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Review

The role of ultrasonography as an adjunct to mammography in the detection of breast cancer: a systematic review

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Abstract

The aim of this review was to summarise the diagnostic performance of ultrasonography as an adjunct to mammography in the detection of breast cancer and to identify clinical indications. A systematic review was performed of all publications in MEDLINE and EMBASE between 1990 and 2000 on the role of ultrasonography as an adjunct to mammography. 22 studies were included, showing a large variety of indications for ultrasonography and variations in the diagnostic performance of mammography and ultrasonography. There were six studies comparing a combined diagnosis of mammography and ultrasonography together with mammography alone, of which three studies had an increased sensitivity at the cost of a lower specificity. The methods of selecting the study population and interpretation of ultrasonography significantly influenced the diagnostic performance of mammography and ultrasonography relative to each other ($P=0.003$, $P=0.03$, respectively). Based on the studies reviewed, little evidence-based support was found to confirm the well recognised value of ultrasonography as an adjunct to mammography in the detection of breast cancer in clinical practice. Furthermore, no clinical indications for additional ultrasonography could be defined. The heterogeneity in the diagnostic performance in these studies may be explained by the methods of patient selection and ultrasonography interpretation, as well as by their poor quality.

Keywords: Breast cancer; Diagnostic imaging; Ultrasonography; Mammography; Systematic review; Diagnostic odds ratio

1. Introduction

Mammography is the basic imaging modality for the evaluation of patients with breast abnormalities [1]. In response to the diagnostic deficiency of mammography in the differentiation between cysts and solid tumours, other imaging modalities have been developed and optimised for their use in breast diagnosis, with the most relevant method being ultrasonography.

Additional breast ultrasonography can lower the number of indeterminate mammographical findings by downgrading them to benign findings or upgrading them to suspect malignant findings and is expected to increase the specificity of mammography and clinical examination [2].

Apart from differentiating cysts from solid masses, other indications for ultrasonography mentioned in the literature are: evaluation of palpable masses not visible in a radiographically dense breast, especially in young women, evaluation of masses not completely evaluated with mammography, inflammation, guidance for intervention procedures, evaluation of mammographic asymmetry and evaluation after augmentation mammoplasty and breast conservation surgery [1–5].

Long-term clinical experience has shown the value of ultrasonography in differentiating cysts from solid breast tumours, but its role in the differentiation between malignant and benign lesions is still under discussion [6–8]. Furthermore, the use of ultrasonography as a screening tool is discouraged because of unacceptably high false-negative and false-positive rates [4,9,10].

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The proportion of patients in whom breast ultrasonography is considered necessary is increasing. In most hospitals in The Netherlands, ultrasonography is currently being used as a supplement to mammography in approximately 40% of patients who are referred for breast imaging. This fact implies that in the remaining 60% of cases it is decided by the consultant that additional ultrasonography examination is not indicated.

This development raises questions as to what the available evidence is for the diagnostic value of ultrasonography as adjunct to mammography in the detection of breast cancer and what the indications are for referring patients who have had mammography to undergo ultrasonography. To answer these questions, a systematic review was performed of studies in which both mammography and ultrasonography were performed.

2. Methods

The MEDLINE, EMBASE and Cochrane databases were searched for all available publications between 1990 and 2000 describing the diagnostic performance of ultrasonographic examination as an adjunct to mammography in the detection of breast cancer. Titles and abstracts were screened for possible inclusion in the study and the references were screened for additional publications.

Studies were selected when meeting the following inclusion criteria: estimates on sensitivity and specificity of both mammography and ultrasonography had to be reported or had to be calculable, articles had to written in English, German, French, Italian or Dutch and the gold standard should be pathology preferably from histological needle biopsy or surgery, or follow-up of preferably 1 year or longer of patients with negative imaging results.

The selected papers were read separately by four reviewers. The following data were extracted when available: year of publication, selection of the study population, number of patients examined by ultrasonography, characteristics of patients in whom ultrasonography was performed, the definition of a positive imaging result, the way in which ultrasonography was interpreted (with or without prior knowledge of mammographical results), the mean or median age of the study population, the age distribution, the percentage of patients with dense breast parenchyma and the prevalence of malignant and benign lesions. Furthermore, estimates of sensitivity and specificity were recorded for mammography and ultrasonography separately and, when available, for the radiological diagnosis in which mammographic and ultrasonographic results were combined into one conclusion.

As a measure for diagnostic accuracy, the diagnostic odds ratio (DOR) was used. The DOR combines the sensitivity and specificity into one estimate and can be derived by dividing the odds of a positive test result among diseased persons by the odds of a positive test result among non-diseased persons ((sensitivity/(1−sens))*(specificity/(1−spec))).

In order to obtain a symmetrical distribution, the natural logarithm of the DOR was calculated for mammography and ultrasonography in each study. The difference between the lnDOR for ultrasonography and mammography (lnDORus−lnDORmam) was taken as the diagnostic performance of mammography and ultrasonography relative to each other.

The influence of the methods of selecting the study population and interpreting ultrasonographic results on the diagnostic performance was evaluated by non-parametric testing.

Three groups of studies were distinguished based on the way in which the study population was selected. Studies classified in group 1 included patients who were referred for breast imaging because of palpable breast lumps or other abnormal findings on clinical examination. Studies in group 2 included patients who underwent ultrasonography because of suspicious lesions on mammography or clinical examination, and studies in group 3 included only patients who were referred for biopsy or surgery.

Within these three groups, a further distinction was made between studies in which ultrasonographic images were interpreted independently or blinded from mammography results and studies in which ultrasonographic interpretation was done with prior knowledge of the mammography results.

The diagnosis from ultrasonographic interpretation with prior knowledge of mammography differs from the combined radiological diagnosis in that mammography results facilitated the detection of abnormalities by ultrasonography, but the diagnosis was still based on the ultrasonographic results.

In order to identify subgroups of patients with the highest diagnostic yield for ultrasonography, ultrasonographic performance was studied for different indications. Finally, the impact of the prevalence of breast cancer, mean or median age of the population, the size of the study population and the year of publication on the diagnostic performance of mammography and ultrasonography relative to each other was studied.

Analyses were performed for all patients in whom both mammography and ultrasonography were performed.

3. Results

The literature search identified 164 publications in MEDLINE, 51 publications in EMBASE and no hits in the Cochrane database. MEDLINE and EMBASE hits

partly overlapped. Screening all titles and abstracts resulted in 47 suitable papers, while screening of the references added another 16 papers. Thus, a total of 63 publications were collected, read and tested on the inclusion criteria. Twenty-one papers were found suitable for inclusion in the review. Reasons for exclusion ($n=42$) are shown in Table 1. Eighteen studies were excluded as they investigated the role of ultrasonography in breast cancer-positive patients [1,11–27]. From these studies, only numbers of true positive- and false-negative results can be derived. The sensitivity of mammography and ultrasonography in these studies ranged from 66 to 95% and 68 to 100%, respectively. One publication was divided into two studies as data were given for two separate study centres [28]. The review therefore included 22 studies.

The median study size was 213 (range 37–2079 patients). The median prevalence of breast cancer in these populations was 45% (range 5.5–72.2%). The studies included were mostly European, with nationalities of the authors being British ($n=6$), German ($n=4$), Dutch ($n=3$), Italian ($n=3$), Norwegian ($n=1$), Finnish ($n=1$) and Turkish ($n=1$). The non-European studies were from Australia ($n=1$), Japan ($n=1$) and China ($n=1$).

The study size, prevalence of breast cancer, mean or median age of the study population and the diagnostic performance of mammography and ultrasonography in these studies are shown in Table 2. In order to study the diagnostic role of ultrasonography, most studies compared the sensitivity and specificity of ultrasonography (range 49–100% and 29–100%, respectively) with those for mammography (range 57–97% and 36–97%, respectively). Six studies compared the results of a combined diagnosis of mammography and ultrasonography with the results of mammography alone [29–34]. In all six studies, the sensitivity increased by using ultrasonography as an adjunct to mammography. However, in three of the six studies, the specificity decreased.

As shown in Table 2, five studies were allocated to group 1, four studies to group 2 and 13 studies to group 3. The influence of the selection of the study population on the diagnostic performance of mammography relative to ultrasonography was statistically significant ($P=0.003$), suggesting a higher relative diagnostic performance in patients selected through clinical examination, which is illustrated in Fig. 1.

A difference between lnDORus and lnDORmam larger than 0 indicates that ultrasonography performed better than mammography, whereas a difference below 0 indicates that mammography performed better. In more than half of the studies, the diagnostic performance of ultrasonography was better than for mammography.

Moreover, Fig. 1 distinguishes between studies in which ultrasonography was interpreted with prior knowledge of mammography results ($n=10$) and studies in which ultrasonography was interpreted independently ($n=11$). In one study, only a final diagnosis of ultrasonography and mammography together was given [30]. Ultrasonography performed better than mammography in four of the 10 studies in which prior knowledge of mammography results was available when interpreting ultrasonography [29,35–37] and in eight of 11 studies in which ultrasonography was interpreted independently [28,32,38–42]. These results indicate a higher relative diagnostic performance when no prior knowledge of mammography was available ($P=0.03$).

A large variety of indications for breast ultrasonography was found, which made it impossible to study the diagnostic performance of mammography and ultrasonography for different subgroups of patients. In some studies on patients with palpable breast lesions, ultrasonography was performed in all patients [34,38–41,43]. In one study, the presence of palpable lesions was an indication for ultrasonography [30]. Other indications were patients' age <35 years [32,44,45] or <25 years [35], non-conclusive abnormalities [30,35,45] or dense breast tissue [32] on mammography. In two studies, ultrasonography was performed only in the last part of the study [29,46] and one study failed to specify the indications for ultrasonography at all [44].

Table 1
Reasons for exclusion of publications ($n=42$)

Reason for exclusion	No. of publications	Reference
Only data on breast cancer-positive patients were reported	18	[1,11–27]
Missing data for completion of 2×2 tables	5	[49–53]
No comparison of ultrasonographic results with mammography results	5	[6,54–57]
Only data on ultrasonographic results of normal mammograms were reported	3	[58–60]
Only the combined radiological diagnosis was given	2	[61,62]
Only data on areas under curves of ROC curves were given	2	[63,64]
Papers could not be obtained from libraries in The Netherlands	2	[65,66]
An automated ultrasonography technique was used	1	[67]
Role of ultrasonography in distinction between malignant and benign lesions studied	1	[7]
Only male patients were included	1	[68]
Study population was identical with another included study	1	[69]
Mammography was used as a gold standard for detection of microcalcifications	1	[70]

Finally, a reverse correlation was found between the mean or median age of the study population, as well as for the prevalence of breast cancer, with the diagnostic performance of mammography and ultrasonography relative to each other (Kendall's tau correlation, $P = 0.01$ and $P = 0.1$, respectively).

The number of included patients or the year of publication did not influence the diagnostic performance ($P = 0.2$ and $P = 0.4$, respectively).

4. Discussion

This review shows that the indications for ultrasonography as an adjunct to mammography vary among the different studies and that evidence for the additional diagnostic value of ultrasonography as an adjunct to mammography is almost lacking in the available literature.

Initially, the aim of this study was to perform a meta-analysis on the diagnostic performance of ultrasonography as an adjunct to mammography in the detection of breast cancer but, because of the lack of required data, a systematic literature review was conducted instead.

We showed that the method of selecting the study population strongly influenced the performance of mammography and ultrasonography relative to each other. The majority of studies in this review included patients who proceeded to biopsy or surgery (group 3) as, for these patients, the results from a gold standard was readily available. However, in daily practice, patients will be selected for ultrasonography on the basis of results of clinical and mammographic examination and

Table 2
Overview of the study size, prevalence of breast cancer, mean or median age and diagnostic performance of mammography (MAM) and ultrasonography (US) in the 22 studies included in this review

Study	Patients (n)[a]	Prevalence (%)	Age[b]	MAM			US[c]			MAM + US[d]		
				sens (%)	spec (%)	DOR	sens (%)	spec (%)	DOR	sens (%)	spec (%)	DOR
Group 1: selection study population based on clinical examination												
US interpreted with knowledge of prior mammography												
Hardy [29]	143	46.2	50 (25–80)	86	78	22.4	96	84	113.7	100	76	∞
US performance independently/blinded												
Lister [42]	205	6.8	40 (25–85)	57	93	17.3	93	97	400.8	–	–	–
Perre [41]	204	56.4	49	91	75	32	97	91	378	–	–	–
Van Oord [40]	232	32.8	48	87	76	21.2	99	67	154.4	–	–	–
Yang [39]	408	16.4	37 (13–85)	92	94	169.6	97	97	962.9	–	–	–
Group 2: selection study population based on clinical examination and mammography												
US interpreted with knowledge of prior mammography												
Catarzi [71]	400	64.5	52	94	36	8.3	49	52	1.1	–	–	–
Ciatto [36]	2079	12.5	48 (17–93)	80	94	57.6	68	98	88.2	–	–	–
Eltahir [45]	1066	5.5	– (15–91)	93	97	401.6	89	97	300	–	–	–
Zonderland [30]	1103	24.7	50	86	89	50.7	–	–	–	95	92	223.5
Group 3: selection study population based on referral for pathology												
US interpreted with knowledge of prior mammography												
Gozzi [37]	221	65.2	–	88	56	9.4	95	41	14.2	–	–	–
Houssami [35]	391	37.6	–	78	80	14.3	88	83	36.1	–	–	–
Muller-Schimpfle [72]	98	60.2	53 (15–75)	83	92	58.8	76	79	12.5	–	–	–
Özdemir [31]	72	72.2	50 (28–77)	92	65	22.3	84	65	10.2	100	85	∞
Purasiri [46]	603	46.9	–	88	73	19.8	70	79	8.8	–	–	–
Roche [44]	306	49.0	–	92	78	40.8	82	79	17.1	–	–	–
US interpreted independently/blinded												
Moss [32]	368	44.0	–	79	79	14.7	89	72	20.1	94	64	29
Reinikanen [43]	63	61.9	48 (18–93)	97	54	44.9	97	54	44.9	–	–	–
Ruhland [33]	199	19.6	54 (29–85)	87	40	4.5	87	29	2.7	100	9	∞
Skaane [34]	200	50.0	–	83	96	117.2	96	73	64.9	87	97	216.4
Yoshihara [38]	39	46.2	45	83	76	16	94	80	72.3	–	–	–
Zuna-b [28]	40	37.5	–	60	74	4.3	100	100	∞	–	–	–
Zuna-a [28]	37	32.4	–	89	91	84	92	88	80.7	–	–	–

sens, sensitivity; spec, specificity; DOR, diagnostic odds ratio.

[a] Number of patients in the study who underwent both test modalities.

[b] Mean (median age was reported when mean age was not available) + range.

[c] Results of ultrasonography alone (performance with or without knowledge of mammography).

[d] Combined radiological diagnosis from results of mammography + ultrasonography together.

ultrasonography will be interpreted with the full knowledge of these results.

The role of ultrasonography as an adjunct to mammography in the detection of breast cancer is therefore studied most accurately with reference to daily practice, by comparing the accuracy of a diagnosis based on mammography alone with the accuracy of a diagnosis based on the use of mammography and ultrasonography as integrated diagnostic modalities within consecutive patients who are selected for ultrasonography based on clinical and mammographic results.

In this review, six studies compared a combined radiological diagnosis of mammography and ultrasonography together with mammography results alone. The acquisition of the combined radiological diagnosis was poorly described or not given at all, although it may be assumed that a positive radiological diagnosis was reached when either mammography or ultrasonography reported a positive diagnosis. The results of these studies seem to conform with the expectation that combining ultrasonography with mammography results in a higher sensitivity, but in three of the six studies the increase in sensitivity was reached at the expense of a substantial decrease in specificity. In only one of these six studies were patients selected through mammographic results [30]. Within this population tested with both modalities, the sensitivity increased significantly (86 and 95%, respectively), while the specificity increased as well (89% versus 92%, respectively).

We also showed that the method of interpreting the ultrasonographic images significantly influenced the performance of mammography and ultrasonography relative to each other. Surprisingly, in six of the 10 studies in which prior knowledge of mammography was available when interpreting ultrasonography, the diagnostic performance of ultrasonography did not exceed the performance of mammography. We have no acceptable explanation for this finding, other than that ultrasonograph can have false-negative and false-positive results. Furthermore, the operator dependence of the technique and the quality of equipment may have an effect on these results.

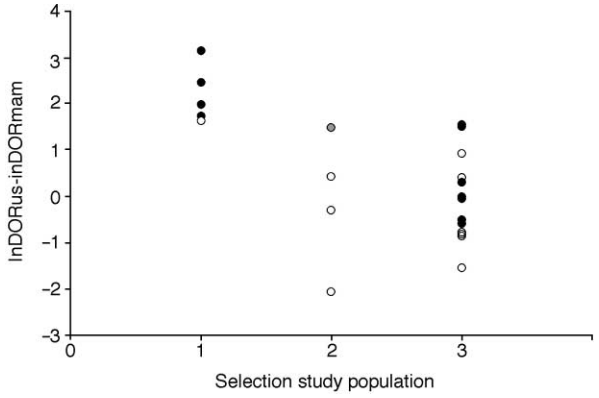

Fig. 1. Diagnostic performance of ultrasonography relative to mammography (lnDORus−lnDORmam) in studies in the review, according to the selection of study population and procedures of ultrasonographic interpretation (group 1 = selection patients based on clinical examination, group 2 = selection of patients based on mammography, group 3 = selection of patients based on pathology; ● = ultrasonography performed without knowledge of prior mammography, ○ = ultrasonography performed with knowledge of prior mammography and clinical examination, ◍ = ultrasonography results only as combined radiological diagnosis with mammography).

The influence of methodology on the diagnostic performance emphasises that one should be cautious in pooling the results of all studies. This is frequently done by employing meta-analytical techniques and may introduce bias in the overall results.

In many papers, basic information on the study procedures and the study population was insufficient or missing, as a result of which it remains unclear to which category of patients the results can be applied. This failing made it very difficult to extract the required data from the papers. As an example, nine studies in this review failed to report the mean age of the study population [28,32,34,35,37,44–47], while the remaining studies reported only mean or median values, the range or the age distribution of the study population. A detailed description of the study population is required to be able to compare the results of studies in a sensible way [30].

The frequent use of breast ultrasonography has had a significant impact on healthcare delivery because it has greatly reduced the number of cytological and histological biopsies performed for benign breast cysts [5]. However, routine application of ultrasonography may generate many unnecessary biopsies [48]. Furthermore, it has a large impact on the time schedule of breast imaging clinics, as it is a time-consuming and operator-dependent technique.

The application of ultrasonography as an adjunct to mammography in the differentiation between cysts and solid breast tumours and in the evaluation of palpable masses in young women is well recognised in clinical practice based on long-term clinical experience.

Meanwhile, ultrasonography is being used in a number of clinical situations in which no efficacy has been demonstrated, such as the routine evaluation of the postoperative breast and asymmetric breast density. Whereas breast ultrasonography causes no harm to the patient, its cost and lack of clinical benefit for the patient make the use of ultrasonography in these situations unwise [10].

Unfortunately, based on this review no subgroups of patients could be selected with the highest or lowest diagnostic yield for ultrasonography. However, such information is necessary to advise in restricting the application of ultrasonography to specific subgroups of patients. Deeming the use of ultrasonography in the remaining patient groups redundant would significantly

reduce claims on healthcare resources (time, personnel, appliances). Therefore, further research is needed in consecutive patients to identify the subgroups of patients in which the highest diagnostic yield from ultrasonography would be obtained.

Concluding, based on the studies reviewed, little evidence-based support was found to confirm the well recognised value of ultrasonography as an adjunct to mammography in the detection of breast cancer in clinical practice. Furthermore, no clinical indications for additional ultrasonography could be defined. The heterogeneity in the diagnostic performance in these studies may be explained by the methods of patient selection and ultrasonography interpretation, as well as by their poor quality.

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