshiba)	10 MHz	Two radiologists independently, then in consensus about disagreements	Open surgical biopsy
Moon et al. 2000[72]	Power Doppler, with and without contrast (Levovist)	HDI 3000 (Advanced Technology Laboratories, Bothell, WA)	5 to 10 MHz	Two radiologists in consensus	Open surgical biopsy
Blohmer et al. 1999[73]	B-mode 2D gray-scale and color Doppler	NR	NR	NR	Open surgical biopsy
Chao et al. 1999[74]	B-mode 2D gray-scale	Aloka SSD-2000 (Aloka, Tokyo, Japan)	7.5 MHz	One of three operators	Histological examination
Schroeder et al. 1999[75]	Power and color Doppler, with and without contrast (Levovist)	Elegra (Siemens AG, Berlin, Germany)	9.0 MHz	Two radiologists independently	Open surgery (n = 75), or 9 to 12 months of followup
Albrecht et al. 1998[76]	Power Doppler, with or without contrast (EchoGen)	Acuson 128 XP10 (Mountain View, CA)	7.0 MHz	Two radiologists independently	Histological examination, FNA (n = 3), or followup six months (n = 1)

Table C15. Ultrasound studies: details of methods (continued)

Study	US Method	US Device	US MHz	US Operators	Reference Standard
Wilkens et al. 1998[77]	B-mode 2D gray-scale and color Doppler	Advanced Technologies Laboratory (Bothell, WA)	10 MHz	One radiologist	Open surgical biopsy
Buadu et al. 1997[78]	Color Doppler	Toshiba SSA-260-A (Toshiba Ltd, Japan)	7.5 MHz	NR	Open surgical biopsy
Stavros et al. 1995[79]	B-mode 2D gray-scale	Diasonics Spectra (Milpitas, CA), Advanced Technology Laboratories (High Definition Imaging, Bothell, WA) or Acoustic Imaging Modell 5200 (Phoeniz, AZ)	7.5 to 10.0 MHz	One of five radiologists	Open surgery (44%) or core-needle biopsy (55%)
Ciatto et al. 1994[80]	B-mode 2D gray scale	Esaote (Esaote Ansaldo, Milano, Italy)	10 MHz	One radiologist	Open surgical biopsy (n = 320) or 1 to 2 years of followup (n = 1,759)
Perre et al. 1994[81]	B-mode 2D gray-scale	Toshiba SSA-270-A (Toshiba Ltd, Japan)	7.5 MHz	One operator, entire study	Open surgical biopsy except cysts

2D Two dimensional
FNA Fine needle aspiration
MHz mega Hertz

Table C16. Ultrasound studies: information for meta-regressions

Study	Consecutive or All Enrollment (1 = Yes)	Prospective Design (1 = Yes)	Probably Affected by Spectrum Bias[a] (1 = Yes)	Accounted for Interreader Differences (1 = Yes)	Readers Blinded to Clinical Information (1 = Yes)	All Diagnoses Confirmed by Histopathology (1 = Yes)	Funded by (1 = Declared No Financial Conflicts of Interest)	Geographic Region[b]	Proportion Malignant
Gokalp et al. 2009[55]	0	1	0	0	0	0	0	2	0.415
Vassiou et al. 2009[8]	0	1	0	0	0	1	0	2	0.68
Liu et al. 2008[56]	1	0	0	1	1	1	1	0	0.413
Vade et al. 2008[57]	1	0	0	0	0	0	0	4	0%
Cha et al. 2007[58]	1	1	0	1	1	0	0	1	0.33
Chala et al. 2007[59]	1	0	1	0	1	0	0	5	0.227
Zhi et al. 2007[60]	1	0	0	1	0	1	0	0	0.294
Cho et al. 2006[61]	1	1	0	1	1	0	0	1	0.4
Pinero et al. 2006[53]	1	1	0	0	0	1	0	3	0.77
Ricci et al. 2006[16]	1	1	0	1	0	1	0	3	0.76
Forsberg et al. 2004[62]	0	0	1	0	0	1	0	4	0.29

Table C16. Ultrasound studies: information for meta-regressions (continued)

Study	Consecutive or All Enrollment (1 = Yes)	Prospective Design (1 = Yes)	Probably Affected by Spectrum Bias[a] (1 = Yes)	Accounted for Interreader Differences (1 = Yes)	Readers Blinded to Clinical Information (1 = Yes)	All Diagnoses Confirmed by Histopathology (1 = Yes)	Funded by (1 = Declared No Financial Conflicts of Interest)	Geographic Region[b]	Proportion Malignant
Meyberg-Solomayer et al. 2004[63]	0	1	0	0	0	0	0	3	0.645
Ozdemir et al. 2004[64]	0	1	0	0	0	0	0	2	0.405
Chen et al. 2003[65]	0	1	0	1	0	1	0	0	0.75
Kook and Kwag 2003[66]	0	1	0	1	1	0	0	1	0.47
Marini et al. 2003[67]	1	0	1	1	1	0	0	2	0.39
Caruso et al. 2002[68]	0	1	0	0	0	1	0	2	0.56
Koukouraki et al. 2001[69]	0	1	0	0	1	1	0	2	0.74
Malich et al. 2001[35]	1	0	0	0	0	0	0	3	0.62
Milz et al. 2001[70]	0	1	0	0	0	1	0	3	0.47
Reinikainen et al. 2001[71]	0	1	0	1	1	1	1	3	0.523
Moon et al. 2000[72]	1	1	0	1	0	1	1	1	0.44

Table C16. Ultrasound studies: information for meta-regressions (continued)

Study	Consecutive or All Enrollment (1 = Yes)	Prospective Design (1 = Yes)	Probably Affected by Spectrum Bias[a] (1 = Yes)	Accounted for Interreader Differences (1 = Yes)	Readers Blinded to Clinical Information (1 = Yes)	All Diagnoses Confirmed by Histopathology (1 = Yes)	Funded by (1 = Declared No Financial Conflicts of Interest)	Geographic Region[b]	Proportion Malignant
Blohmer et al. 1999[73]	0	1	0	0	0	1	0	3	0.495
Chao et al. 1999[74]	0	1	0	0	0	0	0	1	0.24
Schroeder et al. 1999[75]	1	1	0	1	1	0	0	3	0.655
Albrecht et al. 1998[76]	0	1	0	1	1	0	0	3	0.55
Wilkens et al. 1998[77]	0	0	0	0	0	1	0	4	0.4
Buadu et al. 1997[78]	1	0	0	0	0	1	0	1	0.724
Stavros et al. 1995[79]	0	1	0	0	0	0	0	4	0.164
Ciatto et al. 1994[80]	1	1	1	0	0	0	0	2	0.125
Perre et al. 1994[81]	0	1	0	0	1	0	0	3	0.435

[a] Spectrum bias defined as median/mean age greater than 50 and/or % lesions malignant less than 10% or greater than 40%
[b] China = 0; Asia = 1; Turkey, Greece, Italy = 2; Europe and United Kingdom = 3; North America = 4; South America = 5

Data Analysis

MRI

Table C17. MRI accuracy data

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Akita et al. 2009[1]	All	11	0	2	37	84.6% (57.6% to 95.4%)	100.0% (90.3% to 99.9%)
Baltzer et al. 2009[2]	Readers	202	51	59	139	77.4% (71.9% to 82.0%)	73.2% (66.4% to 78.9%)
	CAD	220	51	59	139	78.9% (73.7% to 83.2%)	73.2% (66.4% to 78.9%)
Hara et al. 2009[3]	All	26	6	3	58	89.7% (73.4% to 96.3%)	90.6% (80.9% to 95.5%)
Kim et al. 2009[4]	All	48	82	2	117	96.0% (86.4% to 98.8%)	58.8% (51.8% to 65.4%)
Lo et al. 2009[5]	All	19	1	1	10	95.0% (76.1% to 98.9%)	90.9% (61.9% to 98.1%)
Imbracio et al. 2008[6]	All	44	2	1	8	97.8% (88.3% to 99.5%)	80.0% (48.9% to 94.0%)
Pediconi et al. 2008[7]	Gadopentetic acid	24	8	8	10	75.0% (57.8% to 86.6%)	55.6% (33.8% to 75.3%)
	Gadobenic acid	31	5	1	13	96.9% (84.0% to 99.3%)	72.2% (49.1% to 87.3%)
Vassiou et al. 2009[8]	All	52	14	1	11	98.1% (89.9% to 99.6%)	44.0% (26.7% to 62.9%)
Brem et al. 2007[9]	All	9	18	0	6	100.0% (69.5% to 99.7%)	25.0% (12.2% to 45.0%)
Cilotti et al. 2007[10]	Microcalcifications	19	7	7	22	73.1% (53.8% to 86.2%)	75.9% (57.8% to 87.6%)
Pediconi et al. 2007[11]	All	211	15	0	4	100.0% (98.2% to 100.0%)	21.1% (8.7% to 43.5%)

Table C17. MRI accuracy data (continued)

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Zhu et al. 2007[12]	Microcalcifications	23	2	3	24	88.5% (70.8% to 95.8%)	92.3% (75.6% to 97.7%)
Bazzocchi et al. 2006[13]	Microcalcifications	65	12	10	25	86.7% (77.1% to 92.5%)	67.6% (51.4% to 80.3%)
Gokalp and Topal 2006[14]	BIRADS 3	1	2	0	53	100.0% (20.8% to 99.2%)	96.4% (87.5% to 98.9%)
Kneeshaw et al. 2006[15]	Microcalcifications	15	7	5	61	75.0% (53.0% to 88.6%)	89.7% (80.2% to 94.8%)
Ricci et al. 2006[16]	All	38	2	0	11	100.0% (90.6% to 99.9%)	84.6% (57.6% to 95.4%)
Pediconi et al. 2005[17]	All	49	1	5	13	90.7% (80.0% to 95.9%)	92.9% (68.2% to 98.5%)
Pediconi et al. 2005[18]	Gadopentetic acid	29	0	9	8	76.3% (60.7% to 86.9%)	100.0% (67.0% to 99.7%)
	Gadobenic acid	36	1	2	7	94.7% (82.5% to 98.4%)	87.5% (52.6% to 97.4%)
Wiener et al. 2005[19]	All	68	14	1	36	98.6% (92.1% to 99.7%)	72.0% (58.3% to 82.5%)
Bluemke et al. 2004[20]	All	356	136	48	281	88.1% (84.6% to 90.9%)	67.4% (62.7% to 71.7%)
	Premenopausal	123	68	21	134	85.4% (78.7% to 90.2%)	66.3% (59.6% to 72.5%)
	Postmenopausal	222	72	38	142	85.4% (80.6% to 89.1%)	66.4% (59.8% to 72.3%)
	Palpable	194	51	19	81	91.1% (86.5% to 94.2%)	61.4% (52.8% to 69.2%)
	Nonpalpable	162	85	29	198	84.8% (79.0% to 89.2%)	70.0% (64.4% to 75.0%)

Table C17. MRI accuracy data (continued)

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bluemke et al. 2004[20] (continued)	Microcalcifications	106	42	21	131	83.5% (76.0% to 88.9%)	75.7% (68.8% to 81.5%)
	No microcalcifications	232	84	25	129	90.3% (86.0% to 93.3%)	60.6% (53.9% to 66.9%)
	Mostly fat	49	25	5	27	90.7% (80.0% to 95.9%)	51.9% (38.7% to 64.9%)
	Dense	32	17	5	25	86.5% (71.9% to 94.0%)	59.5% (44.5% to 72.9%)
Huang et al. 2004[21]	All	18	12	0	20	100.0% (82.0% to 99.8%)	62.5% (45.2% to 77.0%)
Bone et al. 2003[22]	All	74	17	5	15	93.7% (85.9% to 97.2%)	46.9% (30.9% to 63.5%)
Daldrup-Link et al. 2003[23]	All	7	5	2	5	77.8% (45.1% to 93.3%)	50.0% (23.8% to 76.2%)
Heinisch et al. 2003[24]	All	23	2	4	11	85.2% (67.4% to 93.9%)	84.6% (57.6% to 95.4%)
Walter et al. 2003[25]	All	17	2	6	17	73.9% (53.4% to 87.3%)	89.5% (68.4% to 96.8%)
Guo et al. 2002[26]	All	28	2	2	15	93.3% (78.5% to 98.0%)	88.2% (65.4% to 96.5%)
Kelcz et al. 2002[27]	All	27	6	4	31	87.1% (71.0% to 94.7%)	83.8% (68.8% to 92.2%)
Schedel et al. 2002[28]	All	32	8	2	15	94.1% (80.7% to 98.2%)	65.2% (44.9% to 81.1%)
Trecate et al. 2002[29]	Microcalcifications	15	5	0	8	100.0% (79.2% to 99.8%)	61.5% (35.5% to 82.1%)
Wiberg et al. 2002[30]	All	77	17	5	15	93.9% (86.4% to 97.3%)	46.9% (30.9% to 63.5%)
	Dense breasts	17	9	1	5	94.4% (73.9% to 98.8%)	35.7% (16.5% to 61.2%)

Table C17. MRI accuracy data (continued)

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brix et al. 2001[31]	All	8	1	2	2	80.0% (48.9% to 94.0%)	66.7% (21.0% to 93.3%)
Cecil et al. 2001[32]	All	22	2	1	13	95.7% (78.7% to 99.0%)	86.7% (61.9% to 96.0%)
Furman-Haran et al. 2001[33]	All	21	2	4	21	84.0% (65.2% to 93.4%)	91.3% (73.0% to 97.4%)
Imbriaco et al. 2001[34]	All	24	6	1	22	96.0% (80.2% to 99.1%)	78.6% (60.4% to 89.6%)
	Younger than 50 yrs	11	3	0	9	100.0% (73.6% to 99.7%)	75.0% (46.7% to 90.8%)
	50 and older yrs	13	3	1	9	92.9% (68.2% to 98.5%)	75.0% (46.7% to 90.8%)
	Lesion 10 mm or larger	19	3	1	13	95.0% (76.1% to 98.9%)	81.3% (56.8% to 93.2%)
	Lesion smaller than 10 mm	5	3	0	5	100.0% (56.0% to 99.6%)	62.5% (30.6% to 86.0%)
Malich et al. 2001[35]	All	53	7	1	29	98.1% (90.1% to 99.6%)	80.6% (64.9% to 90.1%)
Nakahara et al. 2001[36]	Microcalcifications	19	3	1	17	95.0% (76.1% to 98.9%)	85.0% (63.8% to 94.6%)
Torheim et al. 2001[37]	All	57	7	13	50	81.4% (70.7% to 88.7%)	87.7% (76.7% to 93.8%)
Wedegartner et al. 2001[38]	All	37	4	7	14	84.1% (70.5% to 92.0%)	77.8% (54.7% to 90.8%)
Yeung et al. 2001[39]	All	22	1	2	5	91.7% (73.9% to 97.5%)	83.3% (43.5% to 96.5%)
Kvistad et al. 2000[40]	All	63	12	9	46	87.5% (77.8% to 93.2%)	79.3% (67.2% to 87.7%)

Table C17. MRI accuracy data (continued)

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Van Goethem et al. 2000[41]	All	19	8	1	29	95.0% (76.1% to 98.9%)	78.4% (62.7% to 88.5%)
	Microcalcifications	6	2	1	8	85.7% (48.4% to 97.0%)	80.0% (48.9% to 94.0%)

95% CI 95% confidence interval
FN False negative
FP False positive
TN True negative
TP True positive

META-ANALYTIC INTEGRATION OF DIAGNOSTIC TEST ACCURACY STUDIES

Accuracy of MRI in General

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Number of studies = 41

Reference-positive Subjects = 2,209

Reference-negative Subjects = 1,843

Pretest Prob of Disease = 0.545

Between-study variance (varlogitSEN) = 0.831 (95% CI: 0.402 to 1.718)

Between-study variance (varlogitSPE) = 0.901 (95% CI: 0.493 to 1.649)

Correlation (Mixed Model) = -0.607

ROC Area, AUROC = 0.93 (95% CI: 0.90 to 0.95)

Heterogeneity (Chi-square): LRT_Q = 128.856, df = 2.00, LRT_p = 0.000

Inconsistency (I-square): LRT_I^2 = 98.4% (95% CI: 97.6 to 99.3%)

Summary Parameter Estimates (95% CI)

Sensitivity: 91.7% (88.5 to 94.1%)

Specificity: 77.5% (71.0 to 82.9%)

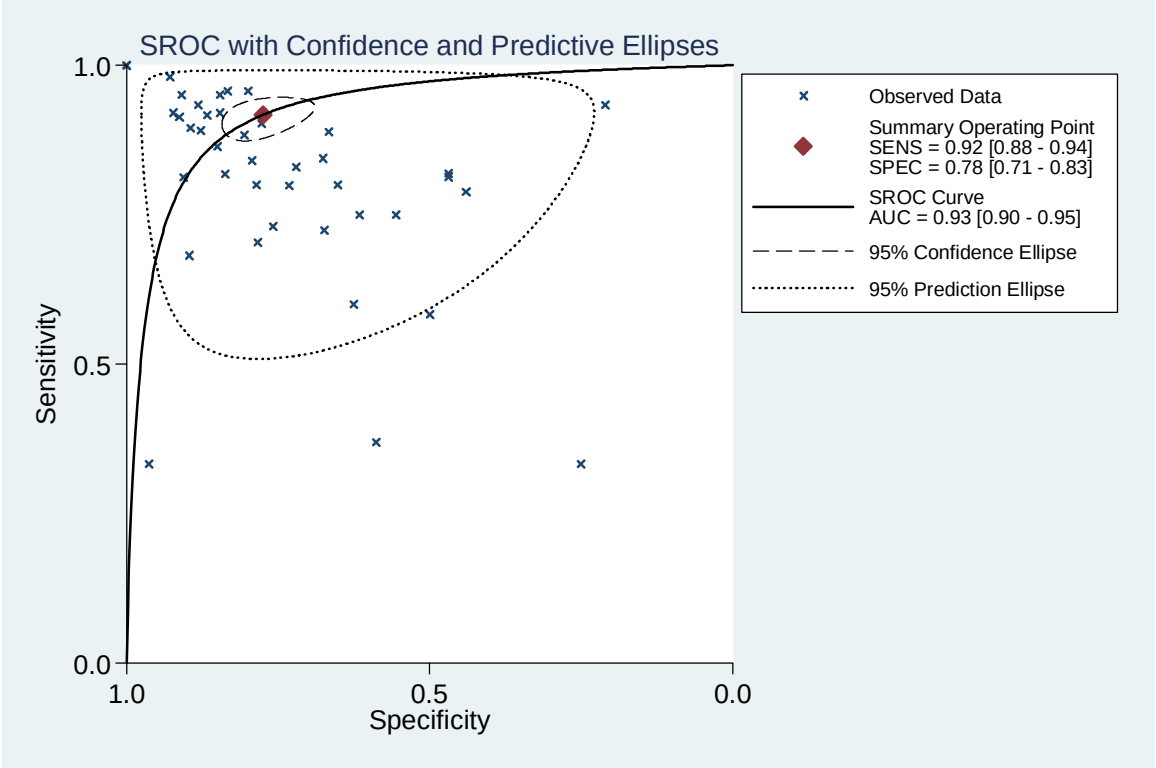
Positive Likelihood Ratio: 4.08 (3.10 to 5.30)

Negative Likelihood Ratio: 0.11 (0.079 to 0.15)

Diagnostic Score: 3.638 (3.253 to 4.023)

Diagnostic Odds Ratio: 38.008 (25.864 to 55.856)

Figure C1. Summary ROC of MRI accuracy: all data



Exploration of Heterogeneity: Accuracy of MRI

Meta-regressions of All Data

Bivariate Model

Variable	p-Value
Prevalence of disease	0.02
Readers blinded to clinical information	0.03
Geographical location	0.08
Enrolled consecutive or all patients	0.13
Prospective design	0.18
All diagnoses verified by histopathology	0.28
Funding source	0.36
Multi-centered	0.52
Accounted for inter-reader differences	0.56
Spectrum bias	0.64
Magnet strength	0.87
Contrast agent	0.97

Statistically Significant Models

Parameter	Prevalence of Disease	Readers Blinded to Clinical Information
I^2 (95% CI)	74.4% (43.5 to 100.0%)	70.2% (33.7 to 100.0%)
Heterogeneity (LRTChi)	7.80	6.72
Sensitivity:	96%	87%
95% CI	91 to 98%	80 to 92%
Coefficient	3.23	1.93
z	2.69	-2.04
p of z	0.01	0.04
Specificity:	56%	75%
95% CI	36 to 73%	63 to 85%
Coefficient	0.23	1.12
z	-3.55	-0.39
p of z	0.00	0.70

Subgroup Analyses of Statistically Significant Models

Accuracy of Studies with Readers Blinded to Clinical Information vs. Not

META-ANALYTIC INTEGRATION OF DIAGNOSTIC TEST ACCURACY STUDIES

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Parameter	Blinded	Not Blinded (or Not Reported)
Number of studies	13	28
Number of patients	1,289	2,763
Prevalence of disease	63.4%	50.4%
I^2	89.9%	98.1%
Sensitivity (95% CI)	86.8% (82.1 to 90.4%)	93.9% (90.0 to 96.4%)
Specificity (95% CI)	74.7% (64.4 to 82.9%)	78.0% (70.0 to 84.5%)
AUROC (95% CI)	0.89 (0.86 to 0.92)	0.94 (0.91 to 0.96)

Figure C2. Graph of MRI sensitivity and specificity relative to prevalence of disease

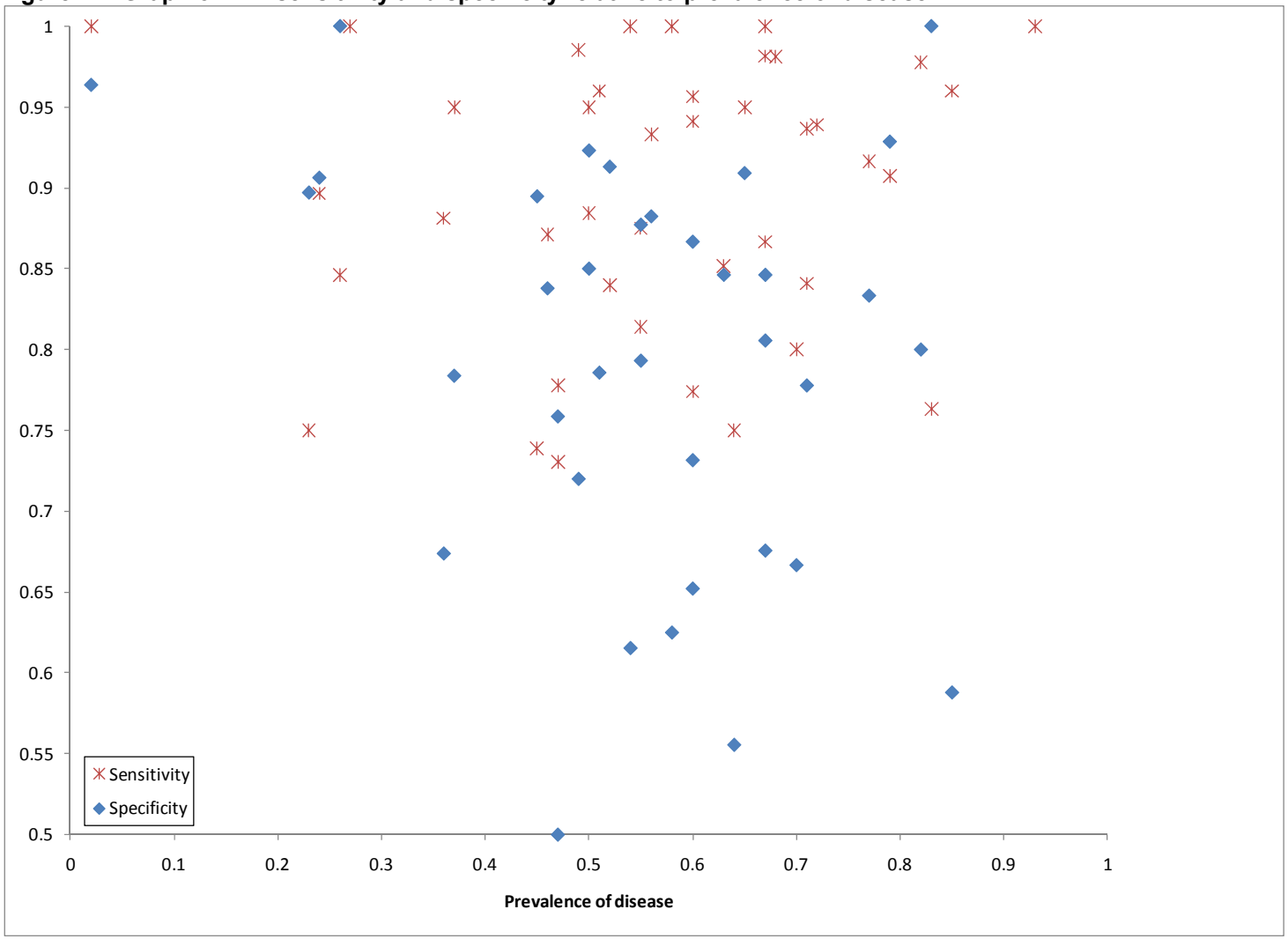
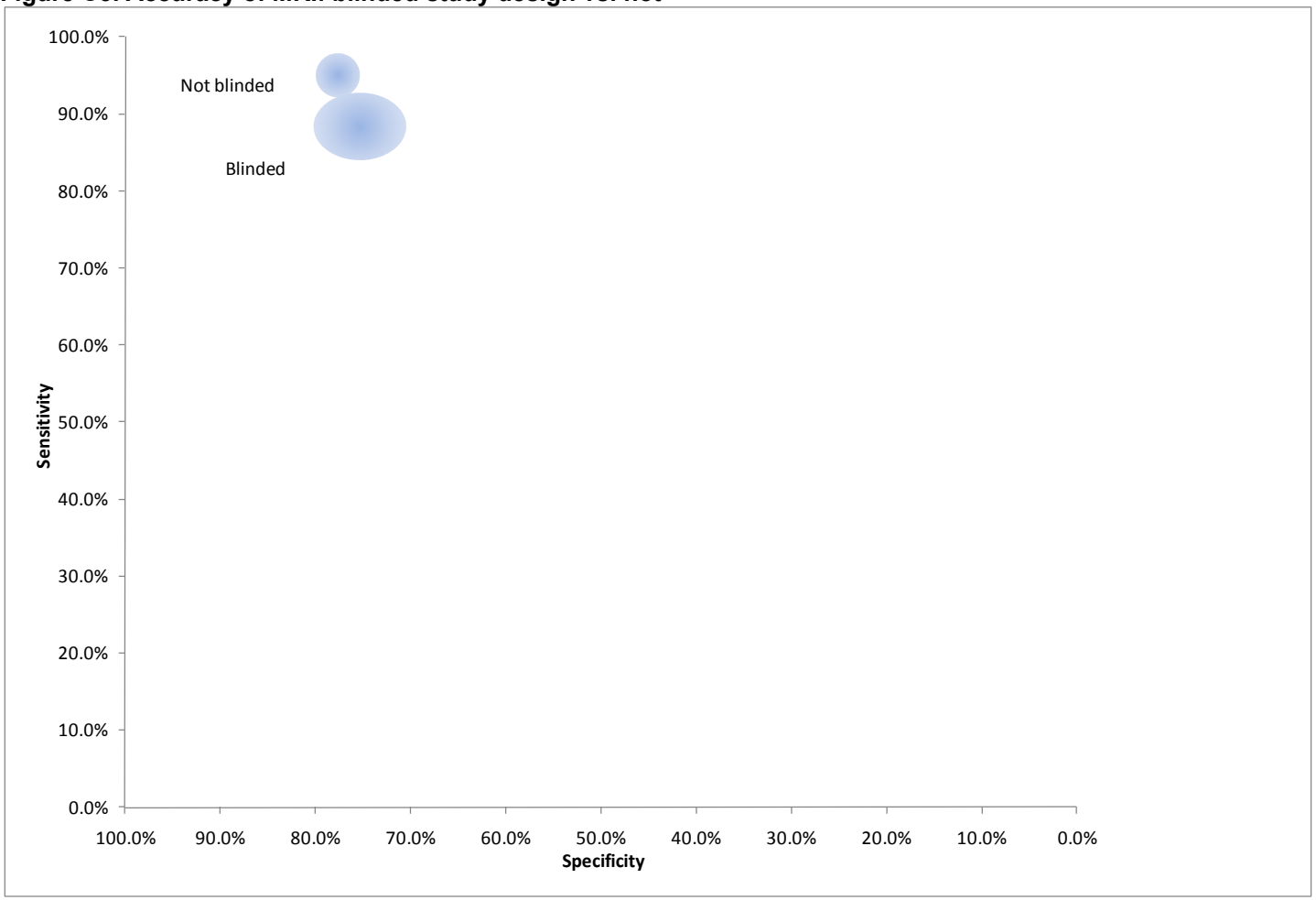


Figure C3. Accuracy of MRI: blinded study design vs. not



Accuracy of Studies with Disease Prevalence Greater or Less than 60%

META-ANALYTIC INTEGRATION OF DIAGNOSTIC TEST ACCURACY STUDIES

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Parameter	Prevalence >60%	Prevalence 60% or less[a]
Number of studies	17	24
Number of patients	1,430	2,622
Prevalence of disease	65.5%	44.5%
I^2	96.0%	64.1 sensitivity; 82.3 specificity
Sensitivity (95% CI)	93.8% (89.1% to 96.6%)	86.3% (84.3% to 88.2%)
Specificity (95% CI)	70.3% (58.1% to 80.1%)	76.1% (73.7% to 78.3%)
AUROC (95% CI)	0.91 (0.88 to 0.93)	0.91

[a] Could not fit a bivariate model; individual parameters estimated using Meta-Disc

Subgroup Analyses of MRI Data

Methods Factors

CAD assistance in interpreting images

Table C18. Accuracy of MRI: CAD

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Baltzer et al. 2009[2]	Readers alone	202	51	59	139	77.4% (71.9% to 82.0%)	73.2% (66.4% to 78.9%)
	CAD assistance	220	51	59	139	78.9% (73.7% to 83.2%)	73.2% (66.4% to 78.9%)

FN False negative
FP False positive
TN True negative
TP True positive

Contrast agent

Table C19. MRI accuracy: studies directly comparing different contrast agents

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pediconi et al. 2008[7]	Gadopentetic acid	24	8	8	10	75.0% (57.8% to 86.6%)	55.6% (33.8% to 75.3%)
	Gadobenic acid	31	5	1	13	96.9% (84.0% to 99.3%)	72.2% (49.1% to 87.3%)
Pediconi et al. 2005[18]	Gadopentetic acid	29	0	9	8	76.3% (60.7% to 86.9%)	100.0% (67.0% to 99.7%)
	Gadobenic acid	36	1	2	7	94.7% (82.5% to 98.4%)	87.5% (52.6% to 97.4%)

FN False negative
FP False positive
TN True negative
TP True positive

Accuracy of Studies: Subgroup analysis comparison of Contrast Agents

META-ANALYTIC INTEGRATION OF DIAGNOSTIC TEST ACCURACY STUDIES

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Parameter	Gadopentetic Acid	Gadodiamide	Gadobenic Acid	Gadoteridol[a]
Number of studies	28	8	5	2
Number of patients	2,918	618	445	167
Prevalence of disease	52.1%	46.0%	83.8%	60.5%
I^2	96.7%	76.2%	92.8%	57.6% (sensitivity) 0.0% (specificity)
Sensitivity (95% CI)	91.8% (88.0 to 94.4%)	86.5% (81.4 to 90.4%)	98.3% (90.9 to 99.7%)	83.2% (74.4 to 89.9%)
Specificity (95% CI)	74.4% (66.0 to 80.9%)	87.8% (79.2 to 93.1%)	75.5% (44.9 to 92.1%)	71.2% (58.7 to 81.7%)
AUROC (95% CI)	0.92 (0.89 to 0.94)	0.91 (0.89 to 0.94)	0.97 (0.95 to 0.98)	NA with only 2 studies

[a] Could not fit a bivariate model; individual parameters estimated using Meta-Disc

Patient Factors

Table C20. Accuracy of MRI: miscellaneous patient factors

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bluemke et al. 2004[20]	All	356	136	48	281	88.1% (84.6% to 90.9%)	67.4% (62.7% to 71.7%)
	Premenopausal	123	68	21	134	85.4% (78.7% to 90.2%)	66.3% (59.6% to 72.5%)
	Postmenopausal	222	72	38	142	85.4% (80.6% to 89.1%)	66.4% (59.8% to 72.3%)
Imbriaco et al. 2001[34]	All	24	6	1	22	96.0% (80.2% to 99.1%)	78.6% (60.4% to 89.6%)
	Younger than 50 years	11	3	0	9	100.0% (73.6% to 99.7%)	75.0% (46.7% to 90.8%)
	50 and older years	13	3	1	9	92.9% (68.2% to 98.5%)	75.0% (46.7% to 90.8%)

FN False negative
FP False positive
TN True negative
TP True positive

Lesion Factors

Microcalcifications on mammography

Accuracy of Studies: Subgroup analysis comparison of studies that enrolled patients with microcalcifications to all studies

META-ANALYTIC INTEGRATION OF DIAGNOSTIC TEST ACCURACY STUDIES

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Parameter	All	Microcalcifications
Number of studies	41	8
Number of patients	4,052	692
Prevalence of disease	54.5%	45.7%
I^2	98.4%	3.86%
Sensitivity (95% CI)	91.7% (88.5% to 94.1%)	84.0% (79.5% to 88.3%)
Specificity (95% CI)	77.5% (71.0% to 82.9%)	79.4% (71.5% to 85.6%)
AUROC (95% CI)	0.93 (0.90 to 0.95)	0.88 (0.85 to 0.91)

Figure C4. Summary ROC MRI: patients with microcalcifications on mammography

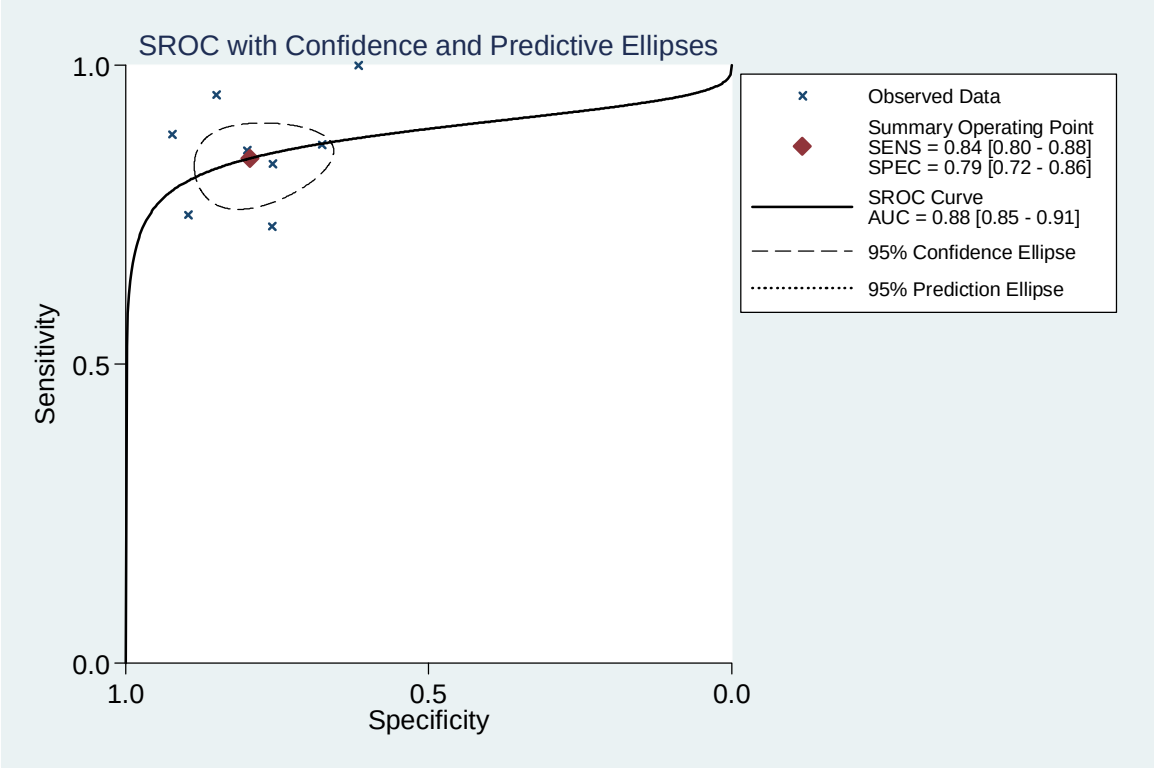


Table C21. Accuracy of MRI for microcalcifications: studies that directly compared microcalcifications to other

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bluemke et al. 2004[20]	No microcalcifications	232	84	25	129	90.3% (86.0% to 93.3%)	60.6% (53.9% to 66.9%)
	Microcalcifications	106	42	21	131	83.5% (76.0% to 88.9%)	75.7% (68.8% to 81.5%)
Van Goethem et al. 2000[41]	All	19	8	1	29	95.0% (76.1% to 98.9%)	78.4% (62.7% to 88.5%)
	Microcalcifications	6	2	1	8	85.7% (48.4% to 97.0%)	80.0% (48.9% to 94.0%)

FN False negative
FP False positive
TN True negative
TP True positive

Table C22. Accuracy of MRI: miscellanous lesion factors

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gokalp and Topal 2006[14]	BIRADS 3	1	2	0	53	100.0% (20.8% to 99.2%)	96.4% (87.5% to 98.9%)
Bluemke et al. 2004[20]	All	356	136	48	281	88.1% (84.6% to 90.9%)	67.4% (62.7% to 71.7%)
	Palpable	194	51	19	81	91.1% (86.5% to 94.2%)	61.4% (52.8% to 69.2%)
	Nonpalpable	162	85	29	198	84.8% (79.0% to 89.2%)	70.0% (64.4% to 75.0%)
	Mostly fat	49	25	5	27	90.7% (80.0% to 95.9%)	51.9% (38.7% to 64.9%)
	Dense	32	17	5	25	86.5% (71.9% to 94.0%)	59.5% (44.5% to 72.9%)
Wiberg et al. 2002[30]	All	77	17	5	15	93.9% (86.4% to 97.3%)	46.9% (30.9% to 63.5%)
	Dense breasts	17	9	1	5	94.4% (73.9% to 98.8%)	35.7% (16.5% to 61.2%)
Imbriaco et al. 2001[34]	All	24	6	1	22	96.0% (80.2% to 99.1%)	78.6% (60.4% to 89.6%)
	Lesion 10 mm or larger	19	3	1	13	95.0% (76.1% to 98.9%)	81.3% (56.8% to 93.2%)
	Lesion smaller than 10 mm	5	3	0	5	100.0% (56.0% to 99.6%)	62.5% (30.6% to 86.0%)

FN False negative
FP False positive
TN True negative
TP True positive

PET

Table C23. PET accuracy data

Study	Position	Patient Subgroup	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kaida et al. 2008[42]	Supine	All	81	12	17	12	82.7% (73.7% to 89.6%)	50.0% (29.1% to 70.9%)
	Prone	All	109	4	5	4	95.6% (90% to 98.6%)	50.0% (15.7% to 84.3%)
Buchmann et al. 2007[43]	Prone	All	25	0	3	1	89.3% (71.8% to 97.7%)	100.0% (02.5% to 100.0%)
Hienisch et al. 2003[24]	Prone	All	17	4	8	11	68.0% (46.5% to 85.1%)	73.3% (44.9% to 92.2%)
Walter et al. 2003[25]	Prone	All	12	2	7	21	63.2% (38.4% to 83.7%)	91.3% (72.0% to 98.9%)
Brix et al. 2001[31]	Prone	All	8	2	1	2	88.9% (51.8% to 99.7%)	50.0% (06.8% to 93.2%)
Schirrmeister et al. 2001[44]	Prone	All	83	7	6	21	93.3% (85.9% to 97.5%)	75.0% (55.1% to 89.3%)
Yutani et al. 2000[45]	Supine	All	30	0	8	2	78.9 (62.7% to 90.4%)	100.0% (15.8% to 100.0%)
		BIRADS 5	26	0	2	2	93% (76.5% to 99.1%)	100.0% (15.7% to 84.3%)
		Lesion 1.5 cm or larger	27	0	1	1	79.4% (62.1% to 91.3%)	100.0% (02.5% to 100.0%)
		Palpable lesion	29	0	7	1	80.6% (64.0% to 91.8%)	100.0% (02.5% to 100.0%)
		Younger than 65	25	0	7	2	78.1% (60.0% to 90.7%)	100.0% (15.8% to 100.0%)

FN False negative
FP False positive
TN True negative
TP True positive

Table C24. PET/CT accuracy data

Study	Time of Scan	Patient Subgroup	True Positive	False Positive	False Negative	True Negative	Sensitivity (95% CI)	Specificity (95% CI)
Imbriaco et al. 2007[6]	Early	All	22	0	14	8	61.1% (43.5% to 76.9%)	100% (63.1% to 100%)
	Late	All	29	0	7	8	80.6% (64.0% to 91.8%)	100% (63.1% to 100%)
	Early	Lesions >10 mm	NR	NR	NR	NR	74.1% (53.7% to 88.9%) Reported by authors	100.0% (63.1% to 100.0%) Reported by authors
	Late	Lesions >10 mm	NR	NR	NR	NR	87.1% (70.2% to 96.4%) Reported by authors	100.0% (39.8% to 100.0%) Reported by authors
	Early	Lesions <10 mm	NR	NR	NR	NR	27.3% (06.0% to 61.0%) Reported by authors	100.0% (66.4% to 100.0%) Reported by authors
	Late	Lesions <10 mm	NR	NR	NR	NR	60.0% (32.3% to 83.7%) Reported by authors	100.0% (47.8% to 100.0%) Reported by authors

FN False negative
FP False positive
TN True negative
TP True positive

META-ANALYTIC INTEGRATION OF DIAGNOSTIC TEST ACCURACY STUDIES

Accuracy of PET

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Number of studies = 7

Reference-positive Subjects = 306

Reference-negative Subjects = 97

Pretest Prob of Disease = 0.759

Between-study variance (varlogitSEN) = 0.308 (95% CI: 0.051-1.868)

Between-study variance (varlogitSPE) = 0.393 (95% CI: 0.043-3.623)

Correlation (Mixed Model) = -0.456

ROC Area, AUROC = 0.86 (95% CI: 0.82 to 0.89)

Heterogeneity (Chi-square): LRT_Q = 5.623, df = 2.00, LRT_p = 0.030

Inconsistency (I-square): LRT_I^2 = 64.4% (95% CI: 19.99 to 100.00%)

Summary Parameter Estimates (95% CI)

Sensitivity: 82.6% (73.5 to 89.1%)

Specificity: 73.9% (57.5 to 85.5%)

Positive Likelihood Ratio: 3.16 (1.86 to 5.38)

Negative Likelihood Ratio: 0.235 (0.15 to 0.37)

Diagnostic Score: 2.599 (1.794 to 3.404)

Diagnostic Odds Ratio: 13.449 (6.011 to 30.090)

Figure C5. Summary ROC of PET

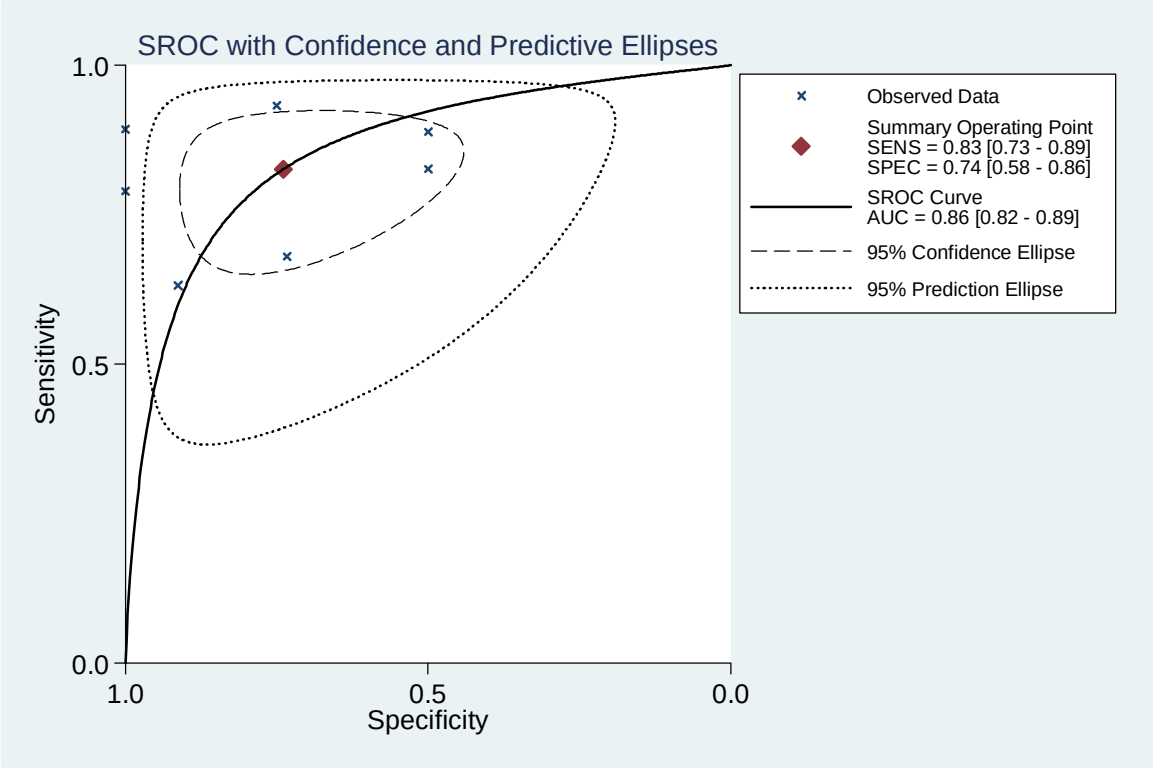


Table C25. PET studies: results of meta-regression

Variable	p-Value
Patient postion	0.52
Palpable lesions only	0.25
Readers blinded to clinical information	0.05
All diagnoses verified by histopathology	0.08

Scintimammography

Table C26. Accuracy of scintimammography

Study	Patient Subgroup	True Positive	False Negative	False Positive	True Negative	Sensitivity (95% CI)	Specificity (95% CI)
Brem et al. 2007[9]	All patients	8	1	7	17	88.9% (51.8 to 99.7)	70.8% (48.9 to 87.4)
Grosso et al. 2009[46]	Nonpalpable lesions	25	7	44	207	78.1% (60.0 to 90.7)	82.5% (77.2 to 87.0)
Habib et al. 2009[47]	Palpable lesions	14	1	2	5	93.3% (68.1 to 99.8)	71.4% (29.0 to 96.3)
Kim et al. 2009[4]	All patients	169	34	10	26	83.3% (77.4 to 88.1)	72.2% (54.8 to 85.8)
Wang et al. 2008[49]	Palpable lesions	34	3	12	6	91.9% (78.1 to 98.3)	33.3% (13.3 to 59.0)
Kim et al. 2008[48]	All patients	30	19	5	21	61.2% (46.2 to 74.8)	80.8% (60.6 to 93.4)
Gommans et al. 2007[50]	Non-palpable lesions	37	8	4	52	82.2% (67.9 to 92.0)	92.9% (82.7 to 98.0)
Kim et al. 2007[51]	All patients	57	9	0	12	86.4% (75.7 to 93.6)	100% (75.3 to 100.0)
Schillaci et al. 2007[52]	All patients	27	10	1	15	73.0% (55.9 to 86.2)	93.8% (69.8 to 99.8)
Pinero et al. 2006[53]	All patients	63	5	10	10	92.6% (83.7 to 97.6)	50.0% (27.2 to 72.8)
Mathieu et al. 2005[54]	All patients	19	1	5	12	95.0% (75.1 to 99.9)	70.6% (44.0 to 89.7)

FN False negative
FP False positive
TN True negative
TP True positive

META-ANALYTIC INTEGRATION OF DIAGNOSTIC TEST ACCURACY STUDIES

Planar Scintimammography

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Number of studies = 9

Reference-positive Units = 552

Reference-negative Units = 442

Pretest Prob of Disease = 0.56

Between-study variance in sensitivity (ICC_SEN) = 0.09 (95% CI: 0.00-0.21)

Between-study variance in sensitivity (MED_SEN) = 0.63 (95% CI: 0.56-0.75)

Between-study variance in specificity (ICC_SPE) = 0.23 (95% CI: 0.00-0.46)

Between-study variance in specificity (MED_SPE) = 0.72 (95% CI: 0.62-0.86)

Correlation (Mixed Model) = -0.76

ROC Area, AUROC = 0.88 (95% CI: 0.85 to 0.91)

Heterogeneity (Chi-square): LRT_Q = 27.288, df = 2.00, LRT_p = 0.000

Inconsistency (I-square): 93.0 % (95% CI: 86.0% to 99.0%)

Summary Parameter Estimates (95% CI)

Sensitivity: 84.0% (76.0% to 89.0%)

Specificity: 79.0% (63.0% to 89.0%)

Positive Likelihood Ratio: 3.9 (2.2 to 6.8)

Negative Likelihood Ratio: 0.21 (0.15 to 0.29)

Diagnostic Odds Ratio: 19 (10 to 35)

Figure C6. Summary ROC of scintimammography

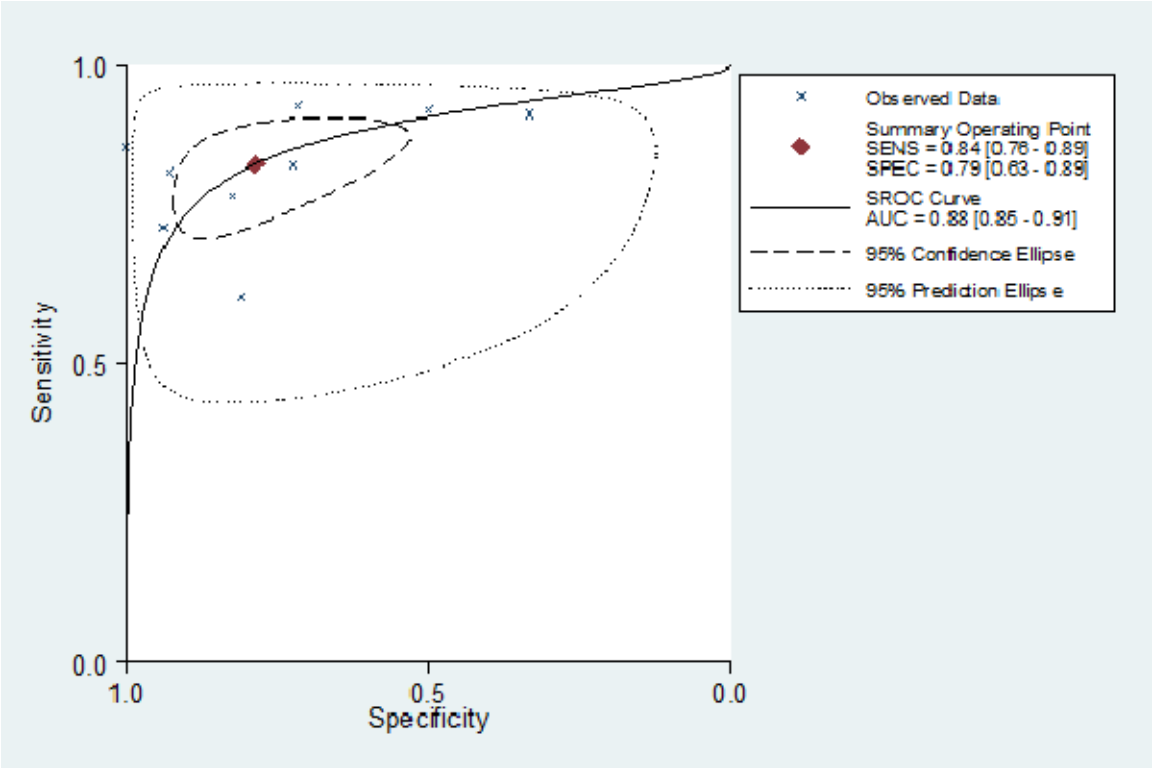


Table C27. Scintimammography studies: results of meta-regression

Variable	p-Value
Consecutive or all enrollment	0.11
All diagnoses verified by histopathology	0.24
Readers blinded to clinical information	0.93

Ultrasound

Ultrasound B-mode 2D grayscale

21 studies, 8,199 lesions

Table C28. Ultrasound accuracy data: B-mode 2D grayscale

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gokalp et al. 2009[55]	All	39	23	0	32	100.0% (91.0% to 100.0%)	58.2% (44.1% to 71.3%)
Vassiou et al. 2009[8]	All	44	6	9	19	83.0% (70.7% to 90.7%)	76.0% (56.5% to 94.3%)
Liu et al. 2008[56]	All	41	15	2	46	95.3% (84.2% to 99.4%)	75.4% (62.7% to 85.5%)
Vade et al. 2008[57]	Palpable lesions	0	6	0	15	Not calculated	Not calculated
Cha et al. 2007[58]	All	29	23	1	38	96.7% (82.8% to 99.9%	62.3% (49.0% to 74.4%)
Chala et al. 2007[59]	All	51	96	1	81	98.1% (89.7% to 100.0%)	45.8% (38.3% to 53.4%)
Zhi et al. 2007[60]	All	62	56	25	153	71.3% (60.6% to 80.5%)	73.2% (66.7% to 79.1%)
Cho et al. 2006[61]	All	58	32	2	59	96.7% (88.5% to 99.6%)	64.8% (54.1% to 74.6%)
Ricci et al. 2006[16]	All	26	4	12	8	68.4% (51.3% to 82.5%)	66.7% (34.9% to 90.1%)
Forsberg et al. 2004[62]	All	10	5	14	24	41.7% (22.1% to 63.4%)	82.8% (64.2% to 94.2%)
Meyberg-Solomayer et al. 2004[63]	All	42	0	0	23	100.0% (91.6% to 100.0%)	100.0% (85.2% to 100.0%)
Chen et al. 2003[65]	Palpable lesions	22	5	2	3	91.7% (73.0% to 99.0%)	37.5% (8.5% to 75.5%)

Table C28. Ultrasound accuracy data: B-mode 2D grayscale (continued)

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kook and Kwag 2003[66]	2 cm or less	17	10	0	9	100.0% (80.5% to 100.0%)	47.4% (24.4% to 71.1%)
Marini et al. 2003[67]	Microcalcifications	81	96	13	48	86.2% (77.5% to 92.4%)	33.3% (25.7% to 41.7%)
Reinikainen et al. 2001[71]	All	34	28	0	3	100.0% (89.7% to 100.0%)	9.7% (2.0% to 25.8%)
Blohmer et al. 1999[73]	All	76	4	81	70	48.45 (40.4% to 56.5%)	94.6% (86.7% to 98.5%)
Chao et al. 1999[74]	All	639	797	103	1,554	86.1% (83.4% to 88.5%)	66.1% (64.1% to 68.0%)
Wilkens et al. 1998[77]	Palpable lesions	19	0	3	33	86.4% (65.1% to 97.1%)	100.0% (89.4% to 100.0%)
Stavros et al. 1995[79]	All	123	202	2	424	98.4% (94.3% to 99.8%)	67.7% (63.9% to 71.4%)
Ciatto et al. 1994[80]	All	176	42	84	1,777	76.7% (61.6% to 73.3%)	97.7% (96.%9 to 98.3%)
Perre et al. 1994[81]	Palpable lesions	168	4	4	211	97.7% (94.2% to 99.4%)	98.1% (95.3% to 99.5%)

FN False negative
FP False positive
TN True negative
TP True positive

META-ANALYTIC INTEGRATION OF DIAGNOSTIC TEST ACCURACY STUDIES

Ultrasound B-mode Grayscale 2D

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Number of studies = 21

Reference-positive Subjects = 2,115

Reference-negative Subjects = 6,084

Pretest Prob of Disease = 0.258

Between-study variance (varlogitSEN) = 2.662 (95% CI: 1.162 to 6.096)

Between-study variance (varlogitSPE) = 2.455 (95% CI: 1.200 to 5.022)

Correlation (Mixed Model) = -0.331

ROC Area, AUROC = 0.92 (95% CI: 0.90 to 0.94)

Heterogeneity (Chi-square): LRT_Q = 612.405, df = 2.00, LRT_p = 0.000

Inconsistency (I-square): 99.7 % (95% CI: 99.6% to 99.78%)

Summary Parameter Estimates (95% CI)

Sensitivity: 92.4% (84.6% to 96.4%)

Specificity: 75.8% (60.8% to 86.3%)

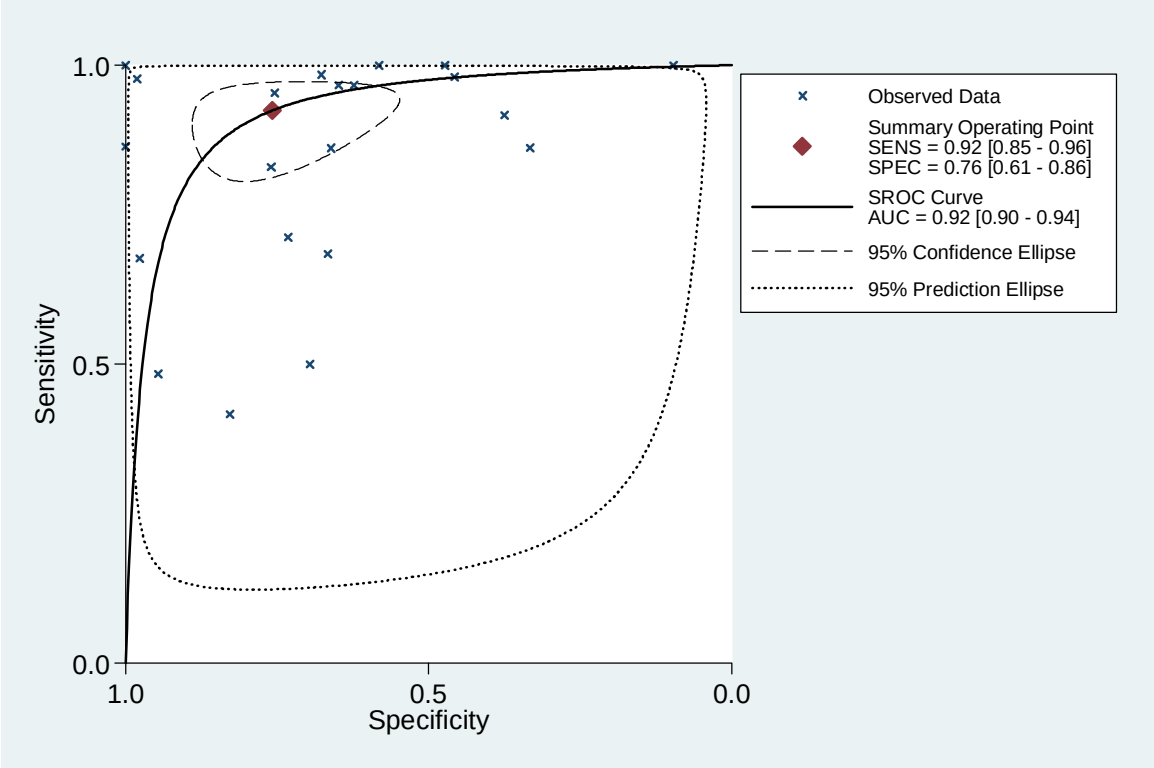
Positive Likelihood Ratio: 3.814 (2.272 to 0.964)

Negative Likelihood Ratio: 0.100 (0.049 to 0.203)

Diagnostic Score: 3.64 (2.738 to 6.403)

Diagnostic Odds Ratio: 38.083 (15.458 to 93.824)

Figure C7. Bivariate binomial mixed-effects model of ultrasound B-mode grayscale 2D: summary ROC



Exploration of Heterogeneity

Bivariate Model

Variable	p-Value
Accounted for inter-reader differences	0.01
Readers blinded to clinical information	0.03
All diagnoses verified by histopathology	0.06
Prospective design	0.18
Funding source	0.20
Enrolled consecutive or all patients	0.40
Geographical location	0.53
Type of lesion enrolled	0.85
Prevalence of disease	0.86

Statistically Significant Models

Parameter	Accounted for Inter-reader Differences	Readers Blinded to Clinical Information
I^2 (95% CI)	76.8% (49.44 to 100.0%)	72.1% (38.05% to 100.0%)
Heterogeneity (LRTChi)	8.63	7.16
Sensitivity:	94%	98%
95% CI	82% to 98%	92% to 99%
Coefficient	2.80	3.70
z	0.33	2.46
p of z	0.74	0.01
Specificity:	52%	59%
95% CI	30% to 73%	33% to 81%
Coefficient	0.08	0.38
z	-3.10	-1.84
p of z	0.00	0.07

Subgroup Analyses of Statistically Significant Models

Accuracy of Studies with Readers Blinded to Clinical Information vs. Not

META-ANALYTIC INTEGRATION OF DIAGNOSTIC TEST ACCURACY STUDIES

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Parameter	Blinded	Not Blinded (or Not Reported)
Number of studies	8	12
Number of patients	1,301	6,820
Prevalence of disease	38.6%	22.9%
I^2	90.7%	99.6%
Sensitivity (95% CI)	96.6% (92.3% to 98.5%)	87.0% (69.7% to 95.1%)
Specificity (95% CI)	59.5% (32.2% to 82.0%)	85.1% (69.0% to 93.6%)
AUROC (95% CI)	0.96 (0.94 to 0.97)	0.93 (0.90 to 0.95)

Accuracy of Studies with Interreader Differences Accounted for vs. Not

META-ANALYTIC INTEGRATION OF DIAGNOSTIC TEST ACCURACY STUDIES

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Parameter	Accounted for	Not
Number of studies	9	11
Number of patients	1,063	7,037
Prevalence of disease	40.2%	23.2%
I^2	96.7%	99.6%
Sensitivity (95% CI)	93.4% (83.1% to 97.6%)	93.0% (77.3% to 98.1%)
Specificity (95% CI)	52.7% (36.6% to 68.3%)	90.1% (74.3% to 96.6%)
AUROC (95% CI)	0.83 (0.79 to 0.86)	0.97 (0.95 to 0.98)

Ultrasound B-mode 3D Grayscale

1 study, 150 lesions

Table C29. Ultrasound accuracy data: B-mode 3D grayscale

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cho et al. 2006[61]	All	59	27	1	63	98.3% (91.1 to 100.0%)	70.0% (59.4 to 79.2%)

FN False negative
FP False positive
TN True negative
TP True positive

Ultrasound B-mode Grayscale: 2D vs. 3D

1 study, 150 lesions

Table C30. Ultrasound accuracy data: B-mode grayscale, 2D vs. 3D

Study	Technology	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cho et al. 2006[61]	2D	58	32	2	59	96.7% (88.5 to 99.6%)	64.8% (54.1 to 74.6%)
	3D	59	27	1	63	98.3% (91.1 to 100.0%)	70.0% (59.4 to 79.2%)

FN False negative
FP False positive
TN True negative
TP True positive

Ultrasound B-mode 2D Contrast Enhanced

2 studies, 154 lesions

Table C31. Ultrasound accuracy data: B-mode 2D grayscale contrast enhanced

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Liu et al. 2008[56]	All	41	7	2	54	95.3% (84.2% to 99.4%)	88.5% (77.8% to 95.3%)
Ricci et al. 2006[16]	All	38	10	0	2	100.0% (90.7% to 100.0%)	Not calculated
Summary (random-effects)						97.5% (91.4% to 99.7%) I^2 = 61.2%	76.7% (65.4% to 85.8%) I^2 = 96.0%

FN False negative
FP False positive
TN True negative
TP True positive

Ultrasound B-mode 2D Contrast Enhanced vs. Not Enhanced

2 studies, 154 lesions

Table C32. Ultrasound accuracy data: B-mode 2D grayscale contrast enhanced vs. not enhanced

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Liu et al. 2008[56]	Contrast Enhanced	41	7	2	54	95.3% (84.2% to 99.4%)	88.5% (77.8% to 95.3%)
	Not Enhanced	41	15	2	46	95.3% (84.2% to 99.4%)	75.4% (62.7% to 85.5%)
Ricci et al. 2006[16]	Contrast Enhanced	38	10	0	2	100.0% (90.7% to 100.0%)	Not calculated
	Not Enhanced	26	4	12	8	68.4% (72.7% to 90.2%)	66.7% (34.9% to 90.1%)
Summary (random-effects) Contrast Enhanced						97.5% (91.4% to 99.7%) I^2 = 61.2%	76.7% (65.4% to 85.8%) I^2 = 96.0%
Summary (random effects) Not Enhanced						82.7% (72.7% to 90.2%) I^2 = 90.9%	74.0% (62.4% to 83.5%) I^2 = 0.0%

FN False negative
FP False positive
TN True negative
TP True positive

Ultrasound Color Doppler

6 studies, 718 lesions

Table C33. Ultrasound accuracy data: color doppler

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Caruso et al. 2002[68]	All	16	1	4	15	80.0% (56.3% to 94.3%)	93.8% (69.8% to 99.8%)
Koukouraki et al. 2001[69]	All	76	4	9	26	89.4% (80.8% to 95.0%)	86.7% (69.3% to 96.2%)
	Palpable lesions	61	2	6	9	91.0% (81.5% to 96.6%)	81.8% (48.2% to 97.7%)
	Non-palpable lesions	14	2	5	17	73.7% (48.8% to 90.9%)	89.5% (66.9% to 98.7%)
Blohmer et al. 1999[73]	All	58	13	20	79	74.4% (63.2% to 83.6%)	85.9% (77.0% to 92.3%)
Schroeder et al. 1999[75]	All	72	23	0	15	100.0% (95.0% to 100.0%)	39.5% (24.0% to 56.6%)
Wilkens et al. 1998[77]	Palpable lesions	16	7	6	26	72.7% (49.8% to 89.3%)	78.8% (61.1% to 91.0%)
Buadu et al. 1997[78]	All	73	11	9	23	89.0% (80.2% to 94.9%)	67.6% (49.5% to 82.6%)

FN False negative
FP False positive
TN True negative
TP True positive

META-ANALYTIC INTEGRATION OF DIAGNOSTIC TEST ACCURACY STUDIES

Ultrasound Color Doppler

Using All Lesions data from Koukouraki et al. 2001[69] and including Wilkens et al. 1998[77] (reported data from palpable lesions only)

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Number of studies = 6

Reference-positive Subjects = 359

Reference-negative Subjects = 243

Pretest Prob of Disease = 0.596

Between-study variance (varlogitSEN) = 1.201 (95% CI: 0.224 to 6.443)

Between-study variance (varlogitSPE) = 0.591 (95% CI: 0.149 to 2.352)

Correlation (Mixed Model) = -1.000

ROC Area, AUROC = 0.89 (95% CI: 0.86 to 0.91)

Heterogeneity (Chi-square): LRT_Q = 41.754, df = 2.00, LRT_p = 0.000

Inconsistency (I-square): 95.2% (95% CI: 91.4 to 99.1)

Summary Parameter Estimates (95% CI)

Sensitivity: 88.5% (74.4% to 95.4%)

Specificity: 76.4% (61.7% to 86.7%)

Positive Likelihood Ratio: 3.760 (2.399 to 5.892)

Negative Likelihood Ratio: 0.150 (0.072 to 0.314)

Diagnostic Score: 3.223 (2.635 to 3.811)

Diagnostic Odds Ratio: 25.096 (13.938 to 45.187)

Exploration of Heterogeneity:

Ultrasound Color Doppler

Using All data from Koukouraki et al. 2001[69] and not including Wilkens et al. 1998[77] (reported data from palpable lesions only)

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Number of studies = 5

Reference-positive Subjects = 337

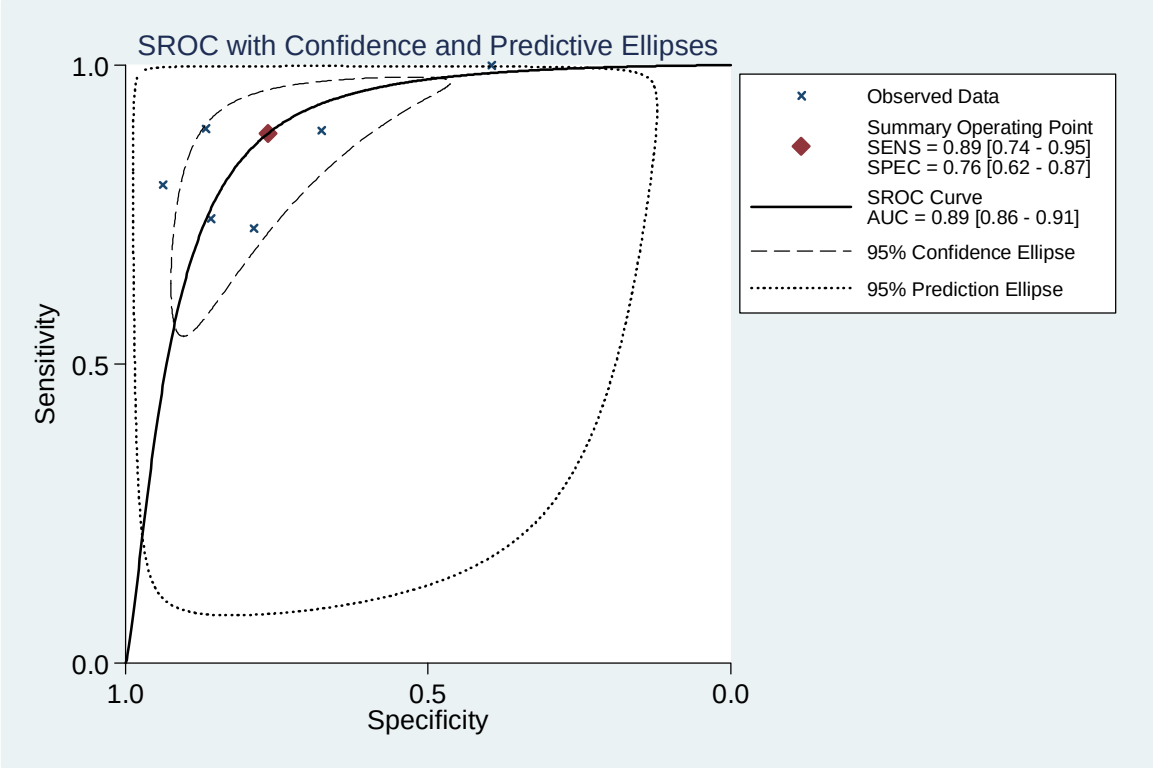
Reference-negative Subjects = 210

Heterogeneity (Chi-square): LRT_Q = 42.292, df = 2.00, LRT_p = 0.000

Inconsistency (I-square): 95.3% (95% CI: 91.48 to 99.06)

Compare to Inconsistency from full data set including Wilkens et al. 1998;[77] I-square: 95.2%, 95% CI (91.4 to 99.1)

Figure C8. Bivariate binomial mixed-effects model of ultrasound color doppler: summary ROC



Too few studies to perform meta-regression

Ultrasound Color Doppler Contrast Enhanced

2 studies, 146 lesions

Table C34. Ultrasound accuracy data: color doppler contrast enhanced

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Caruso et al. 2002[68]	All	18	3	2	13	90.0% (68.3% to 98.8%)	81.3% (54.4% to 96.0%)
Schroeder et al. 1999[75]	All	72	2	0	36	100.0% (95.0% to 100.0%)	94.7% (82.3% to 99.4%)
Summary (random-effects)						97.8% (92.4% to 99.7%) I^2 = 84.0%	90.7% (79.7% to 96.9%) I^2 = 54.6%

FN False negative
FP False positive
TN True negative
TP True positive

Ultrasound Color Doppler Contrast Enhanced vs. Not Enhanced

2 studies, 146 lesions

Table C35. Ultrasound accuracy data: color doppler contrast enhanced vs. not enhanced

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Caruso et al. 2002[68]	Contrast Enhanced	18	3	2	13	90.0% (68.3% to 98.8%)	81.3% (54.4% to 96.0%)
	Not Enhanced	16	1	4	15	80.0% (56.3% to 94.3%)	93.8% (69.8% to 99.8%)
Schroeder et al. 1999[75]	Contrast Enhanced	72	2	0	36	100.0% (95.0% to 100.0%)	94.7% (82.3% to 99.4%)
	Not Enhanced	72	23	0	15	100.0% (95.0% to 100.0%)	39.5% (24.0% to 56.6%)
Summary (random-effects) Contrast Enhanced						97.8% (92.4% to 99.7%) I^2 = 84.0%	90.7% (79.7% to 96.9%) I^2 = 54.6%
Summary (random-effects) Not Enhanced						95.7% (89.2% to 98.8%) I^2 = 92.2%	55.6% (41.4% to 69.1%) I^2 = 93.6%

FN False negative
FP False positive
TN True negative
TP True positive

Ultrasound Color Doppler vs. B-mode Grayscale 2D

2 studies, 225 lesions

Table C36. Ultrasound accuracy data: color doppler vs. B-mode grayscale 2D

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Blohmer et al. 1999[73]	Color Doppler	58	13	20	79	74.4% (63.2% to 83.6%)	85.9% (77.0% to 92.3%)
	B-mode	76	4	81	70	48.4% (40.4% to 56.5%)	94.6% (86.7% to 98.5%)
Wilkens et al. 1998[77]	Color Doppler; palpable lesions only	16	7	6	26	72.7% (49.8% to 89.3%)	78.8% (61.1% to 91.0%)
	B-mode; palpable lesions only	19	0	3	33	86.4% (65.1% to 97.1%)	100.0% (89.4% to 100.0%)
Summary (random-effects) Color Doppler						74.0% (64.3% to 82.3%) I^2 = 0.0%	84.0% (76.4% to 89.9%) I^2 = 0.0%
Summary (random-effects) B-mode						53.1% (45.5% to 60.6%) I^2 = 92.0%	96.3% (90.7% to 99.0%) I^2 = 66.9%

FN False negative
FP False positive
TN True negative
TP True positive

Ultrasound Power Doppler

9 studies, 614 lesions

Table C37. Ultrasound accuracy data: power doppler

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gokalp et al. 2009[55]	All	28	10	11	45	71.8% (55.1% to 85.0%)	81.8% (69.1% to 90.9%)
Forsberg et al. 2004[62]	All	11	4	16	22	40.7% (22.4% to 61.2%)	84.6% (65.1% to 95.6%)
Ozdemir et al. 2004[64]	All	23	26	5	14	82.1% (63.1% to 93.9%)	35.0% (20.6% to 51.7%)
Kook and Kwag 2003[66]	2 cm or less	5	5	12	14	29.4% (10.3% to 56.0%)	73.7% (48.8% to 90.9%)
Milz et al. 2001[70]	All	41	16	14	47	74.5% (61.0% to 85.3%)	74.6% (62.1% to 84.7%)
Reinikainen et al. 2001[71]	All	20	8	14	23	58.8% (40.7% to 75.45)	74.2% (55.4% to 88.1%)
Moon et al. 2000[72]	Non-palpable lesions	8	4	14	24	36.4% (17.2% to 59.3%)	85.7% (67.3% to 96.0%)
Schroeder et al. 1999[75]	All	72	21	0	17	100.0% (95.0% to 100.0%)	44.7% (28.6% to 61.7%)
Albrecht et al. 1998[76]	All	9	1	2	8	81.8% (48.2% to 97.7%)	88.9% (51.8% to 99.7%)

FN False negative
FP False positive
TN True negative
TP True positive

META-ANALYTIC INTEGRATION OF DIAGNOSTIC TEST ACCURACY STUDIES

Ultrasound Power Doppler

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Number of studies = 9

Reference-positive Subjects = 305

Reference-negative Subjects = 309

Pretest Prob of Disease = 0.497

Between-study variance (varlogitSEN) = 1.995 (95% CI: 0.606-6.566)

Between-study variance (varlogitSPE) = 0.576 (95% CI: 0.178-1.870)

Correlation (Mixed Model) = -0.797

ROC Area, AUROC = 0.77 (95% CI: 0.74 to 0.81)

Heterogeneity (Chi-square): LRT_Q = 76.788, df = 2.00, LRT_p = 0.000

Inconsistency (I-square): 97.4% (95% CI: 95.7%-99.1%)

Summary Parameter Estimates (95% CI)

Sensitivity: 70.8% (47.5% to 86.6%)

Specificity: 72.6% (59.9% to 82.5%)

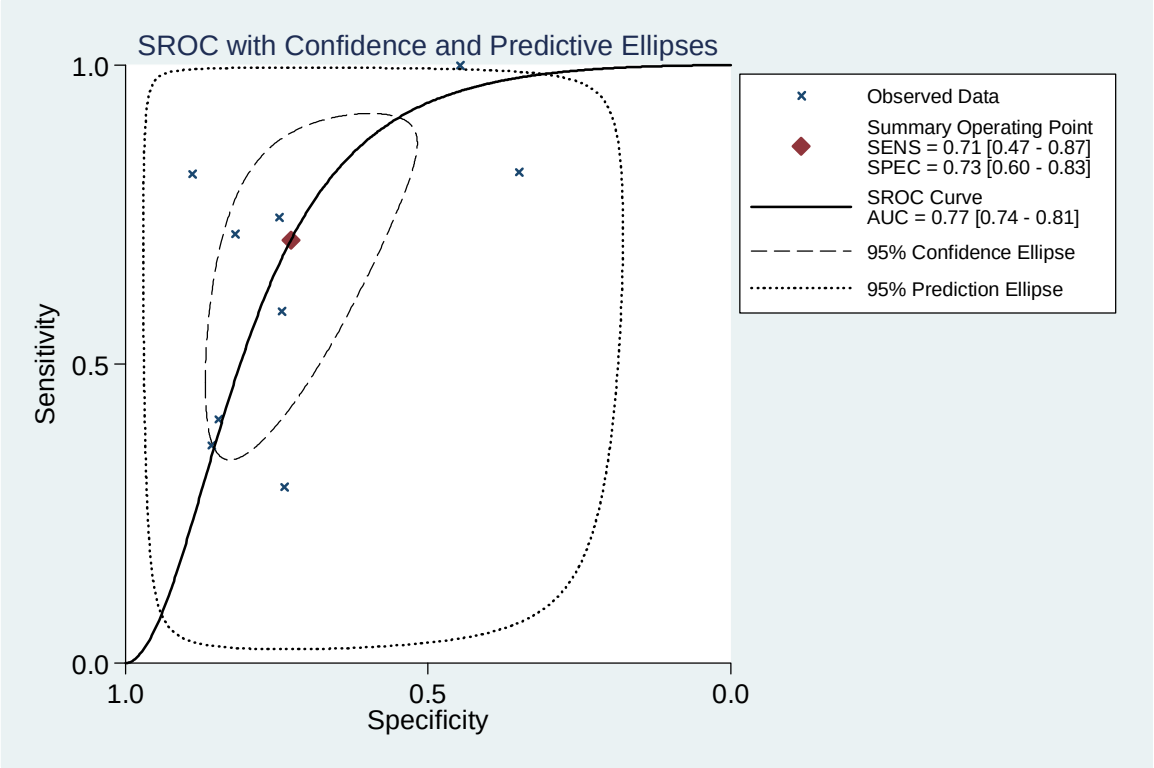
Positive Likelihood Ratio: 2.586 (1.882 to 3.555)

Negative Likelihood Ratio: 0.402 (0.219 to 0.738)

Diagnostic Score: 1.860 (1.110 to 2.611)

Diagnostic Odds Ratio: 6.426 (3.035 to 13.606)

Figure C9. Bivariate binomial mixed-effects model of ultrasound power doppler: summary ROC



Ultrasound Power Doppler vs. B-mode 2D grayscale

4 studies, 248 lesions

Table C38. Ultrasound accuracy data: power doppler vs. B-mode 2D grayscale

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gokalp et al. 2009[55]	B-mode	39	23	0	32	100.0% (91.0% to 100.0%)	58.2% (44.1% to 71.3%)
	Power Doppler	28	10	11	45	71.8% (55.1% to 85.0%)	81.8% (69.1% to 90.9%)
Forsberg et al. 2004[62]	B-mode	10	5	14	24	41.7% (22.1% to 63.4%)	82.8% (64.2% to 94.2%)
	Power Doppler	11	4	16	22	40.7% (22.4% to 61.2%)	84.6% (65.1% to 95.6%)
Kook and Kwag 2003[66]	B-mode, lesions 2 cm or less	17	10	0	9	100.0% (80.5% to 100.0%)	47.4% (24.4% to 71.1%)
	Power Doppler, lesions 2 cm or less	5	5	12	14	29.4% (10.3% to 56.0%)	73.7% (48.8% to 90.9%)
Reinikainen et al. 2001[71]	B-mode	34	28	0	3	100.0% (89.7% to 100.0%)	9.7% (2.0% to 25.8%)
	Power Doppler	20	8	14	23	58.8% (40.7% to 75.45)	74.2% (55.4% to 88.1%)
Summary (random effects) B-mode						87.7% (80.3% to 93.1%) I^2 = 94.3%	50.7% (42.0% to 59.5%) I^2 = 92.2%
Summary (random effects) Power Doppler						54.7% (45.2% to 63.9%) I^2 = 74.1%	79.4% (71.4% to 86.0%) I^2 = 0.0%

FN False negative
FP False positive
TN True negative
TP True positive

Ultrasound Power Doppler with Contrast Agent

7 studies, 403 lesions

Table C39. Ultrasound accuracy data: power doppler with contrast agent

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Forsberg et al. 2004[62]	All	8	7	23	15	25.8% (11.9% to 44.6%)	68.2% (45.1% to 86.1%)
Ozdemir et al. 2004[64]	All	23	14	5	27	82.1% (63.1% to 93.9%)	65.9% (49.4% to 79.9%)
Kook and Kwag 2003[66]	2 cm or less	12	8	5	11	70.6% (44.0% to 89.7%)	57.9% (33.5% to 79.7%)
Reinikainen et al. 2001[71]	All	19	17	15	14	55.9% (37.9% to 72.8%)	45.2% (27.3% to 64.0%)
Moon et al. 2000[72]	Non-palpable lesions	21	6	1	22	95.5% (77.2% to 99.9%)	78.6% (59.0% to 91.7%)
Schroeder et al. 1999[75]	All	72	2	0	36	100.0% (95.0% to 100.0%)	94.7% (82.3% to 99.4%)
Albrecht et al. 1998[76]	All	11	4	0	5	100.0% (71.5% to 100.0%)	55.6% (21.2% to 86.3%)

FN False negative
FP False positive
TN True negative
TP True positive

META-ANALYTIC INTEGRATION OF DIAGNOSTIC TEST ACCURACY STUDIES

Ultrasound Power Doppler with Contrast

SUMMARY DATA AND PERFORMANCE ESTIMATES

Bivariate Binomial Mixed Model

Number of studies = 7

Reference-positive Subjects = 215

Reference-negative Subjects = 188

Pretest Prob of Disease = 0.533

Between-study variance (varlogitSEN) = 5.785 (95% CI: 1.218-27.486)

Between-study variance (varlogitSPE) = 0.548 (95% CI: 0.117-2.560)

Correlation (Mixed Model) = 0.947

ROC Area, AUROC = 0.81 (95% CI: 0.77 to 0.84)

Heterogeneity (Chi-square): LRT_Q = 16.015, df = 2.00, LRT_p = 0.000

Inconsistency (I-square): 87.51% (95% CI: 74.55 to 100.00)

Summary Parameter Estimates (95% CI)

Sensitivity: 89.3% (52.4% to 98.4%)

Specificity: 70.4% (55.4% to 82.0%)

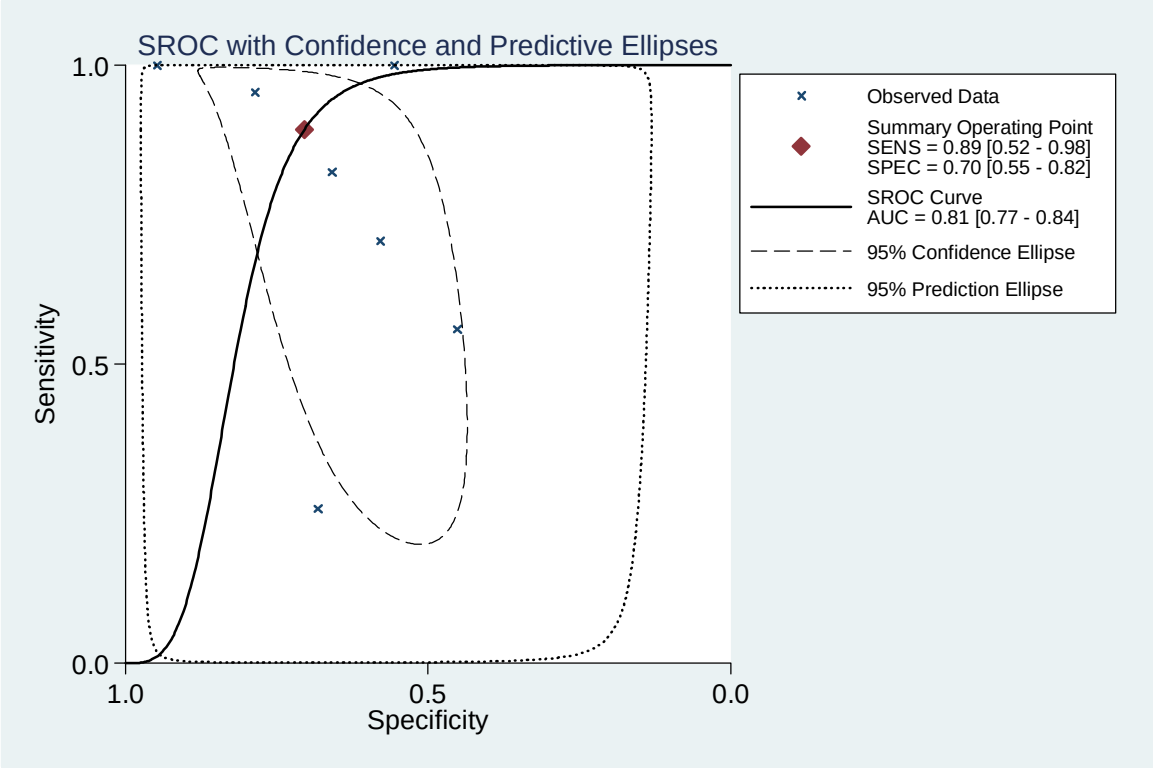
Positive Likelihood Ratio: 3.016 (1.603 to 5.675)

Negative Likelihood Ratio: 0.153 (0.022 to 1.072)

Diagnostic Score: 2.984 (0.452 to 5.517)

Diagnostic Odds Ratio: 19.772 (1.571 to 248.893)

Figure C10. Bivariate binomial mixed-effects model of ultrasound power doppler with contrast: summary ROC



Ultrasound Power Doppler vs. Color Doppler

1 study, 110 lesions

Table C40. Ultrasound accuracy data: power doppler vs. color doppler

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Schroeder et al. 1999[75]	Power Doppler Contrast Enhanced	72	2	0	36	100.0% (95.0% to 100.0%)	94.7% (82.3% to 99.4%)
	Power Doppler Non enhanced	72	21	0	17	100.0% (95.0% to 100.0%)	44.7% (28.6% to 61.7%)
	Color Doppler Contrast Enhanced	72	2	0	36	100.0% (95.0% to 100.0%)	94.7% (82.3% to 99.4%)
	Color Doppler Non enhanced	72	23	0	15	100.0% (95.0% to 100.0%)	39.5% (24.0% to 56.6%)

FN False negative
FP False positive
TN True negative
TP True positive

Ultrasound Tissue Harmonics

1 study, 91 lesions

Table C41. Ultrasound accuracy data: tissue harmonics

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cha et al. 2007[58]	All	29	23	1	38	96.7% (82.8% to 99.9%)	62.3% (49.0% to 74.4%)

FN False negative
FP False positive
TN True negative
TP True positive

Ultrasound Tissue Harmonics vs. B-mode Grayscale

1 study, 91 lesions

Table C42. Ultrasound accuracy data: tissue harmonics vs. B-mode grayscale

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cha et al. 2007[58]	Tissue harmonics	29	23	1	38	96.7% (82.8% to 99.9%)	62.3% (49.0% to 74.4%)
	B-mode grayscale	29	23	1	38	96.7% (82.8% to 99.9%)	62.3% (49.0% to 74.4%)

FN false negative
FP false positive
TN true negative
TP true positive

Ultrasound Combination Methods

4 studies that used multiple ultrasound methods, in combination, to diagnose breast lesions

Table C43. Ultrasound accuracy data: combination methods

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gokalp et al. 2009[55]	Combination of B-mode 2D grayscale and power Doppler	39	26	0	29	100.0% (91.0% to 100.0%)	52.7% (38.8% to 66.3%)
Liu et al. 2008[56]	Combination of B-mode and contrast-enhanced B-mode 2D grayscale	42	6	1	55	97.7% (87.7% to 99.9%)	90.2% (79.8% to 96.3%)
Pinero et al. 2006[53]	Combination power Doppler and color Doppler, contrast enhanced						
	All lesions	60	9	8	11	88.2% (78.1% to 94.8%)	55.0% (31.5% to 76.9%)
	Palpable lesions	42	2	5	8	89.4% (76.9% to 96.5%)	80.0% (44.4% to 97.5%)
	Non-palpable lesions	17	6	4	4	81.0% (58.1% to 94.6%)	40.0% (12.2% to 73.8%)
Malich et al. 2001[35]	Combination of B-mode, power Doppler, and color Doppler	48	4	14	34	77.4% (65.0% to 87.1%)	89.5% (75.2% to 97.1%)

FN false negative
FP false positive
TN true negative
TP true positive

Table C44. Ultrasound accuracy: accuracy of different types of ultrasound

Type of Ultrasound	N Studies	N Lesions	Risk of Bias	Consistency	Precision	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)	Strength of Evidence
B-mode grayscale 2D	21	8,199	Low	Inconsistent	Imprecise	92.4% (84.6% to 96.4%)	75.8% (60.8% to 86.3%)	Low
B-mode grayscale 2D contrast enhanced	2	154	Low	Inconsistent	Imprecise	97.5% (91.4% to 99.7%)	76.7% (65.4% to 85.8%)	Low
B-mode grayscale 3D	1	150	Low	Unknown	Imprecise	98.3% (91.1% to 100.0%)	70.0% (59.4% to 79.2%)	Insufficient
Color Doppler	6	718	Low	Inconsistent	Imprecise	88.5% (74.4% to 95.4%)	76.4% (61.% to 86.7%)	Low
Color Doppler contrast enhanced	2	146	Low	Inconsistent	Imprecise	97.8% (92.4% to 99.7%)	90.7% (79.7% to 96.9%)	Low
Power Doppler	9	614	Low	Inconsistent	Imprecise	70.8% (47.5% to 86.6%)	72.6% (59.9% to 82.5%)	Low
Power Doppler contrast enhanced	7	403	Low	Inconsistent	Imprecise	89.3% (52.4% to 98.4%)	70.4% (55.4% to 82.0%)	Low
Tissue harmonics	1	91	Low	Unknown	Imprecise	96.7% (82.8% to 99.9%)	62.3% (49.0% to 74.4%)	Insufficient

Table C45. Ultrasound accuracy: indirect and direct comparisons of different types of ultrasound

Type of Ultrasound	B-mode Grayscale 2D	B-mode Grayscale 2D Contrast Enhanced	B-mode Grayscale 3D	Color Doppler	Color Doppler Contrast Enhanced	Power Doppler	Power Doppler Contrast Enhanced	Tissue Harmonics
B-mode grayscale 2D	NA	Contrast-enhanced has a higher sensitivity Strength of evidence: Low	Insufficient evidence	B-mode grayscale is more sensitive Strength of evidence: Low	Insufficient evidence	B-mode grayscale is more sensitive Strength of evidence: Low	Insufficient evidence	Insufficient evidence
B-mode grayscale 2D contrast enhanced	NA	NA	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence
B-mode grayscale 3D	NA	NA	NA	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence
Color Doppler	NA	NA	NA	NA	Contrast-enhanced is more accurate Strength of evidence: Low	Color doppler is more accurate Strength of evidence Low	Insufficient evidence	Insufficient evidence
Color Doppler contrast enhanced	NA	NA	NA	NA	NA	Insufficient evidence	Insufficient evidence	Insufficient evidence
Power Doppler	NA	NA	NA	NA	NA	NA	Insufficient evidence	Insufficient evidence
Power Doppler contrast enhanced	NA	NA	NA	NA	NA	NA	NA	Insufficient evidence
Tissue harmonics	NA	NA	NA	NA	NA	NA	NA	NA

Direct Comparisons

Table C46. Direct comparison of PET and MRI

Study	Category	TP	FP	FN	TP	Sensitivity (95% CI)	Specificity (95% CI)
Heinisch et al. 2003[24]	PET	17	4	8	11	68.0% (46.5% to 85.1%)	73.3% (44.9% to 92.2%)
	MRI	23	2	4	11	85.2% (67.4% to 93.9%)	84.6% (57.6% to 95.4%)
Walter et al. 2003[25]	PET	12	2	7	21	63.2% (38.4% to 83.7%)	91.3% (72.0% to 98.9%)
	MRI	17	2	6	17	73.9% (53.4% to 87.3%)	89.5% (68.4% to 96.8%)
Brix et al. 2001[31]	PET	8	2	1	2	88.9% (51.8% to 99.7%)	50.0% (06.8% to 93.2%)
	MRI	8	1	2	2	80.0% (48.9% to 94.0%)	66.7% (21.0% to 93.3%)
Imbriaco et al. 2007[6]	PET-CT	29	0	7	8	80.6% (64.0% to 91.8%)	100% (63.1% to 100%)
	MRI	44	2	1	8	97.8% (88.3% to 99.5%)	80.0% (48.9% to 94.0%)

FN False negative
FP False positive
TN True negative
TP True positive

Table C47. Direct comparison of MRI and ultrasound

Study	Category	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Vassiou et al. 2009[8]	MRI	52	14	1	11	98.1% (89.9% to 99.6%)	44.0% (26.7% to 62.9%)
	US, B-mode 2D grayscale	44	6	9	19	83.0% (70.7 to 90.7%)	76.0% (56.5 to 94.3%)
Ricci et al. 2006[16]	MRI	38	2	0	11	100.0% (90.6% to 99.9%)	84.6% (57.6% to 95.4%)
	US, B mode grayscale, contrast enhanced	38	10	0	2	100.0% (90.7 to 100.0%)	Not calculated
	US, B mode grayscale, not enhanced	26	4	12	8	68.4% (72.7 to 90.2%)	66.7% (34.9 to 90.1%)
Malich et al. 2001[35]	MRI	53	7	1	29	98.1% (90.1% to 99.6%)	80.6% (64.9% to 90.1%)
	Combination of B-mode, power Doppler, and color Doppler	48	4	14	34	77.4% (65.0 to 87.1%)	89.5% (75.2 to 97.1%)

FN False negative
FP False positive
TN True negative
TP True positive
US Ultrasound

Table C48. Direct comparison of scintimammography to doppler ultrasound (combined method)

Study	Category	Patient Subgroup	TP	FP	FN	TN	Sensitivity (95%CI)	Specificity (95%CI)
Pinero et al. 2006[53]	Double phase SMM	All, mixed population	63	10	5	10	92.6% (83.7 to 97.6)	50.0% (27.2 to 72.8)
	Combination power Doppler and color Doppler, contrast enhanced		60	8	9	11	88.2% (78.1 to 94.8)	55.0% (31.5 to 76.9)
Pinero et al. 2006[53]	Double phase SMM	Palpable lesions only	43	3	4	7	91.5% (79.6 to 97.6)	70.0% (34.8 to 93.3)
	Combination power Doppler and color Doppler, contrast enhanced		42	2	5	8	89.4% (76.9 to 96.5)	80.0% (44.4 to 97.5)
Pinero et al. 2006[53]	Double phase SMM	Non-palpable	20	1	6	4	95.2% (76.2 to 99.9)	40.0% (12.2 to 73.8)
	Combination power Doppler and color Doppler, contrast enhanced		17	4	6	4	81.0% (58.1 to 94.6)	40.0% (12.2 to 73.8)

FN False negative
FP False positive
TN True negative
TP True positive

Table C49. Comparison of scintimammography with MRI

Study	Category	TP	FP	FN	TN	Sensitivity (95%CI)	Specificity (95%CI)
Kim et al. 2009[4]	Double phase SMM	169	10	34	26	83.3% (77.4 to 88.1)	72.2% (54.8 to 85.8)
	Dynamic contrast enhanced MRI	196	14	8	21	96.1% (92.4 to 98.3)	60.0% (42.1 to 76.1)

FN False negative
FP False positive
TN True negative
TP True positive

Table C50. Comparison of BSGI to MRI

Study	Type of Scanner	TP	FP	FN	TN	Sensitivity (95%CI)	Specificity (95%CI)
Brem et al. 2007[9]	BSGI	8	7	1	17	88.9% (51.8 to 99.7)	70.8% (48.9 to 87.4)
	Dynamic contrast enhanced MRI	9	18	0	6	100% (66.4 to 100)	25.0% (10.0 to 46.7)

FN False negative
FP False positive
TN True negative
TP True positive

Grading the Strength of Evidence

We applied a formal grading system that conforms with the CER Methods Guide Manual recommendations on grading the strength of evidence.[82,83]

The overall strength of evidence supporting each major conclusion was graded as High, Moderate, Low, or Insufficient. The grade was developed by considering four important domains: the risk of bias in the evidence base, the consistency of the findings, the precision of the results, and the directness of the evidence. The grading system moves stepwise to consider each important domain. These steps are described below.

Risk of Bias

According to the Methods Guide:[82]

> *Risk of bias is the degree to which the included studies for a given outcome or comparison have a high likelihood of adequate protection against bias (i.e., good internal validity) assessed through two main elements:*
>
> - *Study design of individual studies*
> - *Aggregate quality of the studies under consideration.*

The risk of bias of each individual study was rated as being Low, Medium, or High; and the risk of bias of the aggregate evidence base supporting each major conclusion was similarly rated as being Low, Medium, or High.

We used our inclusion/exclusion criteria to eliminate studies with designs known to be prone to bias from the evidence base. Namely, case reports, case-control studies, and retrospective studies that did not enroll all or consecutive patients were not included for analysis. Because we eliminated all studies with a High risk of bias from the evidence base, we consider the remaining evidence base to have either a Low or Medium risk of bias.

We initially used an internal validity rating instrument for diagnostic studies to grade the internal validity of the individual studies (Table 54). This instrument is based on a modification of the QUADAS instrument.[84] Each question in the instrument addresses an aspect of study design or conduct that can help to protect against bias. Each question can be answered "yes," "no," or "not reported," and each is phrased such that an answer of "yes" indicates that the study reported a protection against bias on that aspect. See Table 55 through Table 58 for application of the instrument to the included studies.

Table C51. Quality assessment instrument

N	Question
1	Was patient recruitment either consecutive or random?
2	Was the study prospective in design?
3	Were more than 85% of the patients approached for recruitment enrolled in the study?
4	Were the patient inclusion/exclusion criteria consistently applied to all patients?
5	Was the study free from obvious spectrum bias? Obvious spectrum bias was defined as more than 40% or less than 10% of the breast lesions were diagnosed as malignant; and/or the mean or median age of the enrolled population was less than 50 or greater than 70.
6	Did the study account for inter-reader/scorer differences?
7	Were the reader(s) of the biopsies blinded to the results of the reference standard?
8	Were readers of the reference standard blinded to the results of the biopsy?
9	Were the readers of the biopsy blinded to all other clinical information?
10	Were readers of the reference standard blinded to all other clinical information?
11	Were patients assessed by a reference standard regardless of the biopsy results?
12	Were the patients assessed by the gold standard (open surgical procedure) regardless of the initial biopsy results?
13	Was a diagnostic threshold chosen *a priori* by the study?
14	Were there no intervening treatments or interventions conducted between the time the diagnostic test was performed and the reference standard was performed?
15	Was a complete set of data reported for at least 85% of enrolled lesions?
16	Was funding for this study provided by a source that doesn't have an obvious financial interest in the findings of the study?
17	Was the report of the study free from unresolvable discrepancies?

We conducted meta-regressions investigating the correlation between key individual items on the quality rating instrument and the results reported by the studies (see Appendix C for details). We consistently found that the majority of the items on the instrument had no statistically significant correlation with the reported results. Some (but not most) of the evidence bases were found to have a statistically significant impact of "reader blinded to other clinical information" and "accounted for inter-reader differences" on the study results.

We concluded that the quality instrument was not adequately capturing the potential for bias of the studies. Unlike studies of interventions, diagnostic cohort studies are quite simple in design- one group of patients acting as their own controls. As long as all enrolled patients receive both the diagnostic test and the reference standard test, opportunities for bias to affect the results are limited. As mentioned above, we eliminated all studies with a High risk of bias due to their study design from the evidence base. We did not identify any design flaws in the remaining studies that suggested they were at Medium risk of bias; therefore, we rated all of the included studies, and the aggregate evidence bases, as being at Low risk of bias.

Consistency

According to the Methods Guide:[82]

> *The principal definition of consistency is the degree to which the reported effect sizes from included studies appear to have the same direction of effect. This can be assessed through two main elements:*
>
> - *Effect sizes have the same sign (that is, are on the same side of "no effect")*
> - *The range of effect sizes is narrow.*

The first definition, effect sizes being on the same side of "no effect," is not applicable to meta-analyses of the accuracy of a diagnostic test. Therefore, for these cases, we used the second definition, the range of effect sizes being narrow. We measured the "narrowness" of the range of effect sizes with the statistic I^2.[85,86] Data sets that were found to have an I^2 of less than 50% were rated as being "Consistent"; 50% or greater were rated as being "Inconsistent"; and data sets for which I^2 could not be calculated (e.g., a single study) were rated as "Consistency Unknown."

For qualitative comparisons between different diagnostic tests we used the first definition, that of effect sizes being on the same side of an effect. For example, when comparing the accuracy of ultrasound without a contrast agent to the accuracy of ultrasound with a contrast agent, if the estimates of sensitivity of the individual studies are consistently higher for studies that used a contrast agent, then the evidence base would be rated as "consistent."

Precision

According to the Methods Guide:[82]

> *Precision is the degree of certainty surrounding an effect estimate…if a meta-analysis was performed, this will be the confidence interval around the summary effect size.*
>
> *A precise estimate is an estimate that would allow a clinically useful conclusion.*

Diagnostic test characteristics (sensitivity, specificity) are reported on a scale from 0.0 to 100.0%. We defined a "precise" estimate of sensitivity or specificity as one for which the upper AND lower bound of the 95% confidence interval was no more than 5 points away from the summary estimate; for example, sensitivity 98% (95% CI: 97 to 100%) would be a precise estimate of sensitivity, whereas sensitivity 95% (95% CI: 88 to 100%) would be an imprecise estimate of sensitivity. Precision could be rated separately for summary estimates of sensitivity and specificity for each major conclusion.

For qualitative comparisons between different diagnostic tests, the conclusion is Precise if the confidence intervals around the summary estimates being compared do not overlap.

Directness

According to the Methods Guide:[82]

> *The rating of directness relates to whether the evidence links the interventions directly to health outcomes.*

For studies of diagnostic test accuracy, the evidence is always rated as "Indirect" because the outcome of test accuracy is indirectly related to health outcomes. However, the Key Questions in this particular comparative effectiveness review do not ask about the impact of test accuracy on

health outcomes. We therefore did not incorporate the "Indirectness" of the evidence into the overall rating of strength of evidence for Key Questions that did not ask about health outcomes.

Overall Rating of Strength of Evidence

The initial rating is based on the risk of bias. If the evidence base has a Low risk of bias, the initial strength of evidence rating is High; if the evidence base has a Moderate risk of bias, the initial strength of evidence rating is Moderate; if the evidence base has a High risk of bias, the initial strength of evidence rating is Low. For this particular comparative effectiveness review, as explained above, the rating of risk of bias was Low for all evidence bases, and therefore the initial strength of evidence rating is High.

The remaining two domains are used to up- or down- grade the initial rating as per the following flow charts:

Consistent, Precise: High

Inconsistent, Precise: Moderate

Consistent, Imprecise: Moderate

Inconsistent, Imprecise: Low

"Consistency Unknown," Precise: Low

"Consistency Unknown," Imprecise: Insufficient

MRI

Table C52. MRI studies: quality evaluation

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study	Consecutive	Prospective	≥85% Enrolled	Consistent Criteria	Spectrum Bias	Interreader Differences	Blinded to Reference Results	Blinded to Diagnostic Results	Dx Reader Blinded to Clinical Info	Ref Reader Blinded to Clinical Info	Reference Standard	Gold Standard	*A priori* Threshold	No Intervening Treatment	85% Accounted for	Funding	Discrepancy
Akita et al. 2009[1]	Yes	NR	Yes	Yes	Yes	NR	Yes	NR	No	NR	Yes	Yes	Yes	NR	Yes	NR	Yes
Baltzer et al. 2009[2]	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Hara et al. 2009[87]	Yes	NR	NR	Yes	Yes	NR	Yes	NR	NR	NR	Yes	No	Yes	NR	Yes	NR	Yes
Kim et al. 2009[4]	Yes	NR	NR	Yes	No	NR	Yes	NR	No	NR	Yes	No	No	Yes	Yes	Yes	Yes
Lo et al. 2009[5]	NR	Yes	NR	Yes	No	NR	Yes	NR	Yes	NR	Yes	No	Yes	NR	Yes	NR	Yes
Imbriaco et al. 2008[6]	Yes	Yes	Yes	Yes	No	No	Yes	NR	No	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Pediconi et al. 2008[7]	NR	Yes	NR	Yes	No	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	No
Vassiou et al. 2009[8]	NR	Yes	NR	Yes	No	NR	Yes	NR	NR	NR	Yes	Yes	Yes	NR	Yes	NR	Yes

Appendix Table 52. MRI studies: quality evaluation (continued)

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study	Consecutive	Prospective	≥85% Enrolled	Consistent Criteria	Spectrum Bias	Interreader Differences	Blinded to Reference Results	Blinded to Diagnostic Results	Dx Reader Blinded to Clinical Info	Ref Reader Blinded to Clinical Info	Reference Standard	Gold Standard	*A priori* Threshold	No Intervening Treatment	85% Accounted for	Funding	Discrepancy
Brem et al. 2007[9]	NR	NR	NR	Yes	Yes	NR	Yes	NR	No	NR	Yes	No	Yes	NR	Yes	NR	Yes
Cilotti et al. 2007[10]	NR	No	NR	Yes	No	NR	NR	No	NR	No	Yes	No	Yes	NR	Yes	NR	Yes
Pediconi et al. 2007[11]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes	No	Yes	NR	Yes	NR	Yes
Zhu et al. 2007[12]	Yes	No	Yes	Yes	No	No	Yes	NR	No	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Bazzocchi et al. 2006[13]	NR	Yes	NR	Yes	No	Yes	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	No	Yes	Yes
Gokalp and Topal 2006[14]	Yes	Yes	Yes	Yes	No	No	Yes	NR	No	NR	Yes	No	Yes	NR	Yes	NR	Yes
Kneeshaw et al. 2006[15]	No	Yes	NR	Yes	Yes	No	Yes	NR	No	NR	Yes	No	Yes	NR	Yes	Yes	Yes
Ricci et al. 2006[16]	Yes	Yes	Yes	Yes	No	NR	Yes	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Pediconi et al. 2005[17]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	NR	Yes
Pediconi et al. 2005[18]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes

Appendix Table 52. MRI studies: quality evaluation (continued)

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study	Consecutive	Prospective	≥85% Enrolled	Consistent Criteria	Spectrum Bias	Interreader Differences	Blinded to Reference Results	Blinded to Diagnostic Results	Dx Reader Blinded to Clinical Info	Ref Reader Blinded to Clinical Info	Reference Standard	Gold Standard	*A priori* Threshold	No Intervening Treatment	85% Accounted for	Funding	Discrepancy
Wiener et al. 2005[19]	No	Yes	No	Yes	No	No	Yes	NR	No	NR	Yes	No	Yes	NR	Yes	NR	Yes
Bluemke et al. 2004[20]	NR	Yes	Yes	Yes	No	No	Yes	NR	NR	NR	Yes	No	Yes	Yes	Yes	Yes	Yes
Huang et al. 2004[21]	NR	Yes	NR	Yes	Yes	NR	Yes	NR	NR	NR	Yes	No	Yes	Yes	Yes	Yes	Yes
Bone et al. 2003[22]	Yes	Yes	Yes	Yes	No	No	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Daldrup-Link et al. 2003[23]	No	Yes	No	Yes	No	NR	Yes	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Heinisch et al. 2003[24]	NR	Yes	NR	Yes	No	NR	Yes	NR	No	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Walter et al. 2003[25]	Yes	Yes	Yes	Yes	No	NR	Yes	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Guo et al. 2002[26]	NR	No	NR	NR	No	NR	NR	NR	NR	NR	Yes	Yes	Yes	NR	Yes	NR	Yes
Kelcz et al. 2002[27]	Yes	Yes	NR	Yes	No	NR	Yes	NR	No	NR	Yes	No	Yes	Yes	Yes	Yes	Yes
Schedel et al. 2002[28]	NR	NR	NR	Yes	No	NR	Yes	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes

Appendix Table 52. MRI studies: quality evaluation (continued)

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study	Consecutive	Prospective	≥85% Enrolled	Consistent Criteria	Spectrum Bias	Interreader Differences	Blinded to Reference Results	Blinded to Diagnostic Results	Dx Reader Blinded to Clinical Info	Ref Reader Blinded to Clinical Info	Reference Standard	Gold Standard	*A priori* Threshold	No Intervening Treatment	85% Accounted for	Funding	Discrepancy
Trecate et al. 2002[29]	NR	Yes	NR	Yes	No	NR	Yes	NR	NR	NR	Yes	Yes	Yes	NR	Yes	NR	Yes
Wiberg et al. 2002[30]	Yes	Yes	Yes	Yes	No	No	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Brix et al. 2001[31]	Yes	Yes	NR	Yes	No	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Cecil et al. 2001[32]	Yes	NR	NR	Yes	No	NR	Yes	NR	No	NR	Yes	No	Yes	NR	Yes	Yes	Yes
Furman-Haran et al. 2001[33]	NR	Yes	NR	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	NR	Yes	Yes	Yes
Imbriaco et al. 2001[34]	Yes	Yes	NR	Yes	No	NR	Yes	NR	Yes	NR	Yes	No	Yes	Yes	Yes	Yes	Yes
Malich et al. 2001[35]	Yes	NR	Yes	Yes	No	No	Yes	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Nakahara et al. 2001[36]	No	No	No	Yes	No	NR	Yes	NR	NR	NR	Yes	Yes	Yes	NR	Yes	NR	Yes
Torheim et al. 2001[37]	NR	Yes	NR	Yes	No	No	NR	NR	NR	NR	Yes	No	Yes	NR	Yes	Yes	Yes
Wedegartner et al. 2001[38]	NR	Yes	NR	Yes	No	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	NR	Yes	NR	Yes

Appendix Table 52. MRI studies: quality evaluation (continued)

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study	Consecutive	Prospective	≥85% Enrolled	Consistent Criteria	Spectrum Bias	Interreader Differences	Blinded to Reference Results	Blinded to Diagnostic Results	Dx Reader Blinded to Clinical Info	Ref Reader Blinded to Clinical Info	Reference Standard	Gold Standard	*A priori* Threshold	No Intervening Treatment	85% Accounted for	Funding	Discrepancy
Yeung et al. 2001[39]	Yes	NR	NR	Yes	No	NR	Yes	Yes	NR	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Kvistad et al. 2000[40]	NR	Yes	NR	Yes	No	Yes	Yes	NR	Yes	NR	Yes	No	Yes	Yes	Yes	Yes	Yes
Van Goethem et al. 2000[41]	Yes	No	Yes	Yes	Yes	NR	Yes	NR	NR	NR	Yes	No	NR	NR	Yes	NR	Yes

NR Not reported

PET

Table C53. Quality assessment of studies of PET

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study	Consecutive	Prospective	≥85% Enrolled	Consistent Criteria	Spectrum Bias	Interreader Differences	Blinded to Reference Results	Blinded to Diagnostic Results	Dx Reader Blinded to Clinical Info	Ref Reader Blinded to Clinical Info	Reference Standard	Gold Standard	*A priori* Threshold	No Intervening Treatment	85% Accounted for	Funding	Discrepancy
Kaida et al. 2008[42]	Yes	Yes	NR	Yes	No	NR	Yes	NR	Yes	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Buchmann et al. 2007[43]	Yes	Yes	NR	Yes	No	Yes	Yes	NR	No	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Heinisch et al. 2003[24]	NR	Yes	NR	Yes	No	NR	Yes	NR	No	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Walter et al. 2003[25]	Yes	Yes	Yes	Yes	No	NR	Yes	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Brix et al. 2001[31]	Yes	Yes	NR	Yes	No	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Schirrmeister et al. 2001[88]	Yes	Yes	NR	Yes	No	Yes	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Yutani et al. 2000[45]	Yes	Yes	NR	Yes	No	Yes	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Imbriaco et al. 2008[6]	Yes	NR	NR	Yes	No	Yes	NR	NR	No	NR	Yes	Yes	Yes	Yes	Yes	NR	No

NR Not reported

Scintimammography

Table C54. Quality assessment of studies of scintimammography

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study	Consecutive	Prospective	>85% Enrolled	Consistent Criteria	Spectrum Bias	Interreader Differences	Blinded to Reference Results	Blinded to Diagnostic Results	Dx Reader Blinded to Clinical Info	Reference Reader Blinded to Clinical Info	Reference standard	Gold Standard	A Priori Threshold	No Intervening Treatment	85% Accounted for	Funding	Discrepancy
Grosso et al. 2009[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Habib et al. 2009[47]	NR	Yes	NR	Yes	No	Yes	Yes	NR	Yes	NR	Yes	No	Yes	NR	Yes	NR	Yes
Kim et al. 2009[4]	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	NR	NR	Yes	No	Yes	NR	Yes	Yes	Yes
Kim et al. 2008[48]	NR	Yes	NR	Yes	No	Yes	Yes	NR	Yes	NR	Yes	No	Yes	NR	Yes	NR	Yes
Wang et al. 2008[49]	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes
Brem et al. 2007[9]	NR	NR	NR	Yes	Yes	NR	Yes	NR	No	NR	Yes	No	Yes	NR	Yes	NR	Yes
Gommans et al. 2007[50]	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	NR	Yes	No	Yes	Yes	Yes	NR	Yes

Table C54. Quality assessment of studies of scintimammography (continued)

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study	Consecutive	Prospective	>85% Enrolled	Consistent Criteria	Spectrum Bias	Interreader Differences	Blinded to Reference Results	Blinded to Diagnostic Results	Dx Reader Blinded to Clinical Info	Reference Reader Blinded to Clinical Info	Reference standard	Gold Standard	A Priori Threshold	No Intervening Treatment	85% Accounted for	Funding	Discrepancy
Kim et al. 2007[51]	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	NR	Yes	No	Yes	NR	Yes	Yes	Yes
Schillaci et al. 2007[52]	NR	Yes	NR	Yes	No	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	NR	Yes	NR	Yes
Pinero et al. 2006[53]	Yes	Yes	Yes	Yes	No	NR	Yes	NR	NR	NR	Yes	Yes	Yes	NR	Yes	NR	Yes
Mathieu et al. 2005[54]	NR	No	NR	Yes	No	Yes	NR	NR	NR	NR	Yes	No	No	NR	Yes	NR	Yes

NR Not reported

Ultrasound

Table C55. Ultrasound studies: quality evaluation

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study	Consecutive	Prospective	≥85% Enrolled	Consistent Criteria	Spectrum Bias	Interreader Differences	Blinded to Reference Results	Blinded to Diagnostic Results	Dx Reader Blinded to Clinical Info	Ref Reader Blinded to Clinical Info	Reference Standard	Gold Standard	*A Priori* Threshold	No Intervening Treatment	85% Accounted for	Funding	Discrepancy
Gokalp et al. 2009[55]	NR	Yes	NR	Yes	No	No	NR	NR	NR	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Liu et al. 2008[56]	Yes	NR	No	Yes	No	Yes	NR	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vade et al. 2008[57]	Yes	No	Yes	Yes	No	NR	NR	NR	NR	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Cha et al. 2007[58]	Yes	Yes	Yes	Yes	No	Yes	NR	NR	Yes	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Chala et al. 2007[59]	Yes	No	Yes	Yes	Yes	No	NR	NR	Yes	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Zhi et al. 2007[60]	Yes	NR	Yes	Yes	No	Yes	NR	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Cho et al. 2006[61]	Yes	Yes	Yes	Yes	No	Yes	NR	NR	Yes	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Pinero et al. 2006[53]	Yes	Yes	Yes	Yes	No	No	NR	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes

Table C55. Ultrasound studies: quality evaluation (continued)

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study	Consecutive	Prospective	≥85% Enrolled	Consistent Criteria	Spectrum Bias	Interreader Differences	Blinded to Reference Results	Blinded to Diagnostic Results	Dx Reader Blinded to Clinical Info	Ref Reader Blinded to Clinical Info	Reference Standard	Gold Standard	*A Priori* Threshold	No Intervening Treatment	85% Accounted for	Funding	Discrepancy
Ricci et al. 2006[16]	Yes	Yes	Yes	Yes	No	Yes	NR	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Forsberg et al. 2004[62]	NR	NR	Yes	Yes	Yes	No	NR	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	No	Yes
Meyberg-Solomayer et al. 2004[63]	NR	Yes	NR	Yes	No	No	NR	NR	NR	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Ozdemir et al. 2004[64]	NR	Yes	NR	Yes	No	No	NR	NR	NR	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Chen et al. 2003[65]	NR	Yes	NR	Yes	No	Yes	NR	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Kook and Kwag 2003[66]	NR	Yes	NR	Yes	No	Yes	Yes	NR	Yes	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Marini et al. 2003[67]	Yes	NR	Yes	Yes	Yes	Yes	NR	NR	Yes	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Caruso et al. 2002[68]	NR	Yes	Yes	Yes	No	NR	NR	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Koukouraki et al. 2001[69]	NR	Yes	NR	Yes	No	NR	NR	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes

Table C55. Ultrasound studies: quality evaluation (continued)

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study	Consecutive	Prospective	≥85% Enrolled	Consistent Criteria	Spectrum Bias	Interreader Differences	Blinded to Reference Results	Blinded to Diagnostic Results	Dx Reader Blinded to Clinical Info	Ref Reader Blinded to Clinical Info	Reference Standard	Gold Standard	*A Priori* Threshold	No Intervening Treatment	85% Accounted for	Funding	Discrepancy
Malich et al. 2001[35]	Yes	NR	Yes	Yes	No	No	NR	NR	No	NR	Yes	NR	Yes	Yes	Yes	NR	Yes
Milz et al. 2001[70]	NR	Yes	NR	Yes	No	NR	NR	NR	NR	NR	Yes	Yes	No	Yes	Yes	NR	Yes
Reinikainen et al. 2001[71]	NR	Yes	Yes	Yes	No	Yes	NR	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Moon et al. 2000[72]	Yes	Yes	No	NR	No	Yes	NR	NR	NR	NR	Yes	Yes	No	Yes	No	Yes	Yes
Blohmer et al. 1999[73]	NR	Yes	NR	Yes	No	NR	NR	NR	NR	NR	Yes	Yes	Yes	Yes	No	NR	Yes
Chao et al. 1999[74]	NR	Yes	NR	Yes	No	No	NR	NR	NR	NR	Yes	NR	Yes	Yes	Yes	NR	Yes
Schroeder et al. 1999[75]	Yes	Yes	Yes	Yes	No	Yes	NR	NR	Yes	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Albrecht et al. 1998[76]	NR	Yes	NR	Yes	No	Yes	NR	NR	Yes	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Wilkens et al. 1998[77]	NR	NR	NR	Yes	NR	No	NR	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes

Table C55. Ultrasound studies: quality evaluation (continued)

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study	Consecutive	Prospective	≥85% Enrolled	Consistent Criteria	Spectrum Bias	Interreader Differences	Blinded to Reference Results	Blinded to Diagnostic Results	Dx Reader Blinded to Clinical Info	Ref Reader Blinded to Clinical Info	Reference Standard	Gold Standard	*A Priori* Threshold	No Intervening Treatment	85% Accounted for	Funding	Discrepancy
Buadu et al. 1997[78]	Yes	NR	Yes	Yes	No	NR	NR	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Stavros et al. 1995[79]	NR	Yes	NR	Yes	No	NR	NR	NR	NR	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Ciatto et al. 1994[80]	Yes	Yes	Yes	Yes	Yes	No	NR	NR	NR	NR	Yes	No	Yes	Yes	Yes	NR	Yes
Perre et al. 1994[81]	NR	Yes	NR	Yes	No	No	NR	NR	Yes	NR	Yes	No	Yes	Yes	Yes	NR	Yes

NR Not reported

Appendix D. List of Excluded Studies

MRI Exclusions

103 total excluded

Reasons for Exclusion

Did not enroll the patient population of interest: 54 studies

Did not use an acceptable reference standard to verify diagnoses of at least 85% of patients: 12 studies

Study of experimental methods not clinically relevant: 14 studies

Did not address any of the Key Questions: 9 studies

Did not report sufficient data to calculate the outcomes of interest: 6 studies

Duplicate reports of the same studies/patients: 4 studies

Retrospective study that did not enroll all or consecutive patients: 3 studies

Reported data from fewer than 50% of the enrolled patients: 1 study

Table D1. Studies of MRI that did not meet the inclusion criteria

Study	Reason for Exclusion
Baltzer et al. 2010[89]	Exploratory study of experimental diagnostic methods
Baltzer et al. 2010[90]	Did not enroll the patient population of interest
Baltzer et al. 2010[91]	Exploratory study of experimental diagnostic methods
Belli et al. 2010[92]	Did not use an acceptable reference standard
Benndorf et al. 2010[93]	Did not enroll the patient population of interest
Bhooshan et al. 2010[94]	Exploratory study of experimental diagnostic methods
Carbonaro et al. 2010[95]	Did not enroll the patient population of interest
Dietzel et al. 2010[96]	Exploratory study of experimental diagnostic methods
Dietzel et al. 2010[97]	Exploratory study of experimental diagnostic methods
El Khouli et al. 2010[98]	Exploratory study of experimental diagnostic methods

Table D1. Studies of MRI that did not meet the inclusion criteria (continued)

Study	Reason for Exclusion
Hauth et al. 2010[99]	Did not address any of the Key Questions
Meeuwis et al. 2010[100]	Did not enroll the patient population of interest
Peters et al. 2010[101]	Exploratory study of experimental diagnostic methods
Weinstein et al. 2010[102]	Did not enroll the patient population of interest
Arazi-Kleinman et al. 2009[103]	Enrolled only patients at very high risk of breast cancer
Baltzer et al. 2009[104]	Enrolled only patients at very high risk of breast cancer
Baltzer et al. 2009[105]	Did not enroll the patient population of interest
Baltzer et al. 2009[105]	Enrolled only patients at very high risk of breast cancer
Bluemke et al. 2009[20]	Duplicate patient population as in Bluemke et al.[20]
Calabrese et al. 2009[106]	Enrolled only patients at very high risk of breast cancer
Ciatto et al. 2009[107]	Exploratory study of experimental diagnostic methods
El Khouli et al. 2009[108]	Does not address any of the Key Questions
El Khouli et al. 2009[109]	Retrospective study that did not enroll all or consecutive patients
Gutierrez et al. 2009[110]	Does not address any of the Key Questions
Kim et al. 2009[111]	Enrolled only patients diagnosed with invasive breast cancer
Kurz et al. 2009[112]	Does not address any of the Key Questions
Palle and Reddy et al. 2009[113]	Did not report how or if the MRI diagnoses were verified
Pediconi et al. 2009[114]	Fewer than 85% of the lesions had their diagnoses verified with an acceptable reference standard
Pereira et al. 2009[115]	Exploratory study of experimental diagnostic methods
Perfetto et al. 2009[116]	Retrospective study that did not enroll all or consecutive patients
Pinker et al. 2009[117]	Did not report data for patients with diagnosis verified by followup instead of histopathology (45% of enrolled patients)

Table D1. Studies of MRI that did not meet the inclusion criteria (continued)

Study	Reason for Exclusion
Potente et al. 2009[118]	Enrolled only patients at very high risk of breast cancer
Schuten et al. 2009[119]	Only enrolled patients diagnosed with breast cancer
Stadlbauer et al. 2009[120]	Only 60% of diagnoses were verified with an acceptable reference standard
Woodhams et al. 2009[121]	Does not address any of the Key Questions
Baek et al. 2008[122]	Enrolled only patients at very high risk of breast cancer
Ballesio et al. 2008[123]	Did not enroll the patient population of interest
Choudhury et al. 2008[124]	Did not enroll the patient population of interest
Ertas et al. 2008[125]	Did not report sufficient data to calculate the outcomes of interest
Hatakenaka et al. 2008[126]	Did not enroll the patient population of interest
Heusner et al. 2008[127]	Enrolled only patients diagnosed with breast cancer
Lieberman et al. 2008[128]	Enrolled only patients diagnosed with breast cancer
Okafuji et al. 2008[129]	Enrolled only patients at very high risk of breast cancer
Veltman et al. 2008[130]	Does not address any of the Key Questions
Di Nallo et al. 2007[131]	Did not report sufficient data to calculate the outcomes of interest
Grunwald 2007[132]	Reported MRI results for fewer than 50% of the enrolled patients
Iglesias et al. 2007[133]	Enrolled only patients with benign lesions
Klifa et al. 2007[134]	Retrospective study that did not enroll all or consecutive patients
Meinel et al. 2007[135]	The results of the MRI examination were used to decide which patients to enroll
Williams et al. 2007[136]	Enrolled only patients at very high risk of breast cancer
Bartella et al. 2006[137]	Enrolled only patients at very high risk of breast cancer
Goto et al. 2006[138]	The results of the MRI examination were used to decide which patients to enroll

Table D1. Studies of MRI that did not meet the inclusion criteria (continued)

Study	Reason for Exclusion
Liberman et al. 2006[139]	The results of the MRI examination were used to decide which patients to enroll
Penn et al. 2006[140]	Did not report sufficient data to calculate the outcomes of interest
Rubesova et al. 2006[141]	The results of the MRI examination were used to decide which patients to enroll
Schnall et al. 2006[142]	Did not report sufficient data to calculate the outcomes of interest
Deurloo et al. 2005[143]	The results of the MRI examination were used to decide which patients to enroll
Goethem et al. 2005[144]	Enrolled only patients with breast cancer
Howarth et al. 2005[145]	Enrolled only patients at very high risk of breast cancer
Lehman et al. 2005[146]	The results of the MRI examination were used to decide which patients to enroll
Meisamy et al. 2005[147]	Did not enroll the patient population of interest
Morakkabati-Spitz 2005[148]	Did not report sufficient data to calculate the outcomes of interest
Paakko et al. 2005[149]	Fewer than 85% of the lesions had their diagnoses verified with an acceptable reference standard
Sardanelli et al. 2005[150]	Enrolled only patients at very high risk of breast cancer
Takeda et al. 2005[151]	Enrolled only patients with breast cancer
Wright et al. 2005[152]	Enrolled only patients with breast cancer
Boetes et al. 2004[153]	Enrolled only women diagnosed with invasive lobular carcinoma
Brix et al. 2004[154]	Does not address any of the Key Questions
Chen et al. 2004[155]	Does not address any of the Key Questions
Fischer et al. 2004[156]	Verified diagnoses of only 76% of the enrolled patients using an acceptable reference standard
Gibbs et al. 2004[157]	Did not enroll the patient population of interest
Gibbs et al. 2004[158]	The results of the MRI examination were used to decide which patients to enroll
Rotaru et al. 2004[159]	Did not enroll the patient population of interest

Table D1. Studies of MRI that did not meet the inclusion criteria (continued)

Study	Reason for Exclusion
Schelfout et al. 2004[160]	Did not enroll the patient population of interest
Szabo et al. 2004[161]	The results of the MRI examination were used to decide which patients to enroll
Van Goethem et al. 2004[162]	Did not enroll the patient population of interest
Bagni et al. 2003[163]	Fewer than 85% of the lesions had their diagnoses verified with an acceptable reference standard
Gibbs and Turnbull 2003[164]	Did not report sufficient data to calculate the outcomes of interest
Knopp et al. 2003[165]	Fewer than 85% of the lesions had their diagnoses verified with an acceptable reference standard
LaTrenta et al. 2003[166]	Enrolled only patients at very high risk of breast cancer
Nakahara et al. 2003[167]	Did not enroll the patient population of interest
Szabo et al. 2003[168]	Exploratory study of experimental diagnostic methods
Baum et al. 2002[169]	Enrolled only patients at very high risk of breast cancer
Carriero et al. 2002[170]	Exploratory study of experimental diagnostic methods
Choi et al. 2002[171]	Exploratory study of experimental diagnostic methods
Del Maschio et al. 2002[172]	Discussion of the study Bazzocchi et al.[13]
Hlawatsch et al. 2002[173]	Did not enroll the patient population of interest
Liberman et al. 2002[174]	Enrolled only patients at very high risk of breast cancer
Nakahara et al. 2002[175]	Enrolled only patients diagnosed with breast cancer
Nunes et al. 2002[176]	Fewer than 85% of the lesions had their diagnoses verified with an acceptable reference standard
Reinikainen et al. 2002[177]	Did not enroll the patient population of interest
Teifke et al. 2002[178]	Only 48% of diagnoses were verified with an acceptable reference standard
Trecate et al. 2002[29]	Duplicate report of the same patients enrolled in Trecate et al.[29]
Alamo et al. 2001[179]	Did not enroll the patient population of interest

Table D1. Studies of MRI that did not meet the inclusion criteria (continued)

Study	Reason for Exclusion
Francis et al. 2001[180]	Enrolled only patients diagnosed with invasive lobular carcinoma
Hewwang-Kobrunner et al. 2001[181]	Exploratory study of experimental diagnostic methods
Khatri et al. 2001[182]	Excluded patients without evidence of a lesion at MRI
Lucht et al. 2001[183]	Exploratory study of experimental diagnostic methods
Malur et al. 2001[184]	Did not enroll the patient population of interest
Ando et al. 2000[185]	Only reported data for patients with MRI images suggestive of malignancy
Imbriaco et al. 2000[34]	Duplicate report of the same patients enrolled in Imbracio et al.[34]
Kinkel et al. 2000[186]	Retrospective study that did not enroll all or consecutive patients

MRI Magnetic resonance imaging

PET Exclusions

19 total excluded

Reasons for Exclusion

Did not enroll the patient population of interest: 13 studies

Study of experimental methods not clinically relevant: 3 studies

Did not report sufficient information to calculate the outcomes of interest: 1 study

Duplicate report of the same studies/patients: 2 studies

Table D2. Studies of PET that did not meet the inclusion criteria

Study	Reason
Caprio et al. 2010[187]	Duplicate report of data found in Imbracio et al.[34]
Heusner et al. 2008[127]	Did not study the population of interest. Enrolled only patients with confirmed breast cancer.
Zytoon et al. 2008[188]	Did not study the population of interest. Enrolled only patients with confirmed breast cancer.
Berg et al. 2006[189]	Did not study the population of interest. Forty-three percent (43%) of patients had a confirmed diagnosis of breast cancer and had undergone prior diagnostic biopsies.
Kumar et al. 2006[190]	Did not study the population of interest. Most of the enrolled patients had a confirmed diagnosis of breast cancer and had undergone prior diagnostic/excision biopsies.
Mavi et al. 2006[191]	Did not study the population of interest. Enrolled only patients with confirmed breast cancer.
Tatsumi et al. 2006[192]	Did not study the population of interest. Enrolled only patients with confirmed breast cancer.
Kumar et al. 2005[193]	Did not study the population of interest. Most enrolled patients had a confirmed diagnosis of breast cancer and had undergone prior diagnostic/excision biopsies
Roman et al. 2005[194]	Did not study the population of interest. Enrolled only patients with confirmed breast cancer.
Rosen et al. 2005[195]	Did not study the technology of interest-- experimental methods.
Inoue et al. 2004[196]	Did not study the population of interest. Enrolled only patients with confirmed breast cancer.
Marshall et al. 2004[197]	Did not study the population of interest. Enrolled only patients with confirmed breast cancer.
Smyczek-Gargya et al. 2004[198]	Did not study the population of interest. Enrolled only patients with confirmed breast cancer.
Levine et al. 2003[199]	Did not study the technology of interest-- experimental methods.

Table D2. Studies of PET that did not meet the inclusion criteria (continued)

Study	Reason
Buck et al. 2002[200]	Did not report any of the outcomes of interest.
Danforth et al. 2002[201]	Did not study the population of interest. Enrolled only patients with confirmed breast cancer.
Paul et al. 2002[202]	Did not study the population of interest. Enrolled only patients with confirmed breast cancer.
Avril et al. 2000[203]	Update, with additional patients, of Avril et al.,[203] which reports that it studied a mixed population of patients (some patients had a history of breast cancer).
Murthy et al. 2000[204]	Did not study the technology of interest-- experimental methods.

Scintimammography

18 total excluded

Reasons for Exclusion

Did not use the tracer of interest: 5 studies

Did not use an acceptable reference standard to verify diagnoses of at least 85% of the patients: 5 studies

Did not enroll the patient population of interest: 3 studies

Did not address any of the Key Questions: 3 studies

Study of experimental methods not clinically relevant: 2 studies

Table D3. Studies of scintimammography that did not meet the inclusion criteria

Study	Reason for Exclusion
Brem et al. 2010[205]	Did not address any of the Key Questions
Ozulker et al. 2010[206]	Did not use an acceptable reference standard
Brem et al. 2008[207]	Did not enroll the patient population of interest
Hruska et al. 2008[208]	Exploratory study of experimental diagnostic methods
Sharma et al. 2008[209]	99mTc-methionine tracer
Spanu et al. 2008[210]	Tc99m tetrofosmin tracer
Spanu et al. 2008[211]	Tc99m tetrofosmin tracer
Buchmann et al. 2007[43]	99mTechnetium-Perechnetate or Iodide
Spanu et al. 2007[212]	Tc99m tetrofosmin
Bekis et al. 2005[213]	Does not address any of the Key Questions
Brem et al. 2005[214]	Patients were at high-risk for breast cancer with normal mammograms/ clinical examination
Howarth et al. 2005[145]	26% of subjects had previous breast surgery/29% were positive for a family history of breast cancer
Kim et al. 2005[215]	Did not use an acceptable reference standard to verify diagnoses of at least 85% of the patients
Myslivecek et al. 2005[216]	Did not use an acceptable reference standard to verify diagnoses of at least 85% of the patients

Table D3. Studies of scintimammography that did not meet the inclusion criteria (continued)

Study	Reason for Exclusion
Papantoniou et al. 2005[217]	Does not address any of the Key Questions
Rhodes et al. 2005[218]	Prototype device
Tiling et al. 2005[219]	Did not use an acceptable reference standard to verify diagnoses of at least 85% of the patients
Kim et al. 2003[220]	Did not use an acceptable reference standard to verify diagnoses of at least 85% of the patients

Tc Technetium

Ultrasound Exclusions

153 total excluded

Reasons for Exclusion

Did not enroll the patient population of interest: 63 studies

Did not address any of the Key Questions: 27 studies

Did not use an acceptable reference standard to verify diagnoses of at least 85% of patients: 27 studies

Retrospective study that did not enroll all or consecutive patients: 11 studies

Did not report sufficient information to calculate the outcomes of interest: 8 studies

Study of experimental methods not clinically relevant: 9 studies

Duplicate reports of the same studies/patients: 3 articles

Reported data for fewer than 50% of the enrolled patients: 3 studies

Retrospective case-control design: 1 study

Did not report sufficient details of the US methods to permit analysis: 1 study

Table D4. Studies of ultrasound that did not meet the inclusion criteria

Study	Primary Reason for Exclusion
Caproni et al. 2010[221]	Did not use an acceptable reference standard
Dave et al. 2010[222]	Study of experimental technology
Cheng et al. 2010[223]	Study of experimental technology
Hongjia et al. 2010[224]	Did not enroll the patient population of interest
Moon et al. 2010[225]	Retrospective study that did not enroll all or consecutive patients
Moriguchi et al. 2010[226]	Did not use an acceptable reference standard
Sorelli et al. 2010[227]	Did not use an acceptable reference standard
Wang et al. 2010[228]	Study of experimental technology
Baek et al. 2009[229]	Retrospective study that did not enroll all or consecutive patients
Balleyguier et al. 2009[230]	Did not verify the diagnoses with an acceptable reference standard
Barr et al. 2009[231]	Does not address any of the Key Questions
Devolli-Disha et al. 2009[232]	Did not enroll the patient population of interest
Habib et al. 2009[47]	Did not report any details of the US methods
Kim et al. 2009[233]	Data was reported for fewer than 50% of the enrolled patients
Kotsianos-Hermle et al. 2009[234]	Did not enroll the patient population of interest
Masroor et al. 2009[235]	Did not enroll the patient population of interest
Masroor et al. 2009[236]	Did not enroll the patient population of interest
McCavert et al. 2009[237]	Did not verify the diagnoses with an acceptable reference standard
Su et al. 2009[238]	Retrospective study that did not enroll all or consecutive patients
Barnard et al. 2008[239]	Did not report sufficient data to calculate the outcomes of interest
Bilali et al. 2008[240]	Did not report sufficient data to calculate the outcomes of interest

Table D4. Studies of ultrasound that did not meet the inclusion criteria (continued)

Study	Primary Reason for Exclusion
Choudhury et al. 2008[124]	Did not enroll the patient population of interest
Forsberg et al. 2008[241]	Exploratory study of experimental diagnostic methods
Kang et al. 2008[242]	Data was reported for fewer than 50% of the enrolled patients
Kwak et al. 2008[243]	Data was reported for fewer than 50% of the enrolled patients
LeCarpentier et al. 2008[244]	Did not report sufficient data to calculate the outcomes of interest
Park et al. 2008[245]	Did not enroll the patient population of interest
Singh et al. 2008[246]	Did not verify the diagnoses with an acceptable reference standard
Wenkel et al. 2008[247]	Only 65% of diagnoses were verified with an acceptable reference standard
Abbattista et al. 2007[248]	Did not verify the diagnoses with an acceptable reference standard
Ballesio et al. 2007[249]	Did not enroll the patient population of interest
Ciatto and Houssami 2007[250]	Only enrolled patients diagnosed with carcinomas
Constantini et al. 2007[251]	Only 72% of diagnoses were verified with an acceptable reference standard
Graf et al. 2007[252]	Did not enroll the patient population of interest
Jiang et al. 2007[253]	Does not address any of the Key Questions
Osako et al. 2007[254]	Only enrolled patients diagnosed with carcinomas
Prasad and Houserkova 2007[255]	Only 10% of diagnoses were verified with an acceptable reference standard
Scaperrotta et al. 2007[256]	Did not report data for patients diagnosed as “clearly benign” on the diagnostic test of interest (US)
Thomas et al. 2007[257]	Did not enroll the patient population of interest
Constantini et al. 2006[258]	Duplicate report of data from Constantini et al.[251]
Del Frate et al. 2006[259]	Did not enroll the patient population of interest
Grunwald et al. 2006[260]	Did not enroll the patient population of interest

Table D4. Studies of ultrasound that did not meet the inclusion criteria (continued)

Study	Primary Reason for Exclusion
Malik et al. 2006[261]	Did not verify the diagnoses with an acceptable reference standard
Regner et al. 2006[262]	Does not address any of the Key Questions
Thomas et al. 2006[263]	Did not enroll the patient population of interest
Adepoju et al. 2005[264]	Did not enroll the patient population of interest
Baez et al. 2005[265]	Only 37% of diagnoses were verified with an acceptable reference standard
Berg 2005[266]	Did not enroll the patient population of interest
Cawson et al. 2005[267]	Enrolled only patients diagnosed with radial scars
Cha et al. 2005[268]	Did not report sufficient data to calculate the outcomes of interest
Cho et al. 2005[269]	Did not verify the diagnoses of lesions diagnosed on US as benign
Cho et al. 2005[269]	Only 40% of diagnoses were verified with an acceptable reference standard
Eljuga and Susac 2005[270]	Retrospective study that did not enroll all or consecutive patients
Nagashima et al. 2005[271]	Enrolled only patients diagnosed with ductal carcinoma in situ
Shahid et al. 2005[272]	Did not enroll the patient population of interest
Szabo et al. 2005[273]	Only 62.7% of diagnoses were verified with an acceptable reference standard
Tohno and Ueno 2005[274]	Only enrolled patients diagnosed with carcinomas
Tumyan et al. 2005[275]	Did not enroll the patient population of interest
Benson et al. 2004[276]	Mixed patient population; primarily a study of screening asymptomatic patients
Boetes et al. 2004[153]	Enrolled only women diagnosed with invasive lobular carcinoma
Chen et al. 2004[277]	Retrospective study that did not enroll all or consecutive patients
Cid et al. 2004[278]	Did not enroll the patient population of interest
Cura et al. 2004[279]	Exploratory study of experimental diagnostic methods

Table D4. Studies of ultrasound that did not meet the inclusion criteria (continued)

Study	Primary Reason for Exclusion
Drukker et al. 2004[280]	Does not address any of the Key Questions
Foxcroft et al. 2004[281]	Enrolled only women diagnosed with breast cancer
Georgian-Smith 2004[282]	Enrolled only patients diagnosed with hamartoma
Gibbs et al. 2004[157]	Did not enroll the patient population of interest
Murad and Bari 2004[283]	Only 70% of diagnoses were verified with an acceptable reference standard
Rotaru and Luciani 2004[159]	Only enrolled patients that were difficult to diagnose by US
Santamaria et al. 2004[284]	Enrolled only patients diagnosed with invasive carcinoma
Schelfout et al. 2004[160]	Did not enroll the patient population of interest
Sehgal et al. 2004[285]	Does not address any of the Key Questions
Selinko et al. 2004[286]	Enrolled only women diagnosed with invasive lobular carcinoma
Strano et al. 2004[287]	Does not address any of the Key Questions
Van Goethem et al. 2004[162]	Did not enroll the patient population of interest
Yang and Tse 2004[288]	Enrolled only women with DCIS
Zonderland et al. 2004[289]	Does not address any of the Key Questions
Chen et al. 2003[290]	Does not address any of the Key Questions
Chen et al. 2003[291]	Enrolled only women diagnosed with carcinoma
Drukker and Giger 2003[292]	Does not address any of the Key Questions
Flobbe et al. 2003[293]	Did not report sufficient data to calculate the outcomes of interest
Kazimierz et al. 2003[294]	Did not verify the diagnoses with an acceptable reference standard
Martinez et al. 2003[295]	Did not enroll the patient population of interest
Mesaki et al. 2003[296]	Only 40% of diagnoses were verified with an acceptable reference standard

Table D4. Studies of ultrasound that did not meet the inclusion criteria (continued)

Study	Primary Reason for Exclusion
Nakahara et al. 2003[167]	Did not enroll the patient population of interest
Park et al. 2003[297]	Does not address any of the Key Questions
Puglisi et al. 2003[298]	Enrolled only women with papillary breast lesions
Shetty et al. 2003[299]	Did not report sufficient data to calculate the outcomes of interest
Chen et al. 2002[300]	Did not enroll the patient population of interest
Chen et al. 2002[301]	Does not address any of the Key Questions
Germer et al. 2002[302]	Does not address any of the Key Questions
Gunhan-Bilgen et al. 2002[303]	Enrolled only women diagnosed with inflammatory carcinoma
Hlawatsch et al. 2002[173]	Did not enroll the patient population of interest
Krestan et al. 2002[304]	Does not address any of the Key Questions
Kuo et al. 2002[305]	Does not address any of the Key Questions
Kuo et al. 2002[306]	Does not address any of the Key Questions
Lee et al. 2002[307]	Retrospective study that did not enroll all or consecutive patients
Muttarak et al. 2002[308]	Enrolled only patients diagnosed with phyllodes tumors
Reinikainen et al. 2002[177]	Did not enroll the patient population of interest
Tan et al. 2002[309]	Enrolled only patients diagnosed with invasive lobular carcinoma
Taylor et al. 2002[310]	Did not report sufficient data to calculate the outcomes of interest
Teifke et al. 2002[178]	Only 48% of diagnoses were verified with an acceptable reference standard
Wang et al. 2002[311]	Duplicate report of data from Chen et al.[311]
Wang et al. 2002[312]	Duplicate report of data from Chen et al.[311]
Yilmaz et al. 2002[313]	Enrolled only women diagnosed with medullary carcinomas

Table D4. Studies of ultrasound that did not meet the inclusion criteria (continued)

Study	Primary Reason for Exclusion
Alamo et al. 2001[179]	Did not enroll the patient population of interest
Allen et al. 2001[314]	Does not address any of the Key Questions
Arger et al. 2001[315]	Does not address any of the Key Questions
Bhatti et al. 2001[316]	Did not enroll the patient population of interest
Chou et al. 2001[317]	Does not address any of the Key Questions
Cwikla et al. 2001[318]	Enrolled only patients diagnosed with multi-focal carcinomas
Francis et al. 2001[180]	Enrolled only patients diagnosed with invasive lobular carcinoma
Malur et al. 2001[184]	Did not enroll the patient population of interest
Ozdemir et al. 2001[319]	Did not report sufficient data to calculate the outcomes of interest
Rosen and Soo 2001[320]	Does not address any of the Key Questions
Soo et al. 2001[321]	Enrolled only patients with negative US findings who were later diagnosed with carcinomas
Whitehouse et al. 2001[322]	Does not address any of the Key Questions
Chaudhari et al. 2000[323]	Does not address any of the Key Questions
Choi et al. 2000[324]	Retrospective study that did not enroll all or consecutive patients
Evans and Lyons 2000[325]	Enrolled only patients diagnosed with small invasive lobular carcinomas
Klaus et al. 2000[326]	Only enrolled patients who underwent a biopsy because of findings on the diagnostic test of interest (ultrasound)
Madjar et al. 2000[327]	Does not address any of the Key Questions
Stuhrmann et al. 2000[328]	Did not enroll the patient population of interest
Thibault et al. 2000[329]	Only 31% of diagnoses were verified with an acceptable reference standard
Baker et al. 1999[330]	Does not address any of the Key Questions
Blohmer et al. 1999[331]	Exploratory study of experimental diagnostic methods

Table D4. Studies of ultrasound that did not meet the inclusion criteria (continued)

Study	Primary Reason for Exclusion
Chao et al. 1999[332]	Exploratory study of experimental diagnostic methods
Eltahir et al. 1999[333]	Retrospective study with only 33.7% of the consecutively enrolled patients examined by ultrasound
Huang et al. 1999[334]	Did not enroll the patient population of interest
Kook et al. 1999[335]	Retrospective study that did not enroll all or consecutive patients
Moss et al. 1999[336]	Only 33% of diagnoses were verified with an acceptable reference standard
Obwegeser et al. 1999[337]	Did not verify the diagnoses with an acceptable reference standard
Rahbar et al. 1999[338]	Does not address any of the Key Questions
Rotten et al. 1999[339]	Did not enroll the patient population of interest
Skaane 1999[340]	Enrolled only patients diagnosed with malignant tumors
Zonderland et al. 1999[341]	Did not enroll the patient population of interest
Brnic et al. 1998[342]	Only 13% of diagnoses were verified with an acceptable reference standard
Carson et al. 1998[343]	Does not address any of the Key Questions
Delorme et al. 1998[344]	Exploratory study of experimental diagnostic methods
Giuseppetti et al. 1998[345]	Only 70% of diagnoses were verified with an acceptable reference standard
Hayashi et al. 1998[346]	Retrospective study that did not enroll all or consecutive patients
Huber et al. 1998[347]	Does not address any of the Key Questions
Wright et al. 1998[348]	Did not report what reference standard, if any, was used to verify the diagnoses
Cabasares et al. 1997[349]	Did not enroll the patient population of interest
Jain et al. 1997[350]	Did not verify the diagnoses with an acceptable reference standard
Madjar et al. 1997[351]	Did not enroll the patient population of interest
Muller-Schimpfle et al. 1997[352]	Does not address any of the Key Questions

Table D4. Studies of ultrasound that did not meet the inclusion criteria (continued)

Study	Primary Reason for Exclusion
Raza and Baum 1997[353]	Only enrolled patients that were referred for biopsy on the basis of the US examinations
Schelling et al. 1997[354]	Exploratory study of experimental diagnostic methods
Skaane et al. 1997[355]	Retrospective case-control study
Yang et al. 1997[356]	Only enrolled patients diagnosed with carcinomas
Edde 1994[357]	Did not enroll the patient population of interest
Saitoh et al. 1994[358]	Retrospective study that did not enroll all or consecutive patients

US Ultrasound

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