REVIEW ARTICLE

Imaging Studies for the Early Detection of Breast Cancer

Sylvia H. Heywang-Köbrunner, Ingrid Schreer, Walter Heindel, Alexander Katalinic

SUMMARY

Introduction: The effectiveness of mammographic screening has been proven at evidence level 1A. Mammography offers the best ratio of benefits to side effects of any screening method tested to date. In this literature review, we ask whether early detection might be improved still further by combining mammography with other imaging modalities.

Methods: The authors performed a selective literature search for combined key words in the Medline and Cochrane Library databases from 1/2000 to 11/2007, screened all titles, and evaluated the full text of all original articles. We selected articles for further analysis according to systematic criteria (minimum numbers, avoidance of overlap) and also considered published guidelines.

Results: No screening studies of comparable size to those for mammography are available for ultrasound or MRI. Smaller studies have indicated that the use of these two modalities might lead to the detection of additional cancers in selected subgroups. For mass screening an increase in the detection rate of 10% to 15% might become possible. This increase would probably be associated with a tripling of the breast biopsy rate, compared to mammography alone. The number of indeterminate cases in which short-term follow-up (i.e., at 6 months) would be recommended would increase roughly tenfold with MRI, and to an unknown extent with ultrasound. The related quality-assurance issues remain to be addressed.

Discussion: Randomized controlled studies are needed for a realistic assessment of the achievable benefits and unavoidable side effects of combined screening. For women whose risk of breast cancer is not elevated, mammography remains the standard screening method.

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The effects and adverse effects of mammography screening have been comprehensively studied. It is estimated that by screening women aged 50 to 69 at two-year intervals (over a period of 20 years) 2 to 7 of 15 expected breast cancer deaths can be avoided per 1000 participants (e1–e6). Further, early detection enables less invasive treatment – if standardized methods are used – e.g., sentinel node removal rather than complete axillary lymph node removal or avoiding aggressive chemotherapy, as well as better cosmetic results and a higher rate of breast conservation (e5, e7–e10).

For population based early detection, however, many investigations are required that also include healthy women. Furthermore, screening investigations may be potentially harmful. The balance of effects and adverse effects is still under discussion (e1–e6, e11–13).

To achieve the desired results in the safest way and to simultaneously minimize undesirable side effects, mammography screening in Europe has been combined with a comprehensive quality assurance program (e14, e15). For mammography screening, it has been proved that the radiation dose applied is justified by the benefits (e16). In every early detection measure that is conducted across large population groups, there are clinical side effects but also false positive diagnoses (false alarms), overdiagnoses, and overtreatment.

False positive findings are unavoidable in almost all investigations. Their number will have to be kept low especially in early detection examinations of asymptomatic women, since less than 1% of patients have breast cancer at this point. The time span from reporting a positive finding to concluding the investigation should be as short as possible to ensure that the patient's mind can be put at rest. The current screening program monitors the implementation of this regulation (e14, e15). Psycho-oncology studies have shown that especially short term stress situations whose outcome is good are well tolerated and do not affect the women negatively in the long term (e17). Especially in early detection screening, however, re-investigating unclear findings within 4 to 6 months, possibly several times, should be avoided so as to keep the affected woman's mind at rest. To make the diagnostic procedure as minimally invasive as possible – and to avoid unnecessary surgical procedures – percutaneous biopsy methods such as core needle biopsy or vacuum biopsy are used (e18).

TABLE 1

Studies of ultrasonography in asymptomatic women (n >1000)

Authors	Number of investigations	Cancers/ 1000 investigations	% positive findings by ultrasonography only	% of additional cytological/histological investigations*1	Proportion of positive biopsies among needle biopsies (%)
Buchberger et al. (1)	8103	4.1	5	3.3	14
Crystal et al. (2)*2	1199	4.6	6	1.8	25
Corsetti et al. (3)*2	6449	4.4	N/A	7.5	3
Honjo S et al. (4)*3	3453	0.9	N/A	N/A	N/A
Kaplan (5)	1862	2.6	13.4	5.3	10.5
Kolb et al. (6)	13 547	2.7	N/A	2.6	10.35
Leconte et al. (7)*3	4236	3.7	N/A	N/A	N/A
Berg et al. (8)	2637	4.2	8.8	5.7	11.2

Selection, see chapter on methods

*1 No explicit data about open biopsies; *2 No increased risk ("mammographically dense breast");

*3 No exact data about the patient cohort; N/A: not available

The term overdiagnosis describes a situation whereby in subsequent screening rounds – after the prevalence round – more breast cancers are detected than are expected. A proportion of these would have not resulted in death as the woman would have died from other causes beforehand. However, the patient undergoes breast cancer treatment with all its consequences. These correctly diagnosed breast tumors from whose discovery no benefit results for the patient in terms of reducing mortality, are called "overdiagnoses." Their number can be only statistically estimated. The literature reports widely divergent data; the scientific evidence is scant. Overdiagnoses can be assumed to apply for 10% to 20% of breast cancers detected during screening – mainly slow growing cancers in elderly women and particularly carcinoma in situ (e19, e20). However, as it cannot be predicted which woman will die from another cause before the breast cancer is potentially fatal, all breast cancers have to be treated appropriately. In order to save lives, overdiagnosis and overtreatment are unavoidable.

The term interval carcinoma describes all tumors that are detected in participants between screening rounds. They can occur even with the most stringent quality assurance measures in place. At the time of diagnosis, 10% to 15% of breast cancers are probably not visible on the mammogram (e21–e23). The total proportion of interval carcinomas in a mammography screening program at two-year intervals is (relative to the incident cancers) up to over 40%. The number of interval carcinomas depends on:

- The sensitivity and quality assurance of the investigative method
- The screening interval
- The frequency of use and sensitivity of the methods possibly used during the screening interval
- Tumor biology and growth speed (e15, e23).

For this reason, the recommendation to women is to attend the complimentary check-up examinations at their

gynecologist following the German health insurance plan. The invited women are further informed of the fact that there are breast cancers that are invisible on a mammogram and they are instructed to seek their gynecologist's advice if clinical changes develop. As previously, in patients with clinical abnormalities and increased risk the doctor can instigate or conduct further investigations.

The fact that effective early detection is possible in mammography screening, while the adverse effect rate is minimized, is amply shown in the literature (e1, e3–5). We analyze whether the results so far could be improved further – e.g., by using additional imaging techniques – and which potential adverse effects will need to be taken into consideration.

Material and methods

We conducted a selective literature search (1/2000 to 11/2007) in Medline and the Cochrane Library for the use of ultrasonography in screening, using the following search terms: "ultrasound AND breast screening," "breast ultrasound AND asymptomatic" (>5300 publications in total). We evaluated all titles, 28 publications met our criteria and were analyzed (1–8, e24–42). A current study from the German Agency for Quality in Medicine (Ärztliches Zentrum für Qualitätssicherung in der Medizin, www.aezq.de) also deals with the topic of ultrasonography for the early detection of breast cancer (e20).

We included original research articles of prospective cohort studies (table 1) if they described more than 1000 ultrasound investigations of asymptomatic women older than 40 with no findings on mammography screening and if they described more than 5 cancer findings (1–8).

For magnetic resonance imaging we searched from the year 2000 for:

- "breast AND MRI screening"
- "breast MRI AND asymptomatic"
- "breast MRI AND genetic"

TABLE 2

Detection and sensitivity of MRI plus conventional diagnostic tests (mammography, ultrasound guided where needed) versus conventional diagnostic tests alone in women at high risk

Authors	Number of MRI scans	Detected cancers	Detection rate per 1000 investigations	Sensitivity of all methods (%)	Sensitivity of MRI (%)	Sensitivity of Mx (+US)* ¹ (%)
Hagen et al. (9)* ²	867	25	29	95	86	52
Kriege et al. (10)* ²	4169	51	12	90	79	33
Kuhl et al. (11)* ²	1542	43	28	93	91	49* ¹
Leach et al. (12)* ²	1881	35	19	94	77	40
Sardanelli et al. (13)* ²	377	18	48	100	94	66* ¹
Warner und Causer (14)* ²	457	22	48	94	77	36* ¹
Lehman et al. (15)* ³	962	33	34	NA	91	NA

Selection, see chapter on methods

*¹ Studies with ultrasound; *² Medium to high familial risk; *³ Positive according to patient's own history (MRI of contralateral breast); Mx, mammography; US, ultrasound; N/A, not applicable (selection of asymptomatic women at high risk with inconspicuous mammography 3 to 6 months before MRI)

- "breast MRI AND risk"
- "breast MRI AND contralateral".

We complemented our findings by hand search (identifying more than 3500 articles). Evaluating the titles yielded 33 publications that met our criteria (9–15, e34, e41, e43–e66). In the absence of larger sample sizes, we included prospective cohort studies with >300 participants, in which more than 5 cases of cancer were diagnosed (tables 2 and 3). However, these were conducted in (high) risk cohorts that had a much higher rate of cancer findings (9–15).

We did not include studies with fewer than 5 cancers because of a high degree of statistical uncertainty for small numbers.

In multiple publications of the same authors we selected the most recent publication, except where no overlap of the populations was to be expected. Current guidelines were included (e10, e67–e70), as was a recently published meta-analysis (16). No randomized studies are available for ultrasonography nor for MRI.

Results

There are no studies of methods other than mammography screening (figure 1) in the early detection of breast cancer.

We investigated whether additional methods would result in the early detection of more cancers and which adverse effects may be expected. Table 4 provides an overview of the undesirable side effects associated with mammography screening (e14, e15).

Ultrasonography

It has been known for a long time that ultrasonography complements mammography in patients with dense glandular tissues and in differentiating foci (figure 2). Ultrasonography is therefore an essential component of quality assured imaging assessment of screen-detected abnormalities.

Because of initially unsatisfactory results and the still difficult nationwide coverage of quality assurance (differences between technical equipment, dependence on examiner's technique), ultrasonography has thus far not

TABLE 3

Specificity and assessment rates by additional use of MRI in women at high risk

Authors	Specificity of MRI	Recall rate	Needle biopsies and open biopsies after positive MRI (relative to all MRI scans [%])	Recommendation of early controls after MRI (%)
Hagen et al. (9)* ²	N/A	N/A	N/A	N/A
Kriege et al. (10)* ²	90%* ¹	N/A	N/A	N/A
Kuhl et al. (11)* ²	(97%)* ⁴	N/A	5	11.5
Leach et al. (12)* ²	81%	11 %	6	7.3
Sardanelli et al. (13)* ²	N/A	N/A	7	N/A
Warner und Causer (14)* ²	(95%)* ⁴	N/A	11	13.0
Lehman et al. (15)* ³	(88%)* ⁴	N/A	12.5	N/A

*¹ Calculated according to data from the publication; *² medium to high familial risk;

*³ Positive according to patient's own history (MRI of contralateral breast); *⁴ Does not include the proportion of women with additional further imaging or short term controls; N/A, not available

Figure 1: Mammographically detected ductal carcinoma in situ 8 mm Stage pT1bN0 (craniocaudal mammography scan). The cancer is visible as a non-specific focus without microcalcifications. It is easily visible because it is surrounded by fatty tissues. Another 40% to 50% of early cancers are detectable thanks to microcalcifications. These are visible even in dense glandular tissue. Mass lesions, however, may be concealed in dense tissues.

been used in mass screening programs worldwide. There are no randomized studies of the efficacy of ultrasonography (accuracy, reproducibility, influence on mortality reduction, assessment rate), nor are there systematic data about ultrasonography in asymptomatic women not at risk.

More recent studies (1–8) enable an estimate of the potential and the limitations of ultrasonography in the context of screening. They were conducted in asymptomatic women that did not match the age and risk profile of usual mass screening of women beyond age 50.

These studies (table 1) show that it is possible to use ultrasonography in addition to mammography to detect additional cancers. The detection rates from these studies cannot be transferred to the screening situation owing to other selection criteria.

The extent of the increase in detection rate that can be achieved by using ultrasonography in the screening cohort – e.g., in women with dense glandular tissue – cannot be estimated with any degree of certainty. It would be desirable to achieve an increase in the detection rate of 10% to 15% by using ultrasound as complementary modality, with a corresponding reduction of the rate in interval carcinomas (e21, e22). The use of any complementary method in addition to mammography means that additional false positive findings are to be expected.

The mean proportion of women who received additional biopsies as a result of ultrasonography accompanying mammography screening was at least 3%. This rate varies widely between several studies, however (table 1). The proportion of histological investigations can be assumed to triple if ultrasonography is used additionally to mammography. After 10 years, 250 in 1000 women screened in this way may have experienced a histological test with a positive result. The corresponding rate for mammography alone is 50–75/1000 women for the same time period. Exact data for additional 6 months follow-up examinations are mostly lacking. A current US multicenter study (8) has reported a detection rate of 4.2/1000 cancers by additional ultrasonography for a mixed cohort (at risk and at high risk). However, in 10.4% of women, false positive biopsies were ordered and in others, 10.8% short term control investigations.

According to what is known today, it may be assumed that systematic additional use of ultrasonography (also at two-year intervals) in women with dense glandular tissue will lead to the detection of more cancers. Simultaneously, the proportion of histological investigations and control investigations brought forward may also be assumed to rise notably. The efficacy of quality assurance and reproducibility of the results for regular widespread use of breast ultrasound in screening are thus far not known.

MR-mammography (MRM)

Magnetic resonance imaging (MRI) or magnetic resonance mammography (MRM) of the breast is free of radiation. For breast cancer detection the intravenous application of paramagnetic contrast agent is mandatory. The investigation takes a minimum of 20 minutes and, including contrast medium, films, etc. costs more than five times the amount incurred by screening mammography (including overhead for quality assurance) (e71).

Since contrast-enhanced MRI of the breast was first described by the authors in 1985 (e72), MRM has been found to be the most sensitive method for detecting breast cancer (17–19). As shown by a multicenter study of histological investigations of thin sections of mastectomy specimens (18), ductal carcinoma in situ (DCIS)

TABLE 4

Adverse effects of mammography screening (two-year intervals)

Adverse effects	Per round per 1000 women	Per 10 years per 1000 women	Remarks
Recall rate	< 50/1000	<250 in 1000 women or 5000 investigations	Additional imaging, ultrasonography, further tests if required
of which needle biopsies (ultrasound punch biopsy, stereotactic vacuum biopsy)	15–20/1000	75–100 in 1000 women or 5000 screening investigations	Needle biopsies done on an outpatient basis under local anesthesia
of which open biopsies without confirmation of cancer	1–2/1000	5–10 in 1000 women or 5000 screening investigations	The very low rate is possible thanks to the use of modern minimally invasive needle biopsies

According to EU guidelines and German regulations (e14, e15)

can partly be visualized by mammography, partly by MRI (*figure 3*). Some earlier studies (20, e73, e74) and a current study from Bonn (21) have reported that high grade DCIS is often more easily detected by MRI than low grade DCIS. Other working groups have not confirmed the finding that MRI shows mainly high grade DCIS and mammography mainly low grade DCIS (20, e73, e74).

The detection of all DCIS has only a small influence on mortality since a substantial proportion of DCIS is not life-threatening. However, DCIS may have a high prevalence (e5, 22). Because of the risk of increased overdiagnoses and overtreatment, the general detection of DCIS can thus not be the aim of systematic screening.

In order for MRI to be used systematically in screening asymptomatic unselected women, a confirmed effect on the reduction of mortality rates would be required. Such studies – especially randomized studies – are lacking.

Larger studies exist of the use of MRI in asymptomatic women with clearly increased risk. MRI, mammography, and sometimes ultrasonography are used annually in these studies.

These studies (*tables 2 and 3*) include more than 10 000 investigations in total (9–15). The prevalence was notably higher owing to selection, and more than 220 cancers were found on imaging. All studies show that in high risk women, additional MRI increased the sensitivity substantially.

In these special women at high risk cohorts in the context of intensive surveillance programs (annual investigations using all methods), breast cancers were detected at earlier stages (23). A reduction in mortality is likely. Whether all women or only certain women at high risk will benefit from additional MRI, and whether these results are transferable to groups at lower risk is not clear (24).

A large multicenter study of breast cancer patients (15) confirmed what was already known (17, e54, e77–79), that MRI can detect additional cancers in the contralateral breast (12 carcinomas in situ and 18 small invasive cancers in 969 women). The question whether the detection of secondary tumors results in improved survival cannot be answered. There are no data on the value of MRI in unselected asymptomatic women. The Study from Bonn does not allow conclusions for screening due to its very heterogeneous cohort of patients.

The most important adverse effect of MRI are false positive findings. After additional MRI screening alone, biopsies are ordered in 0.2% to 9% of all screened women (an average of >4%) that yield a positive result (*table 3*). This rate is two to three times that of mammography screening.

Changes detected on MRI alone must be investigated further using MRI-guided biopsy and histological analysis, a delicate and time consuming procedure which places additional strain on the patient. Special equipment and enormous experience are indispensable for MRI guided percutaneous biopsies, but these are available in only a few institutions in Germany.

Our own results from the first multicenter study have shown that the rate of malignancies found in MRI guided biopsies varies clearly with a woman's pre-existing risk (25, e80).

What is mostly not discussed is the rate of findings for which short-term follow-up (after 3 to 6 months) is recommended after MRI. In MRI screening of women at high risk, short-term follow-up may be recommended in 7% to 13% of cases, almost 10 times the rate of that in mammography screening. Also, the reliability of such MR diagnoses called “probably benign” appears to be lower than that of “probably benign” mammography diagnoses (e81–83). The reported false positive rate (biopsies plus short-term follow-ups) for MRI screening is 11% to 21%; if recommendations for additional imaging assessment after MRI are counted as well, the reported false positive rate increases up to 20% to 27% (16). Some authors have reported specificities of over 95% (*tables 2 and 3*) (11, 14), but these do not take into account short-term follow-up and additional imaging.

In view of the notably higher sensitivity of MRI in patients at high risk, several countries – including

Figure 2: Tubular breast cancer detected by ultrasonography (6 mm pT1bN0). The tumor had been conspicuous as a permanent sound shadow in dense tissue.

Germany – have “familial breast cancer” programs (e84), and breast MRI scans are recommended and done in the context of these programs. A recommendation for the use of breast MRI except in high risk cohorts (*figure 4*) does currently not exist anywhere in the world, even taking into account the latest knowledge (e67–e70).

Before more widespread use of MRI can be discussed, its efficacy under screening conditions would have to be demonstrated – e.g., in the context of a randomized controlled trial – and the availability of potentially required MR interventions would have to be ensured.

Discussion

In order to reduce breast cancer mortality by means of early detection, a large number of healthy women (more than 99% of findings per round are negative) will have to be examined regularly. To ensure the early detection of small breast cancers and minimize potential disadvantages at the same time, excellent quality assurance throughout the country is required. The standard in mammography screening in Germany is that further

Figure 3: Ductal carcinoma in situ (DCIS) Stage 1–2, detected on MRI, visible thanks to asymmetrical concentration, not visible on mammography or ultrasonography (frontal aspect). Subtraction image (after administration of contrast medium minus before administration of contrast medium), coronal plane.

Figure 4: Breast cancer that is tomographically almost non-distinguishable on the MRI scan from the remaining, blotchily concentrated glandular tissue. It corresponds to the mammographically detected cancer in figure 1 (frontal aspect). Subtraction image (after administration of contrast medium minus before administration of contrast medium), coronal plane.

methods are used in the further investigation of conspicuous findings. The use of additional imaging techniques discussed in this article in women without suspected breast cancer may enable earlier detection of additional breast cancers. The real prognostic gain that goes beyond earlier diagnosis or overdiagnosis and overtreatment will have to be analyzed critically, like the reproducibility. This is because adverse effects such as false alarm or overdiagnosis with overtreatment affect all investigated women and per screening round they add up (in up to 10 screening rounds between the ages of 50 and 69).

Because of the known limitations of mammography it seems advisable to test possible uses of other methods. A relevant reduction in mortality could be expected if especially higher cancer stages (>II) could be reduced notably and the detected tumors were not due to overdiagnoses (e5).

As the simplest and most cost effective measure, ultrasonography should be considered. Its known limitations make it a requirement for its potential use to be tested in controlled, optimally randomized studies. Open questions remain currently with regard to:

- Reproducibility
- Standardization
- False positive rates/biopsy rates

- Control investigations brought forward
- Assurance of excellent quality throughout the country.

For the most sensitive procedure, MRI, additional problems are posed by possible overdiagnosis/overtreatment due to its higher sensitivity for DCIS. Problems also concern the high number of recommended follow-up investigations.

that impose longer term strain on asymptomatic women because of the uncertain diagnosis. Further, more widespread use of MRI will need to be preceded by widespread availability of high quality MR-guided interventions for the histopathological assessment of MR-detected lesions.

To obtain a balance between risks and benefits, a careful and responsible analysis on the basis of confirmed, objective data is required. If a screening method that costs five times more were used for population screening or for selected (yet undefined) subgroups, the cost-benefit ratio would first need to be analyzed and potential harms should be proven to be balanced. The appropriate use of available resources is essential to ensure that these resources are available when they are really needed.

Before imaging techniques beyond mammography can be considered for population screening, analyzing these under study conditions and fitting them into a quality assured system is vital even for screening of subgroups.

Conflict of interest statement

PD Dr Katalinic is a member of the Expert Committee of the Kooperationsgemeinschaft Mammographie-Screening. The other authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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