The role of ultrasonography in diagnostic breast imaging

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THE ROLE OF ULTRASONOGRAPHY IN DIAGNOSTIC BREAST IMAGING

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THE ROLE OF ULTRASONOGRAPHY IN DIAGNOSTIC BREAST IMAGING

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
Aan de Universiteit Maastricht,
Op gezag van de Rector Magnificus
Prof. Dr. A.C. Nieuwenhuijzen Kruseman,
Volgens het besluit van het College van Decanen,
In het openbaar te verdedigen
Op vrijdag 14 februari 2003 om 12.00 uur

door

Karin Flobbe
Geboren te Wemeldinge (Zld)

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1

INTRODUCTION

Introduction.

Breast cancer is the most common malignancy in women and comprises 18% of all female cancers. Yearly, 1 million new cases of breast cancer are detected worldwide¹. In The Netherlands, about 10,000 new breast cancers are reported every year and the lifetime risk is 10%. Suggested risk factors for breast cancer include: increasing age with a slowing rate after menopause, low age at menarche or late menopause, late age at first pregnancy or nulliparity, a family history, previous benign breast disease like atypical epithelial hyperplasia, oral contraceptive use and use of hormone replacement therapy¹.

Diagnostic breast imaging

Women with breast problems are generally referred for diagnostic breast imaging to the radiology department of a hospital by general practitioners and specialists. Reasons of referral can be the presence of a palpable mass, other symptomatology e.g. pain or nipple discharge, radiological follow up of a prior breast malignancy or a benign abnormality e.g. a fibroadenoma, an abnormal screening mammogram made as part of the national breast cancer screening program or asymptomatic reasons like a family history or fear of breast cancer.

Routine breast imaging consists of clinical examination and mammography, which may be complemented with ultrasonography when clinically indicated. The imaging work-up should have a high sensitivity and high specificity, in order to prevent diseased patients from being sent home wrongly (false-negative results) and prevent healthy patients from undergoing further unnecessary work-up (false-positive results). Many centers offer patients the service of a "one-stop diagnosis", in which all diagnostic tests are performed during one hospital visit and the patient is provided with the diagnosis within one day^{2,3}.

In patients with a palpable breast lump, clinical guidelines recommend additional fine needle aspiration cytology (FNAC) to be included in the routine work-up, next to clinical examination and mammography. The "triple test" combines the results of these diagnostic tests in planning the treatment⁴⁻⁷. Furthermore, it is advised to investigate non-conclusive non-palpable abnormalities further by histological core needle biopsies⁸⁻¹⁰.

Additional ultrasonography

Although mammography has been the major breast imaging tool for decades, its accuracy is greatly dependent on the composition of breast parenchyma and the presentation of breast tumors. The sensitivity of mammography is lower in younger patients with dense, glandular breasts and in patients with noncalcified tumors.

Ultrasonography has become the most important adjunct to mammography¹¹⁻¹³. It's first application in the examination of the breast was described by Wild and Neal in 1951¹⁴ and the technique gained importance with the development of B-mode techniques which were able to visualize palpable lesions, as published first in 1954¹⁵.

Currently, the most important indications for breast ultrasonography are:

- **Differentiation between cyst and solid mass** ^{11-13, 16-20}
Cysts are the most common benign breast masses. Ultrasonography can reach a 100% accuracy in the diagnosis of a cyst when strict criteria are used: a round oval shape or gently lobulated, circumscribed margin, anechoic echogenicity and acoustic enhancement ²¹.
- **Evaluation of a palpable mass not visible in a dense breast** ^{11, 13, 16-18, 22}
In cases where normal fibroglandular tissue may partially or completely obscure masses on a mammogram, ultrasonography may determine whether the mass is cystic or solid. However, nonvisualization of a palpable mass by both mammography and ultrasonography suggests the lesion is solid and a biopsy should be strongly considered.
- **Evaluation of nonpalpable or palpable abnormalities with an uncertain mammographic diagnosis** ¹¹⁻¹³
Concerns the evaluation of non-palpable oval, round and circumscribed mammographic lesions as well as palpable masses, which are difficult to place within the field of view on the mammogram.
- **Initial evaluation of a palpable mass in young women (<35 years)** ^{11-13, 16, 18-21}
As breasts of young women are more sensitive to radiation and breast cancer is relatively rare in this group, ultrasonography should be performed as initial imaging study of a palpable mass.

Other indications for breast ultrasonography are inflammation or mastitis ^{11, 13, 18, 19}, the evaluation of problems in breasts with breast implants ^{19, 21} and guidance for interventional procedures ^{11-13, 17, 19, 20}.

There is an ongoing discussion about the use of ultrasonography in the differentiation between benign and malignant lesions. Although several studies have tried to define characteristic ultrasonographic features of benign and malignant breast masses ^{11, 19, 20, 23-25}, more research needs to be done to develop one universal lexicon which may be used in clinical practice.

Finally, ultrasonography is being debated as a screening modality for breast cancer. It has been argued that in order to do so, it must not only detect all cancers visible on mammography, but also show a substantial number of non-palpable cancers that are mammographically occult. Ultrasonography does not yet perform either of these tasks and has shown to have a high false-positive rate when used as a screening modality ^{11, 13, 19, 26, 27}.

The application of breast ultrasonography as adjunct to mammography in clinical practice can greatly reduce the number of biopsies performed for benign breast disease and reduce patient anxiety ^{13, 28}. Several studies have reported the diagnostic performance of mammography combined with ultrasonography and show a sensitivity of 87%-100% and a specificity of 64%-98% ²⁹⁻³⁵.

After the performance of the tests, one final imaging assessment should be composed; reflecting combined mammographic and ultrasonographic findings. Final assessment and patient management should be based on the most suspicious features present ²¹, although others believe that whenever the mammographic findings cannot be correlated with the ultrasonography findings, the mammographic findings should prevail, avoiding possible incorrect conversion ¹⁷.

Context of the thesis

The increasing availability and accessibility of ultrasonography in hospitals has led to an increase in its application. Other reasons for possible "excessive" testing in diagnosis can be found in the pressure from patients and their families, the clinician's concern about malpractice and fear of missing a diagnosis^{36,37}. Although this practice may comfort the patient and satisfy the clinician's desire to use every possible diagnostic avenue, more tests do not necessarily produce more certainty³⁶. Furthermore, an increasing use of tests will lead to an increase in healthcare costs resulting in a financial burden to the healthcare system.

Numbers from the radiology department of Maastricht University Hospital show an increase in the application of ultrasonography as adjunct to mammography from 28% of all patients referred for breast imaging in 1994³⁸ to over 35% in 1999. This hospital is a 700-bed referral hospital with an important regional function for the south of The Netherlands. At the radiology department about 3500 breast examinations are performed yearly.

The increased use of breast ultrasonography leads to the question whether additional diagnostic information is obtained in all occasions where it is applied. In order to reduce the number of unnecessary examinations, ultrasonography should be mainly performed in the patients who benefit most from it. Furthermore, the test should be withheld from patients in whom it does not yield additional diagnostic information. To optimize and facilitate the logistic planning of diagnostic breast imaging in the radiology department, the selection of patients for ultrasonography is, from a practical point of view, preferably made at the stage of referral and therefore based on patient characteristics known at referral.

MAMMOED study

In response to these clinical questions, the MAMMOED study (MAMmacarcinoom-studie Maastricht: Optimalisatie Echografische Diagnostiek; Breast cancer study Maastricht: Optimizing Ultrasonographic Diagnostics) was performed at Maastricht University Hospital as part of the Cost Containment Research Program of the Dutch Health Care Insurance Board. In this prospective study all patients referred for breast imaging underwent ultrasonography as adjunct to mammography and clinical examination.

The objectives of this thesis are:

1. To assess the diagnostic value of breast ultrasonography as adjunct to mammography and clinical examination in the diagnosis of breast cancer.
2. To study the feasibility of defining subgroups of patients who benefit most from additional ultrasonography.
3. To study the costs and effects of the application of breast ultrasonography in patients with palpable breast masses.

Outline of the thesis

In chapter 2 of this thesis, a prospective study is described which assesses the diagnostic performance of breast imaging in a non-screening population in daily clinical practice. In 3816 breasts in 1944 examinations, palpation and mammography

was performed, supplemented with ultrasonography when clinically indicated. ROC curve analysis assessed the diagnostic value of radiological breast imaging and its value in addition to information from palpation and age of the patient.

To study the available evidence for the diagnostic value of ultrasonography as adjunct to mammography and to define clinical indications for ultrasonography, a systematic literature review was performed and discussed in **chapter 3**. All available publications between 1990 and 2000 describing the diagnostic performance of ultrasonography as an adjunct to mammography, were selected. Apart from the diagnostic performance, the methodological quality of the different studies is discussed.

In **chapter 4**, results of the MAMMOED study are reported, in which the diagnostic value of ultrasonography as an adjunct to mammography and clinical examination was studied in 2020 consecutive patients referred for breast imaging. ROC curve analysis assessed the additional diagnostic value of ultrasonography in the whole study population as well as in subgroups of patients according to the reason for referral for breast imaging and age.

Following, multivariate logistic regression analysis was performed on diagnostic variables of the medical history, clinical examination, mammography and ultrasonography, on patient data from the MAMMOED study to assess the specific contribution of each consecutive test in the prediction of breast cancer. The results of this analysis are reported in **chapter 5**.

Chapter 6 describes a decision analytical model of the costs and effects of incorporating ultrasonography in the triple test for evaluating palpable breast masses. A conventional strategy of immediate fine needle aspiration cytology (FNAC) following mammography and clinical examination was compared with 3 different experimental strategies of prior ultrasonography.

Chapter 7 discusses the results of the studies presented in this thesis and emphasizes their clinical impact. Finally, **chapter 8** summarizes the most important findings.

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2

DIAGNOSTIC VALUE OF RADIOLOGICAL BREAST IMAGING IN A NON-SCREENING POPULATION.

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Int J Canc 2001;92:616-618.

Abstract

Aim

The aim of this study was to assess the diagnostic performance of breast imaging in the diagnosis of breast cancer in a non-screening population.

Methods

In a consecutive set of patients referred for mammography in one year, the results of palpation and radiological breast imaging were scored on a 5-point grading scale and linked to pathology as gold standard after a follow up period of one year. The diagnostic performance was studied by logistic regression analysis and ROC curves.

Results

There were 1944 breast examinations in 1890 patients and 3816 breasts. Pathology results reported 118 malignancies in 115 women. With a cut-off point between benign and uncertain benign a sensitivity of 89% and a specificity of 98% was found for radiological imaging.

ROC curves showed a significant increase in diagnostic performance when radiology was added to results of palpation and age ($p=0.007$).

Conclusion

Radiological imaging tests have a large diagnostic value in the detection of breast cancer in addition to palpation and age. A sensitivity close to 100% could be reached.

Introduction

Breast cancer is one of the leading causes of death among women in Western countries. The overall risk for the development of breast cancer over lifetime is estimated to be 12.5% among American women^{1,2} and about 10% among women in The Netherlands³.

The diagnostic triad for evaluation of breast symptoms, the so-called 'triple assessment system', involves clinical examination, radiological imaging and fine needle aspiration (FNA) cytology. If all investigations are carried out together a sensitivity of more than 99% can be obtained^{4,5}.

The value of mammography in screening for breast cancer is well studied, but the diagnostic value of non-screening breast imaging, using a combination of mammography and ultrasonography when indicated, is not well established.

Many studies discussing the value of non-screening breast imaging describe populations diagnosed with breast cancer⁵⁻⁹. Very few studies describe breast imaging in a clinical population^{10,11}, and these studies did not examine the role of palpation and age in the diagnostic process.

The aim of this prospective study was to assess the diagnostic performance of breast imaging in the diagnosis of breast cancer among a non-screening population.

Material and methods

All consecutive patients referred for mammography to the Radiology Department of the University Hospital Maastricht in 1994 were included in the study.

Investigations were performed in fixed order. Palpation was followed by standard craniocaudal and mediolateral oblique mammograms. When indicated according to the opinion of the radiologist, patients subsequently underwent ultrasonography. For the purpose of this study, the combination of mammography and ultrasonography will be called 'radiological breast imaging'.

Imaging examinations obtained as follow up to breast saving surgery or amputation were excluded. For patients with multiple examinations during the study period, all examinations were included except those done after breast cancer was already diagnosed. Furthermore, when cancer was detected at later examinations the result of the first examination was considered false negative and only this examination was included in the analysis. When ultrasonography was performed without mammography, patients were not included in the study.

Registration forms were used to score all examinations. Palpation was scored per breast as: 0 = palpation not performed, 1 = no palpable abnormality, 2 = vaguely palpable abnormality, 3 = circumscribed abnormality, 4 = evident abnormality, not sharply defined.

The results of mammography and ultrasonography were combined into an overall radiological imaging conclusion, according to the BI-RADS lexicon as developed by the American College of Radiology, classified as: 1 = normal, 2 = benign, 3 = uncertain benign, 4 = suspect malignant, 5 = malignant¹².

Mammography was performed using a Siemens Mammomat-2 unit and a Kodak Min-R film screen combination. Ultrasonography was done with a General Electric scanner (RT3600) and a 7.5 MHz linear array transducer. Palpation and radiological examinations were carried out and reported by a radiologist with a special interest in mammography and over 5 years of experience in this field.

A follow up period of one year after breast imaging was used. Pathology results retrieved from our hospital pathology department and the Dutch National Archives of Pathology (PALGA) were used as the gold standard for the presence or absence of breast cancer and linked to the imaging results. As all pathology laboratories in The Netherlands are connected to PALGA, we covered the whole study population, including patients who were diagnosed elsewhere. Patients for whom no pathology results were reported in either system were interpreted as free of malignancy.

Logistic regression analysis was used to identify the role of radiological imaging, palpation and the age of the patient in predicting the presence or absence of malignancy.

By dichotomizing the results of logistic regression and calculating the sensitivity and specificity for different cut-off points of the predicted probabilities that were generated, receiver operating characteristic (ROC) curves were drawn for palpation and age and for the whole process of breast diagnosis, consisting of radiology, palpation and age results.

The areas under the curve (AUC) were calculated according to the method of Hanley and McNeil¹³ and differences between AUC were tested¹⁴.

Results

A total of 2676 breast examinations were recorded during the study period.

Six hundred twenty-two examinations were not included in the study because mammography was done as a follow up to breast-saving surgery or amputation and 92 examinations were not included because ultrasonography was done without mammography.

Furthermore, 18 examinations were excluded because breast cancer was diagnosed on a previous visit during the study period and no examination was excluded because breast cancer was diagnosed at a subsequent visit.

Consequently, 1944 examinations were included for 1890 different patients: 1840 patients were included once, 46 were included twice (2%) and 4 were included three times (0.2%). In the analysis the total number of examinations included (1944) was taken as the total number of patients.

Referral for breast imaging was made by general practitioners in 1507 patients (77%), specialists in 420 patients (22%) and others in 17 patients (1%).

The main reasons for referral were the occurrence of a breast lump ($n=528$, 27%), pain ($n=408$, 21%), control mammography of former benign pathology ($n=208$, 11%), mastitis ($n=177$, 9%), family history of breast cancer ($n=146$, 8%), patients' own requests ($n=95$, 5%) and further investigation of an abnormality found by the nation-wide breast cancer screening program ($n=33$, 2%). The mean age of the patients was 46.1 years (range 14-94 years).

Bilateral mammography was performed in 1872 patients (96%), and a single breast was investigated in 72 patients (4%). The total number of breasts examined was 3816.

Additional ultrasonography was performed in 542 patients (28%) in 791 breasts. The main reason to perform ultrasonography was to differentiate cystic from solid masses. These patients were significantly younger than the group who did not undergo ultrasonography (4.6 years).

Further results are presented on the level of breasts, referred to as cases.

After 12 months pathology results were available for 393 cases, obtained from FNA cytology ($n=193$), lumpectomy ($n=69$), surgical biopsy ($n=47$), amputation ($n=47$) and excision under radiological localization ($n=37$). There were 118 malignancies, of

which 116 were diagnosed within 3 months after mammography. The remaining 2 cases of cancer were reported 7 and 10 months after breast imaging. All cases without pathology data were assumed to be free of malignancy ($n=3698$). No malignancies were found within the group patients with multiple examinations. In 3 patients breast cancer was diagnosed in both breasts, leading to a prevalence of breast cancer in this population of 6.1% (115/1890 patients).

Table 1: Palpation and radiological breast imaging scores for pathology positive and negative cases ($n=3816$).

PATHOLOGY		RADIOLOGY					Total
		1	2	3	4	5	
0	PALPATION						
	0	528	147	7	2	1	685
	1	2173	408	6	7	3	2597
	2	51	35	4	2	0	92
	3	35	250	11	9	5	310
	4	1	1	5	2	5	14
	Total	2788	841	33	22	14	3698
1	PALPATION						
	0	1	1	0	3	12	17
	1	3	1	2	7	6	19
	2	0	2	2	4	3	11
	3	1	4	2	14	40	61
	4	0	0	0	4	6	10
	Total	5	8	6	32	67	118

Pathology scores: 0= Normal, benign, 1= Malignant.

Radiology scores: 1= Normal, 2= Benign, 3= Uncertain benign, 4= Suspect malignant, 5= Malignant.

Palpation scores: 0= Palpation not performed, 1= No palpable abnormality, 2= Vaguely palpable abnormality, 3= Circumscribed abnormality, 4= Evident abnormality, not sharply defined.

Figure 1: ROC curves for palpation with age and for radiological breast imaging combined with palpation and age (AUC, 95% CI between brackets)

The results on palpation and radiological breast imaging in the presence and absence of malignancy for all 3816 cases are shown in Table 1. The sensitivity and specificity of radiological imaging depends on the cut-off point used to define positive cases and can be calculated using data from Table 1. The largest diagnostic value of radiological imaging was found at the cut-off point

between benign and uncertain benign, with a sensitivity of 89% and a specificity of 98% on the level of individual breasts (sensitivity=105/118x100%, specificity=3629/3698x100%). There were 69 false-positive and 13 false-negative cases. When analyzing on patient level, the sensitivity and specificity at this cut-off point was 90% and 97%, respectively.

Logistic regression analysis showed that radiological imaging, palpation and the age of the patient were all significant predictors of malignancy ($p<0.001$, $p=0.004$, $p=0.01$, respectively). Using the results of this analysis ROC curves were plotted for the results of palpation and age (AUC=0.919, 95%CI=0.898-0.940) and for the process of breast diagnosis, consisting of radiology combined with palpation and age (AUC=0.981, 95%CI=0.970-0.992)(Figure 1). The AUC differed significantly ($p=0.007$). From these curves it can be deduced that, hypothetically, breast imaging can reach a sensitivity of 100%, with a specificity of 60% as a consequence. The AUC for results of radiological imaging only was 0.961 (95%CI 0.936-0.986), which was similar to the AUC for breast diagnosis ($p=0.2$, curve not shown).

Discussion

In our non-screening clinical population, radiological breast imaging had a sensitivity and specificity of 89% and 98%. These results are comparable to of Zonderland et al.¹¹, who reported a sensitivity of 91% and specificity of 98% for mammography combined with ultrasonography, and to those of Duijm et al.¹⁰, who reported a sensitivity of 92% and specificity of 98% for integrated mammography and ultrasonography in a clinical population. In our study population a 6.1% prevalence of breast cancer was found, which is similar to Zonderland et al. and Duijm et al., who reported a prevalence of 7% and 5%, respectively^{10, 11, 15}.

Our follow up period is shorter than that used in these other studies. A 1-year follow up was chosen to maximize the chance of detecting malignancies that were actually missed and to minimize the chance of finding newly developed cancers^{9, 16, 17}. Because only 2 of 118 malignancies were detected after 3 months of follow up, we believe that only a few additional cases of cancer would have been found through longer follow up and that these cases are likely to be newly developed rather than missed cases.

Ultrasonography was performed in 28% of all patients. Other descriptive studies report a range of 23-51% of patients undergoing additional ultrasonographic examination on clinical indication^{5, 8, 10, 11, 18}.

Radiological imaging, palpation and age were all significant predictors of malignancy in this study, which is concordant with the results of Purasiri et al.⁸.

Procedures were carried out in fixed order by the same radiologist, leading to included prior knowledge of the clinical status and age of the patient in the interpretation of radiological imaging tests. Furthermore, knowledge of mammography results probably influenced the interpretation of the ultrasonographic examination. As it would be impossible to study them as separate modalities here, one integrated radiological diagnosis was registered for mammography and ultrasonography together.

The dependence of the diagnostic modalities in this study is shown by the equality of the AUC of ROC curves for radiological imaging tests with and without results on palpation and age. This finding suggests that prior results of palpation and age have influenced the interpretation of radiological breast imaging. A possible way to fully

separate these diagnostic modalities would be to blind the radiologist to results of prior examinations when scoring the diagnostic test under study. Nevertheless, current procedures represent the way breast imaging is performed in most clinics, which makes our results applicable to daily practice.

The ROC curve shows that the process of breast diagnosis can theoretically detect all breast cancers. The clinical work-up in this population confirms these results as 116 of 118 (98%) cancers were diagnosed.

This study shows the large diagnostic value of radiological imaging tests in addition to results on palpation and age in the detection of breast cancer. A sensitivity close to 100% can be reached.

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3

THE ROLE OF ULTRASONOGRAPHY AS ADJUNCT TO MAMMOGRAPHY IN THE DETECTION OF BREAST CANCER: A SYSTEMATIC REVIEW

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Abstract

Aim

To summarize the diagnostic performance of ultrasonography as adjunct to mammography in the detection of breast cancer and to identify clinical indications.

Methods

A systematic review was performed of all publications in MEDLINE and EMBASE between 1990-2000 on the role of ultrasonography as an adjunct to mammography.

Results

22 studies were included, showing a large variety in 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).

Conclusion

Based on the studies reviewed, little evidence-based support was found to confirm the well recognized 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.

Introduction

Mammography is the basic imaging modality for the evaluation of patients with breast abnormalities¹. In response to the diagnostic deficiency of mammography in the differentiation between cysts and solid tumors, other imaging modalities have been developed and optimized 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 examination².

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 surgery¹⁻⁵.

Long-term clinical experience has shown the value of ultrasonography in differentiating cysts from solid breast tumors, but its role in the differentiation between malignant and benign lesions is still under discussion⁶⁻⁸. Furthermore, the use of ultrasonography as screening tool is discouraged because of unacceptably high false-negative and false-positive rates^{4, 9, 10}.

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 an 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.

Methods

The MEDLINE, EMBASE and Cochrane databases were searched for all available publications between 1990-2000 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 be 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 ($((\text{sensitivity}/(1-\text{sens})) * (\text{specificity}/(1-\text{spec})))$).

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 $\ln\text{DOR}$ for ultrasonography and mammography ($\ln\text{DOR}_{\text{us}} - \ln\text{DOR}_{\text{mam}}$) 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 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.

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 centers²⁸.

The review therefore included 22 studies.

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

Reason for exclusion	No of publ	References
Only data on breast cancer positive patients were reported	18	1, 11-27
Missing data for completion of 2x2 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 gold standard for detection of microcalcifications	1	70

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 alone²⁹⁻³⁴.

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.

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 22 studies included in the review.

Study	No	Prev	Age ²	MAM			US ³			MAM + US ⁴		
	pat ¹			sens	spec	DOR	sens	spec	DOR	sens	spec	DOR ⁵
Group 1: selection study population based on clinical examination												
Ultrasonography interpreted with knowledge of prior mammography												
Hardy (1990) ²⁹	143	46.2	50 (25-80)	86	78	22.4	96	84	113.7	100	76	∞
US performance independently / blinded												
Lister (1998) ⁴²	205	6.8	40 (25-85)	57	93	17.3	93	97	400.8			
Perre (1993) ⁴¹	204	56.4	49	91	75	32	97	91	378			
Van Oord (1991) ⁴⁰	232	32.8	48	87	76	21.2	99	67	154.4			
Yang (1996) 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												
Ultrasonography interpreted with knowledge of prior mammography												
Catarzi (1992) ⁷¹	400	64.5	52	94	36	8.3	49	52	1.1			
Ciatto (1994) ³⁶	2079	12.5	48 (17-93)	80	94	57.6	68	98	88.2			
Eltahir (1999) ⁴⁵	1066	5.5	- (15-91)	93	97	401.6	89	97	300			
Zonderland (1999) ³⁰	1103	24.7	50	86	89	50.7				95	92	223.5
Group 3: selection study population based on referral for pathology												
Ultrasonography interpreted with knowledge of prior mammography												
Gozzi (1990) ³⁷	221	65.2		88	56	9.4	95	41	14.2			
Houssami (1998) ³⁵	391	37.6		78	80	14.3	88	83	36.1			
Muller-Schimpfle (1997) ⁷²	98	60.2	53 (15-75)	83	92	58.8	76	79	12.5			
Özdemir (1997) ³¹	72	72.2	50 (28-77)	92	65	22.3	84	65	10.2	100	85	∞
Purasiri (1996) ⁴⁶	603	46.9		88	73	19.8	70	79	8.8			
Roche (1998) ⁴⁴	306	49.0		92	78	40.8	82	79	17.1			
Ultrasonography interpreted independently / blinded												
Moss (1999) ³²	368	44.0		79	79	14.7	89	72	20.1	94	64	29
Reinikanen (1999) ⁴³	63	61.9	48 (18-93)	97	54	44.9	97	54	44.9			
Ruhland (2000) ³³	199	19.6	54 (29-85)	87	40	4.5	87	29	2.7	100	9	∞
Skaane (1997) ³⁴	200	50.0		83	96	117.2	96	73	64.9	87	97	216.4
Yoshihara (1999) ³⁸	39	46.2	45	83	76	16	94	80	72.3			
Zuna-b (1998) ²⁸	40	37.5		60	74	4.3	100	100	∞			
Zuna-a (1998) ²⁸	37	32.4		89	91	84	92	88	80.7			

¹ number of patients in the study who underwent both test modalities

² mean or median age (which of both was given) + range

³ results of ultrasonography alone (performance with or without knowledge of mammography)

⁴ combined radiological diagnosis from results of mammography + ultrasonography together

⁵ diagnostic odds ratio

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 figure 1.

A difference between $\ln\text{DOR}_{\text{US}}$ and $\ln\text{DOR}_{\text{mam}}$ 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, figure 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 mammography and ultrasonography together was given³⁰. 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 ($p=0.03$).

Figure 1: Diagnostic performance of ultrasonography relative to mammography ($\ln\text{DOR}_{\text{US}} - \ln\text{DOR}_{\text{mam}}$) 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).

A large variety of indications for breast ultrasonography were 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 ^{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.

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).

Discussion

This review shows that the indications for ultrasonography as an adjunct to mammography vary among 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 ultrasonography will be interpreted with 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 to 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 of 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% and 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 ultrasonography 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.

The influence of methodology on the diagnostic performance emphasizes 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 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 way³⁰.

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 cysts⁵. However, routine application of ultrasonography may generate many unnecessary biopsies⁴⁸. 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 tumors and in the evaluation of palpable masses in young women is well recognized 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 unwise¹⁰.

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 health care 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-recognized value of ultrasonography as 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 their poor quality.

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4

THE ADDITIONAL DIAGNOSTIC VALUE OF ULTRASONOGRAPHY IN THE DIAGNOSIS OF BREAST CANCER

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Abstract

Background

The use of ultrasonography in diagnostic breast imaging is increasing. Restricting ultrasonography to subgroups of patients who benefit most, would result in a more efficient and effective application. This study assessed the diagnostic value of ultrasonography as adjunct to mammography and clinical examination in the detection of breast cancer and the feasibility of selecting subgroups of patients who benefit most.

Methods

Between October 1999 and August 2000 all consecutive patients referred for breast imaging underwent additional ultrasonography after mammography and clinical examination. Results were scored on a 5-point grading scale of increasing suspicion for malignancy. Pathology results during 12 months follow up were used as criterion standard.

ROC curve analysis assessed the diagnostic value of ultrasonography in the whole population and in subgroups of patients according to indication for referral and age.

Results

3835 breasts were examined in 2020 patients, with a 6.3% prevalence of breast cancer.

Breast ultrasonography detected 8 extra malignancies and correctly downgraded 332 cases to a negative diagnosis. ROC curves showed a significant improvement in diagnostic value by adding ultrasonography to mammography and clinical examination (AUC CE+MAM+US: 0.99 versus CE+MAM: 0.95, $p=0.002$). The diagnostic yield improved significantly in patients referred for palpable breast lumps or referred from the national breast cancer screening program. Less pronounced was the value in patients referred for other symptomatology or for follow up of a prior breast malignancy.

When screening breast imaging of the contralateral breast was performed, or in asymptomatic patients referred for reassurance or follow up of a prior benign lesion, the value of additional ultrasonography remained undefined because of the small number of malignancies.

Conclusion

Systematic application of breast ultrasonography improved the overall diagnostic yield.

The diagnostic value increased most in patients with palpable breast lumps and patients referred with abnormal screening mammograms.

Introduction

With a lifetime risk of 10% breast cancer is a major public health problem in women in Western countries ¹. Its diagnosis and treatment is creating a financial burden to the health care system.

In addition to mammography, ultrasonography has become the most widely used imaging method in the diagnosis of breast disease, especially in patients with palpable masses and normal or non-conclusive mammographic results ²⁻⁴. Numbers from our hospital show that the application of additional ultrasonography has increased from in 28% of patients referred for mammography in 1994 ⁵ to over 35% in 1999. This is partly the result of the wider availability and accessibility, the broadening clinical indications and the idea that physicians believe to be less likely to be blamed for doing more testing than for doing too little ⁶.

As a consequence, many examinations are actually redundant and will not only lead to rising health care costs, but also to unnecessary inconvenience and discomfort to the patient, unnecessary work-up because of false-positive results and increasing waiting lists.

To reduce this health care problem and to aim for a more effective and efficient use, additional ultrasonography should be restricted to those subgroups of patients who benefit most from it.

A number of studies have assessed the diagnostic value of clinically indicated breast ultrasonography as adjunct to mammography ⁷⁻¹². Despite combining mammography with ultrasonography resulted in a higher sensitivity, in 3 studies the increase in sensitivity was reached at the expense of a decrease in specificity ^{7, 8, 10}. None of these studies have applied ultrasonography systematically in consecutive patients in order to obtain evidence-based information on subgroups of patients with the highest diagnostic yield.

The aim of this prospective study was therefore to assess the diagnostic value of breast ultrasonography as adjunct to mammography and clinical examination in a consecutive set of patients referred for diagnostic breast imaging. Furthermore, the feasibility of selecting subgroups of patients who benefit most from additional ultrasonography was studied.

Patients and Methods

Between October 1999 and August 2000 all consecutive patients referred to our radiology department for diagnostic breast imaging underwent additional ultrasonography after clinical examination and mammography. Maastricht University Hospital is a 700-bed referral hospital with a large regional function.

Patients were informed about the study by mail preceding their scheduled visit as well as in the department prior to their imaging examination, after which informed consent was signed. Patients were excluded from the study when ultrasonography could not be performed because of logistic reasons or when no informed consent was given. As in The Netherlands a system of collective health insurance makes health care available to the whole population, no patients were excluded from the study due to inability to pay or lack of insurance.

Investigations were performed in fixed order during a single visit. Bilateral clinical examination, performed in standing and sitting position, was followed by standard craniocaudal and mediolateral oblique mammograms (Siemens Mammomat-2 unit /

Kodak Min-R film screen combination) then followed by whole breast ultrasonography (ATL5000, 12.5 MHz linear array transducer). Conforming to clinical practice all examinations were performed and interpreted with full knowledge of prior test results. Tests were carried out by a team of radiologists with a special interest in diagnostic breast imaging and over 5 years of experience in mammography and breast ultrasonography. In one patient all examinations were performed by the same radiologist. Additionally, study procedures were monitored and registered by a resident who was present at all examinations of all patients (AMB).

All relevant patient characteristics and the description, size and location of lesions found at the different diagnostic examinations, were registered in a standardized fashion. The diagnosis based on clinical examination, mammography and ultrasonography was scored separately per breast on a 5-point grading scale with increasing suspicion for malignancy, as 1 = normal, 2 = benign, 3 = uncertain benign, 4 = suspect malignant, 5 = malignant, 0 = indeterminate (based on the BI-RADS lexicon for mammography and under development for ultrasonography by the American College of Radiology^{13, 14}).

Additional to these separate diagnoses a combined diagnosis of clinical examination and mammography together (CE+MAM) was calculated by taking the maximum diagnostic score of these modalities. Finally, a final diagnosis based on clinical examination, mammography and ultrasonography together (CE+MAM+US) was defined mathematically as the maximum score of the modalities in case of a benign or malignant diagnosis. When scores differed more than one grade of suspicion of malignancy or when either of the two modalities included an uncertain benign score, the overall diagnosis of the radiologist interpreting all examinations ruled.

The additional diagnostic value of ultrasonography was determined by comparing the accuracy of CE+MAM+US with the accuracy of CE+MAM.

As it approaches clinical implications, indeterminate clinical examinations (score=0) as in e.g. mastopathy, were recoded as benign (score=2) and indeterminate mammography or ultrasonography results as uncertain benign (score=3) for analysis.

The criterion standard for the presence or absence of breast cancer was determined by pathology results from core needle biopsies, excision biopsies and other surgical interventions during a follow up period of 12 months. An additional 2 months was added accounting for administrative routing of test results at the end of the follow up period.

Pathology results were retrieved from the hospital pathology department and the Dutch Network and National Database for Pathology (PALGA). As all national hospital pathology departments are linked to this database, subsequent malignancies diagnosed elsewhere would not go unnoticed. Breast cancer status was considered negative when no pathology was reported in either system.

Receiver operating characteristic (ROC) curves were constructed for the imaging results of clinical examination, CE+MAM and CE+MAM+US. Areas under the curve (AUC) were calculated as a measure for the diagnostic performance and differences were calculated and tested according to the methods of Hanley et al.^{15, 16}. Furthermore, ROC curves were analyzed for subgroups of patients according to indications for referral and age.

Results

There were 2720 scheduled imaging examinations, of which 112 were cancelled and 84 were excluded from the study, as patients had been included on earlier visits. In 279 cases additional ultrasonography was not realized because of logistical reasons and 225 patients refused informed consent. The patients excluded from the study had a comparable prevalence of breast cancer, age distribution, reason for referral, and imaging interpretation.

A total of 2020 consecutive patients were included in the study and underwent clinical, mammographic and ultrasonographic examination of both breasts. The population consisted of 2000 women and 20 men with a mean age of 50.2 years (range 16.8 – 90.3). Patients were referred by general practitioners ($n=1044$), surgeons ($n=712$) and other specialists ($n=264$). Indications for referral were: a palpable breast lump ($n=470$ patients), other breast symptomatology like pain, skin or nipple abnormalities ($n=486$), follow up of prior breast malignancy ($n=438$), follow up of prior benign breast disease ($n=152$), mammographic abnormalities detected through the national breast cancer screening program ($n=144$), family history of breast cancer ($n=234$), patients' anxiety ($n=13$) or other asymptomatic reasons ($n=83$). These last 3 indications for referral were combined as "reassurance".

One patient was included twice as both visits concerned different indications in different breasts. There were 182 patients who had prior mastectomy because of a history of breast cancer in whom the contralateral breast was investigated and in 23 cases only one breast was examined for other reasons.

Consequently 3835 breasts were examined in 2020 patients.

After a follow up of 12 months a total of 129 malignancies were found in 127 patients, leading to a prevalence of 6.3% (127/2020). Two patients had bilateral breast cancer. Thirteen malignancies were carcinomas in situ only, 116 were invasive carcinomas.

In 123 cases malignant pathology was found as a result of the diagnostic imaging described. Six malignancies were detected after respectively 3, 7, and 12 ($n=4$) months follow up. In 3 cases a malignancy was found during the radiological follow up of benign calcifications (1 after 3 and 2 after 12 months). Two patients presented with a new palpable lesion at 7 and 12 months after the initial breast imaging in this study, which reported normal readings. Finally, in 1 patient yearly radiological follow up of a prior breast malignancy led to the detection of a new lesion after 12 months.

Diagnostic performance

Using a cut-off point between benign and probably benign results, thus defining scores 3, 4 and 5 as positive and scores 1 and 2 as negative results, clinical examination detected 69% of all malignancies (89/129), mammography detected 83% (107/129), and ultrasonography detected 88% (113/129). The specificity reached 93% (3616/3910) for clinical examination, 92% (3405/3706) for mammography and 96% (3556/3723) for ultrasonography.

Table 1 shows the test results of CE+MAM+US and CE+MAM categorized by absence or presence of breast cancer. The sensitivity and specificity of CE+MAM was 92% (118/129) and 87% (3226/3706) respectively, for CE+MAM+US this was 97% (125/129) and 95% (3512/3706) respectively.

Table 1: Results of clinical examination combined with mammography (CE+MAM) and the final diagnosis (CE+MAM+US) by malignancy for all cases (n=3835). Part A includes cases positive for malignancy, part B includes cases negative for malignancy.

Part A: cases positive for malignancy			
CE+MAM	CE+MAM+US		Total
	Negative	Positive	
Negative	3	8	11
Positive	1	117	118
Total	4	125	129
Part B: cases negative for malignancy			
CE+MAM	CE+MAM+US		Total
	Negative	Positive	
Negative	3180	46	3226
Positive	332	148	480
Total	3512	194	3706

Calculations: sensitivity CE+MAM= $118/129 = 92\%$, specificity CE+MAM= $3226/3706 = 87\%$, positive predictive value CE+MAM= $118/(118+480) = 20\%$, negative predictive value CE+MAM= $3226/(11+3226) = 99.6\%$, sensitivity CE+MAM+US= $125/129 = 97\%$, specificity CE+MAM+US= $3512/3706 = 95\%$, positive predictive value CE+MAM+US= $125/(125+194) = 39\%$, negative predictive value CE+MAM+US= $3512/(4+3512) = 99.8\%$

Breast ultrasonography detected 8 extra malignancies (7 invasive ductal carcinomas and 1 lobular carcinoma in situ), which were missed by clinical examination and mammography. A detailed description of these cases is shown in table 2. Furthermore, ultrasonography correctly downgraded 332 cases from a positive to a negative diagnosis. On the contrary, there were 46 false-positive ultrasonographic examinations and in 1 case ultrasonography incorrectly downgraded the imaging result to a negative diagnosis.

ROC curves

ROC curves were constructed for the results of clinical examination, CE+MAM and CE+MAM+US for all 3835 cases (figure 1). Comparing the AUC of these curves, there was a significant increase in diagnostic performance by application of additional ultrasonography (AUC CE+MAM+US: 0.99 versus CE+MAM: 0.95, $p=0.002$). Furthermore, AUC for CE+MAM and CE+MAM+US were both significantly different from the AUC for CE alone (AUC CE+MAM+US: 0.99 and CE+MAM: 0.95 versus CE: 0.84, both $p<0.001$). Twelve hundred twenty-eight patients were referred for imaging of a single breast; 792 patients for examination of both sides. Thus, of the 3835 breasts examined, breast imaging was done on referral in 2812 cases and as screening of the contralateral side in 1023 cases. In table 3 AUC of ROC curves for these groups show that the additional diagnostic value of ultrasonography was highest in the referred cases (AUC: 0.98 versus 0.95, $p=0.001$). In patients where screening breast imaging of the contralateral side was performed or when reassurance was the reason for referral, no additional diagnostic value was demonstrated for ultrasonography (p =not applicable because of small numbers).

Table 2: Results of diagnostic imaging tests of 8 extra cases of breast cancer detected by ultrasonography (age, menopausal state, indication for referral, results from clinical examination, mammography and ultrasonography)

Age	Men ¹	Referr ²	Clinical examination Score (description)	Mammography Score (description)	Ultrasonography Score (description)
42	Pre	Palp	1 (No abnormalities)	1 (No abnormalities)	3 (Lobulated, hypoechoic, homogeneous, smooth bordered lesion)
45	Pre	Palp	2 (Palpable lump: round, circumscribed)	1 (No abnormalities)	3 (Irregular, round, hypoechoic, heterogeneous lesion behind aspirated cyst)
36	Pre	Palp	0 (Palpable lump: lobular)	1 (No abnormalities)	4 (Irregular, lobulated, hypoechoic, heterogeneous lesion)
43	Pre	FU benign	0 (No abnormalities, indeterminate)	1 (No abnormalities, dense tissue)	4 (Irregular, hypoechoic lesion)
45	Pre	FU malign	1 (No abnormalities)	1 (No abnormalities)	4 (Irregular, lobulated, hypoechoic, heterogeneous lesion with shadowing)
66	Post	FU malign	1 (No abnormalities)	1 (No abnormalities)	4 (Irregular, lobulated, hypoechoic, heterogeneous lesion)
77	Post	Symp	1 (No abnormalities)	2 (Circumscribed benign lesion)	5 (Irregular, lobulated, hypoechoic, heterogeneous lesion with shadowing)
57	Post	Contra lat	2 (Palpable lump: round)	2 (Benign calcifications)	5 (Irregular, hypoechoic, heterogeneous lesion with shadowing)

¹ Menopausal state: pre = premenopausal, post = postmenopausal

² Reason for referral: palp = palpable breast mass, FU benign = follow up of a prior benign lesion, FU malign = follow up of a prior malignant lesion, symp = symptomatology, contralat = no reason for referral, examination of the contralateral breast.

Table 3: Areas under the ROC curves for clinical examination combined with mammography (CE+MAM) and the final diagnosis (CE+MAM+US) for cases with and without a reason for referral for diagnostic breast imaging

	n	Pos (%)	Area under curve (+ 95% CI)		p-value ¹
			CE+MAM	CE+MAM+US	
All cases	3835	129 (3.4%)	0.95 (0.93-0.98)	0.99 (0.97-1.0)	0.002
Referred	2812	125 (4.4%)	0.95 (0.92-0.97)	0.98 (0.97-1.0)	0.001
Contralateral side	1023	4 (0.04%)			NA ³
No clinical indication ²	1677	5 (0.03%)			NA ³

¹ testing of CE+MAM+US vs. CE+MAM

² defined as examination of contralateral breasts + cases of referral for "reassurance"

³ not applicable, too few malignancies in this group

Test modality	Area under curve	Std. error	95% confidence interval	
CE	0.84	0.03	0.79	0.89
CE+MAM	0.95	0.01	0.93	0.98
CE+MAM+US	0.99	0.06	0.97	0.997

Figure 1: ROC curve of clinical examination (CE), clinical examination combined with mammography (CE+MAM) and the final diagnosis (CE+MAM+US) for all cases (n=3835) Table shows areas under the curve

Indications for breast ultrasonography

In order to study subgroups of patients who benefit most from additional ultrasonography, the diagnostic value was calculated through ROC curves by indication for referral and age categories (table 4). The diagnostic value improved significantly in patients with palpable breast lumps ($p=0.004$), most pronounced for age group <50 years, and in patients referred through the national breast cancer screening program (women >50 years, $p=0.05$).

In the patients referred for palpable lumps ultrasonography correctly downgraded 133 positive clinical and mammographic examinations. Furthermore, ultrasonography detected 3 new malignancies at the cost of 11 false-positive results.

Of the 147 cases referred by the national breast cancer screening program, 40 mammograms and clinical examinations were negative. Ultrasonography did not detect new malignancies in this group, but correctly downgraded 29 positive mammograms to a negative diagnosis.

Additional ultrasonography also increased the diagnostic value in patients referred for other symptomatology like pain and nipple or skin abnormalities ($p=0.28$) and in patients referred for follow up of prior breast malignancy ($p=0.16$), although the difference in AUC was not statistically significant.

In patients referred for follow up of a prior benign abnormality, additional ultrasonography detected 1 extra malignancy and confirmed 2 malignant diagnoses

Table 4: Areas under the ROC curves for clinical examination combined with mammography (CE+MAM) and the final diagnosis (CE+MAM+US) by indication for referral and age groups (n=2812)

Referral criteria	Age	N	Pos (%)	Area under curve (+ 95%CI)		p ¹	Mal ²
				CE+MAM	CE+MAM+US		
Palpable lump	Total	496	55 (11%)	0.92 (0.88-0.97)	0.98 (0.96-1.0)	0.004	
	≤50 y	354	21	0.87 (0.77-0.97)	0.96 (0.92-1.0)	0.03	3
	>50 y	142	34	0.95 (0.91-0.99)	0.99 (0.98-1.0)	0.03	
Follow up NBCSP ³	>50 y	147	41 (28%)	0.92 (0.87-0.97)	0.96 (0.93-0.99)	0.05	
Symptomatic complaints	Total	600	17 (3%)	0.94 (0.87-1.0)	0.98 (0.95-1.0)	0.28	
	≤50 y	397	5	0.97 (0.92-1.0)	0.96 (0.90-1.0)	0.89	
	>50 y	203	12	0.93 (0.82-1.0)	0.98 (0.95-1.0)	0.24	1
Follow up malignancy	Total	692	8 (1%)	0.78 (0.57-1.0)	0.92 (0.77-1.07)	0.16	
	≤50 y	156	4	0.72 (0.39-1.0)	0.84 (0.56-1.13)	0.26	1
	>50 y	536	4	0.85 (0.58-1.12)	0.99 (0.99-1.0)	0.30	1
Follow up benign abn.	Total	223	3 (1%)			N.A. ⁴	
	≤50 y	123	1			N.A. ⁴	1
	>50 y	100	2			N.A. ⁴	
Reassurance ⁵	Total	654	1 (<1%)			N.A. ⁴	
	≤50 y	459	1			N.A. ⁴	
	>50 y	195	0			N.A. ⁴	

¹ testing of CE+MAM+US vs. CE+MAM² malignancies detected only by breast ultrasonography (1 case was referred for the contralateral breast)³ national breast cancer screening program⁴ not applicable, too few malignancies in this group⁵ including family history or fear of breast cancer, asymptomatic patients

by clinical examination and mammography (p=not applicable because of small numbers).

Finally, among the 654 cases referred for reassurance, because of fear or a family history of breast cancer, ultrasonography missed the single malignancy in this group, which was detected by clinical examination and mammography (p=not applicable because of small numbers). There were 12 false-positive ultrasonographic examinations of which 4 were also false-positive mammographically.

For the 8 patients in whom only breast ultrasonography detected a malignancy the indications for referral were: palpable breast lumps (n=3), follow up of prior malignancy (n=2), follow up of prior benign abnormality (n=1) and breast symptoms (n=1). In 1 case the cancer was found "by chance" while the reason for referral was a palpable mass on the contralateral side.

Discussion

In this outpatient population systematic application of ultrasonography as adjunct to clinical examination and mammography significantly increased the diagnostic performance. The diagnostic gain of ultrasonography was found in the detection of 8 extra malignancies that were missed at clinical examination and mammography. Further profit was shown by the downgrading of false-positive clinical and

mammographic results ($n=332$). Most of these were cysts or fibroadenoma, although not all of them were confirmed by pathology^{2, 4, 17, 18}.

On the other hand, diagnostic loss was reflected by 46 false-positive and 1 false-negative ultrasonographic result.

The final diagnosis of CE+MAM+US had a sensitivity of 97% and specificity of 95%. Integrated diagnoses combining results of mammography and ultrasonography have been reported in several studies^{2, 5, 7-12, 19}. However, many studies fail to explain how this integrated diagnosis was obtained and only few studies describe consecutive sets of patients. Comparison with our data should therefore be done carefully, but lower sensitivities and slightly higher specificities are reported^{5, 12, 19}. This may be explained by their study design in which ultrasonography was only applied on clinical indication. In our study, systematic ultrasonography increased the number of true and false-positive diagnoses, affecting both sensitivity and specificity.

The prevalence of breast cancer in this population was 6.3% and is consistent with results of these other studies in consecutive patients, reporting prevalences of 5 – 7.1%^{5, 12, 19}.

The prevalence was somewhat lower in patients excluded from the study (4%), but we believe this does not affect the generalizability of the study.

Despite the overall increase in diagnostic yield by systematic application, breast ultrasonography should be restricted to subgroups of patients who benefit most in order to reduce costs, time load and harmful consequences of unnecessary examinations. According to our results the application of breast ultrasonography was most beneficial to patients referred for palpable breast lumps and patients with an abnormal screening mammogram referred by the national breast cancer screening program. Applying these criteria to our population, ultrasonography would be indicated in 30% of patients referred for diagnostic breast imaging to the radiology department of a referral hospital (614/2020).

In the current literature the presence of a palpable mass in young women is a well-described indication for breast ultrasonography as initial diagnostic imaging test^{3, 4, 18,}

²⁰ or as adjunct to mammography^{12, 19}. While most studies are referring to women of 35 years and younger, our results are applicable to women of 50 years and younger.

Ultrasonography detected additional malignancies in 8 patients, of whom 3 were referred because of a palpable mass and 1 patient had a palpable lump at clinical examination. According to current clinical guidelines all palpable masses should undergo cytological investigation, which would have detected these malignancies as well. However, ultrasonography still has an important diagnostic role in these cases by completing "triple assessment", consisting of clinical examination, radiological imaging and cytology diagnosis, which facilitates treatment planning. Furthermore, as a proportion of the cytological investigations will be indeterminate, these ultrasonography results will be very valuable.

An abnormal screening mammogram has not been reported in the literature as indication for additional ultrasonography, but palpable or non-palpable non-conclusive mammographic abnormalities are discussed^{12, 18, 19, 21, 22}. In the patients referred from the national breast cancer screening program, ultrasonography reduced the number of false-positive mammograms, by downgrading a quarter of all positive cases.

The increase in diagnostic value was not significant in patients referred with breast symptoms or patients referred for follow up of a prior malignancy. Remarkably, in this last group the largest absolute increase in AUC was found, but the small number of

positive cases and the relatively high standard errors prevent us from drawing any definitive conclusions¹⁵.

Furthermore, in the groups of patients referred for follow up of a previous benign lesion or for reassurance there were too few malignant cases for constructing ROC curves and no additional value for ultrasonography could be demonstrated.

The role of breast ultrasonography in screening asymptomatic patients is a controversial one, because of the high numbers of false-positive and false-negative results^{2, 4, 23, 24}. Our data show 5 malignancies in the cases without a clinical indication (table 3), of which 4 malignancies were found in contralateral breasts and only 1 malignancy in the group referrals for reassurance (table 4), suggesting a poor diagnostic yield of breast imaging as a whole in these patients.

An alternative way for recoding indeterminate test results for analysis, would be through the comparison of likelihood ratios for each level of suspicion²⁵, and recoding them as the level that is most alike. Doing so, the results would change slightly as indeterminate mammograms would be recoded as negative findings, but our final conclusions would be similar. However, we believe that our applied method of recoding approaches clinical practice best, as indeterminate mammograms will always result in additional testing. Furthermore, the BI-RADS lexicon also treats indeterminate mammograms as positive¹³.

Recoding indeterminate clinical examinations as positive results, as done for mammography and ultrasonography, also would not affect the AUC (0.83 vs 0.84) or change our conclusions.

Many diagnostic studies report unequal follow up periods for patients included over several months or years, by using one end point. As a consequence, these studies are biased in their definition of the criterion standard, as the length of follow up is different for each case. Therefore, in the current study an equal follow up period of 12 months was used for all patients, extended with 2 months for administrative transactions of results at the end of this period. The period of 12 months was chosen to minimize the chance of detection of newly developed (interval) cancers and maximizing the chance of detecting the malignancies present. Nevertheless, when including the total range of follow up from October 1999 to October 2001 (median: 19 months, range: 14 – 24 months) no additional false-negative imaging results were found. It should be noted that despite the passive nature of the follow up in which patients did not undergo repeat testing after 12 months, we believe that the registration system used covered all pathology available for the whole study population.

It should be noted that the indications for breast imaging in this study were defined by the referring doctors and symptoms could not always be confirmed by the specialist conducting the clinical examination, e.g. the palpation of a palpable lump. As such situations reflect clinical practice we decided to use the specified reason for referral in these cases rather than our findings at clinical examination.

Associated is the fact that additional indications for ultrasonography could be defined based on results of clinical examination and mammography. However, by applying the current set of criteria in daily practice, the advice to perform or withhold additional ultrasonography could be given at the stage of referral for breast imaging. Doing so, the planning of breast imaging could be optimized and the number of redundant ultrasonographic examinations reduced. Additional research will be needed to determine the cost-effectiveness of the application of breast ultrasonography in these specified groups of patients.

Concluding, systematic application of additional breast ultrasonography improved the diagnostic performance in this population. Although the overall diagnostic yield

improved, the number of unnecessary examinations can be reduced by restricting breast ultrasonography mainly to patients with palpable breast lumps and patients referred with abnormal screening mammograms. Implementation of these evidence-based indications in clinical practice is expected to lead to more efficient and effective use of breast ultrasonography.

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5

PREDICTIVE DIAGNOSTIC VARIABLES IN THE DIAGNOSIS OF BREAST CANCER: THE ROLE OF ULTRASONOGRAPHY

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(Submitted)

Abstract

Aim

To determine which diagnostic information from medical history, clinical examination, mammography and ultrasonography contributes to the prediction of breast cancer.

To study the contribution of additional ultrasonography next to mammography and clinical examination in the prediction of breast cancer for different patient populations.

Methods

2020 consecutive patients referred for breast imaging underwent bilateral clinical examination, mammography and ultrasonography. Pathology results during 12 months follow up were used as reference standard for breast cancer.

A prediction model was designed by multivariate logistic regression analysis.

ROC curve analysis studied the contribution of ultrasonography for different subgroups of patients according to the reason for referral and other characteristics.

Results

The diagnostic algorithm for breast cancer included: age, menopause, specific breast symptoms, diagnosis of clinical examination, mammographic calcifications and the integrated diagnosis resulting from ultrasonography, mammography and clinical examination.

ROC curve analysis showed that each step in the diagnostic work-up improved the predictive value of the model. Using all available diagnostic information a sensitivity of 95% and specificity of 92% could be reached.

Stratified analysis showed that additional ultrasonography significantly improved the predictive value of the model in patients referred for palpable masses ($p=0.04$). Among patients without a palpable lump, ultrasonography contributed most to the diagnosis in the subgroup of premenopausal patients ($p=0.39$).

Conclusion

All stages of the diagnostic imaging work-up contributed to the diagnosis of breast cancer. Additional ultrasonography improved the predictive value of the model most significantly in patients referred for a palpable lump.

Introduction

Every year about 10.000 new breast cancers are diagnosed in The Netherlands. Apart from the group of patients who are diagnosed through the national breast cancer screening program, most new cases are detected by diagnostic breast imaging performed by radiologists in a hospital setting.

Routine diagnostic breast imaging in the radiology departments of most hospitals consists of clinical examination, mammography, and ultrasonography when indicated. All information on the lesions and abnormalities found by these tests is combined with the knowledge of patient characteristics from medical history into one overall diagnosis indicating the suspicion of breast cancer. Much has been written in the literature about the typical features of breast malignancies on clinical examination, mammography and ultrasonography, but very little has been reported about the specific contribution of each test in defining an overall diagnosis.

The most common clinical indications for breast ultrasonography as adjunct to mammography are the differentiation between cysts and solid masses and the further evaluation of a palpable mass when mammography is inconclusive¹⁻⁵. However, as a result of broadening indications and increasing availability and accessibility, the application of ultrasonography has increased strongly over the past decade and it is also being used in a number of clinical situations in which no efficacy has been demonstrated. Although 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 unwise⁶. This raises the question of which subgroups of patients obtain most diagnostic information from additional ultrasonography.

The purpose of this study was to determine which diagnostic information from medical history, clinical examination, mammography and ultrasonography contributes most to the prediction of breast cancer. More specifically, the contribution of additional ultrasonography in the prediction of breast cancer was studied for different patient populations.

Patients and Methods

Study population

Between October 1999 and August 2000, 2020 consecutive patients referred to our radiology department for diagnostic breast imaging, underwent additional ultrasonography after clinical examination and mammography. Bilateral clinical examination, performed in upright and supine position, was followed by bilateral standard craniocaudal and mediolateral oblique diagnostic mammograms (Siemens Mammomat-2 unit / Kodak Min-R film screen combination), and then followed by bilateral whole breast ultrasonography (ATL5000 12.5 MHz linear array transducer). Additional mammographic views were employed when considered necessary. Conforming to clinical practice, all examinations were carried out and interpreted with full knowledge of prior test results.

The mean age of the study population was 50.2 (range 16.8 – 90.3). Patients were referred by general practitioners (n=1044), surgeons (n=712) and other specialists (n=264). Unilateral examination was performed in 182 patients with breast amputations and in 23 patients for other reasons. Consequently 3835 breasts were examined in 2020 patients.

Indications for referral for breast imaging were: a palpable breast lump ($n=496$ breasts), other breast symptomatology like pain, skin or nipple abnormalities ($n=601$), follow up for prior breast malignancy ($n=692$), follow up for prior benign breast disease ($n=223$), mammographic abnormalities detected through the national breast cancer screening program ($n=147$) and reassurance (family history of breast cancer, patients' anxiety or other asymptomatic reasons, $n=654$). Furthermore, 1022 contralateral breasts with no clinical indication for breast imaging were examined.

After a follow up of 12 months during which pathology results from core needle biopsies, excision biopsies and other surgical interventions were registered, a total of 129 malignancies were found in 127 patients, leading to a prevalence of breast cancer of 6.3% (127/2020). The period of 12 months was chosen to minimize the chance of detection of newly developed (interval) cancers and maximizing the chance of detecting the malignancies present.

All relevant patient characteristics and the description, size and location of lesions found at the different examinations, were registered. A conclusive diagnosis was scored per breast on a 3-point grading scale with increasing suspicion for malignancy, for clinical examination alone, for mammography combined with clinical examination and for ultrasonography integrated with mammography and clinical examination. This 3-point grading scale was largely based on the 5-point BI-RADS grading scale for mammography and under development for ultrasonography^{7, 8}, and on the prevalence of breast cancer per grade on this scale. Normal scores were coded with indeterminate results into one group, benign and probably benign scores in another, and suspicious malignant and malignant scores in the third group.

Prediction model

The predictive value of different diagnostic variables in detecting breast cancer was studied by multivariate logistic regression analysis. Corresponding to the process of diagnostic breast imaging 4 categories of diagnostic variables were defined: the first category consisted of information generally available from medical history at referral, such as the reason for referral, history of breast disease, and age.

The second category of variables included those obtained by clinical examination, like the presence of a palpable lump or specific breast symptoms. Following, the third category consisted of variables obtained from consequent mammographic examination, like the margins of mammographic lesions and calcifications. Finally, the fourth category of variables was obtained by ultrasonography and included the characteristics of lesions identified. A more detailed description of the included variables is shown in table 1.

First, univariate analysis selected the variables with a significant association with breast cancer ($p<0.15$). Consequently, these variables were included in a stepwise multivariate regression analysis with the presence of breast cancer as dependent variable (entry at $p<0.10$, removal at $p>0.15$ level). Significant variables of preceding categories were fixed in the model before variables of the next category were added. Then, backward regression analysis was done to eliminate variables with little contributing value on the complete model. The effectiveness of the model in predicting breast cancer was assessed by Hosmer and Lemeshow goodness-of-fit testing⁹.

The final model was converted into a diagnostic algorithm scoring system. Probability calculation can be done for individual patients by adding up the scores for the outcomes of the different variables. Converting this into a Z-score, a p-value can be calculated which represents the probability of breast cancer based on these results.

Table 1: Diagnostic variables from medical history, clinical examination (CE), mammography (MAM) and ultrasonography (US) and their significance (Sign) in univariate logistic regression analysis for the prediction of breast cancer (S= significant ($p < 0.10$), NS = not significant)

Category	Variable	Coding	Sign
I Medical history	Age	1 = <35.0 years	S
		2 = 35.01 – 50.0 years	
		3 = >50.01 years	
	Reason for referral	0 = no referral, contralateral breast	S
		1 = reassurance (family history, fear of patient)	
		2 = follow up of prior malignant abnormality	
		3 = follow up of prior benign abnormality	
		4 = symptomatology	
		5 = palpable lump	
		6 = referral from national screening program	
	Menopause	1 = premenopausal	S
		2 = postmenopausal	
	History of breast disease	0 = no prior breast disease	S
		1 = prior benign breast disease	
		2 = prior malignant breast disease	
	Hormone use	0 = none, never	S
		1 = yes, ever (oral contraceptives/replacement therapy)	
	Family history ^{21, 27}	0 = no	NS
		1 = yes	
	Body mass index	Continuous variable	NS
II Clinical examination ¹	Palpable lump	0 = no	S
		1 = yes	
	Specific symptoms	0 = no	S
		1 = yes: skin retraction, nipple discharge, edema, peau d'orange, ulceration	
	Aspecific symptoms	0 = no	NS
		1 = yes: pain, asymmetry, eczema, scarring, venous marking	
	Diagnosis CE	0 = normal / indeterminate	S
		1 = benign / probably benign	
		2 = suspicious malignant / malignant	
III Mammography ²	Lesion present	0 = no	S
		1 = yes	
	Margin lesion	0 = none, not applicable	S
		1 = circumscribed	
		2 = ill-defined or spiculated	
	Calcification	0 = no	S
		1 = benign calcifications	
		2 = suspect or malignant calcifications	
	Density breast parenchyma ⁷	1 = 0 – 25%: fat containing	NS
		2 = 26 – 50%: scattered densities	
		3 = 52 – 75%: heterogeneously dense	
		4 = 76 – 100%: extremely dense	

	Diagnosis	0= normal / indeterminate	S
	CE+MAM	1= benign / probably benign	
		2= suspicious malignant / malignant	
IV Ultrasonography ³	Lesion present	0= no	S
		1= yes	
	Margins of lesion	0= none, not applicable	S
		1= smooth	
		2= irregular	
	Structure of lesion	0= none, not applicable	S
		1= hypoechoic	
		2= hyperechoic	
	Shape of lesion	0= none, not applicable	S
		1= round, egg-shaped	
		2= lobulated	
	Homo/heterogeneity	0= none, not applicable	S
		1= homogeneous lesion	
		2= heterogeneous lesion	
	Diagnosis	0= normal / indeterminate	S
	CE+MAM+US	1= benign / probably benign	
		2= suspicious malignant / malignant	

¹ Univariate analysis of variables from CE (category 2), giving fixed variables in the model from the stage of referral (category 1).

² Univariate analysis of variables from MAM (category 3), giving fixed variables in the model from category 1 and 2.

³ Univariate analysis of variables from US (category 4), giving fixed variables in the model from category 1, 2 and 3.

By calculating sensitivities and specificities for the different cut-off points of the predicted probabilities that were generated for each category of variables, receiver operating characteristic (ROC) curves were drawn. Areas under the curve (AUC) were calculated as a measure for the diagnostic performance. The additional diagnostic value of each category was determined by testing the difference in AUC according to the method of Hanley et al.^{10, 11}.

In order to study the contribution of breast ultrasonography in the prediction of breast cancer, a backward regression analysis was performed including variables of category 1-4 as well as variables of category 1-3 and the resulting ROC curves were compared. Finally, analyses were stratified for different subgroups of patients, according to reason for referral and clinical features.

Results

Diagnostic algorithm

Table 1 shows the results of univariate regression analysis of variables from all 4 categories. A family history of breast cancer, the body mass index, aspecific breast symptoms and the density of breast parenchyma on mammography were not related to the presence of breast cancer.

Including the remaining variables in stepwise multivariate regression analysis resulted in a model with 10 variables. Backward elimination of redundant variables excluded 4 variables, namely the reason for referral, history of prior breast disease, margins of mammographic lesions and the diagnosis of mammography and clinical examination. The resulting prediction model thus included 6 variables: age, menopause, specific breast symptoms, conclusive diagnosis from clinical examination, calcifications at mammography and the integrated diagnosis from ultrasonography, mammography and clinical examination. Hosmer and Lemeshow goodness-of-fit testing showed a good fit of this model ($p=0.808$).

This model was converted into a diagnostic algorithm scoring system for individual breast cancer probability calculation, which is shown in table 2.

Table 2: Diagnostic algorithm for breast cancer including variables from medical history, clinical examination (CE), mammography (MAM) and ultrasonography (US) based on multivariate logistic regression analysis

Category	Variable	Coding	Score
I Medical history	Age	1 = <35.00 years	0
		2 = 35.01 – 50.00 years	14
		3 = >50.01 years	2
	Menopause	1 = premenopausal	0
		2 = postmenopausal	18
II Clinical examination	Specific symptoms	0 = no	0
		1 = yes: skin retraction, nipple discharge, edema, peau d'orange, ulceration	9
	Diagnosis CE	0 = normal / indeterminate	0
		1 = benign / probably benign	13
		2 = suspicious malignant / malignant	27
III Mammography	Calcification	0 = no	0
		1 = benign calcifications	-5
		2 = suspect or malignant calcifications	10
IV Ultrasonography	Diagnosis	0 = normal / indeterminate	0
	CE+MAM+US	1 = benign / probably benign	31
		2 = suspicious malignant / malignant	79

Probability calculation for individual patient: $X =$

Add up all scores in total score (X), range -5 – 157 $Z =$

Calculate Z-score: $Z = X - 98$ $P =$

Calculate probability of malignancy $P: e^{z/10} / (1 + e^{z/10})$

example 1: a premenopausal patient, 48 years old, is having no specific breast symptoms and a probably benign clinical examination because of a palpable lump. Some benign calcifications are found by mammography and the combined diagnosis from ultrasonography, mammography and clinical examination was suspicious. The total score according to our algorithm is: 101, $Z=3$, and the predicted probability of malignancy is $p=0.574$

example 2: a postmenopausal patient, 60 years old, is referred with an abnormal screening mammogram from the national breast cancer screening program. She has no specific breast symptoms and a normal clinical examination. There are some suspect calcifications on mammography but the overall diagnosis from ultrasonography, mammography and clinical examination was benign. The total score according to our algorithm is: 61, $Z=-37$, and the predicted probability of malignancy is $p=0.024$

Contribution of ultrasonography

ROC curves of the generated predicted probabilities from this model are plotted in figure 1. The AUC increased when adding diagnostic variables from each consecutive category.

Figure 1: ROC curve of predictive value of variables included from medical history, clinical examination (CE), mammography (MAM) and ultrasonography (US) by multivariate logistic regression analysis.

An AUC of 0.984 was obtained when including information from all categories. When selecting the point of the curve that is nearest the top left-hand corner, a sensitivity of 95% and a specificity of 92% can be reached.

Comparing the ROC curve of the complete model, including variables from medical history, clinical examination, mammography and ultrasonography (cat1-4, AUC: 0.984) with the curve for medical history, clinical examination and mammography only (cat1-3, AUC: 0.966) showed that the increase in predictive value by adding ultrasonography approached statistical significance ($p=0.057$).

Subgroups of patients

The prediction model was further analyzed for different subgroups of patients according to the reason for referral. The AUC of the resulting ROC curves are shown in table 3.

Table 3: Areas under the ROC curves (AUC) for prediction models by multivariate logistic regression with ultrasonography (variables category 1-4) and without ultrasonography (variables category 1-3) for different reasons of referral

Reason for referral	N (mal)	AUC cat 1-4	AUC cat1-3	p-value
Palpable lump	496 (55)	0.986	0.955	0.04
National screening program	147 (41)	0.953	0.941	0.64
Symptomatology	601 (17)	0.995	0.990	0.38
Follow up malignancy	692 (8)	0.917	0.834	0.29
Follow up benign abnormality	223 (3)		0.919	
Reassurance	654 (1)	0.969	0.969	
No reason: contralateral side	1022 (4)	1.000	1.000	

In patients referred for a palpable breast lump additional ultrasonography significantly improved the predictive value of the model ($p=0.04$). The largest increase in AUC was found for patients referred for follow up of a prior breast malignancy ($p=0.29$).

In patients referred from the national screening program and patients with other breast symptomatology there was a smaller increase in AUC ($p=0.64$ and $p=0.38$ respectively).

Finally, in patients referred for follow up of a benign lesion, for reassurance and when the contralateral side was examined, no increase in AUC was demonstrated when adding ultrasonography to the model.

Table 4 shows similar analyses for different clinical situations in patients without palpable lumps. For premenopausal women there was an increase in AUC of 0.062 when adding ultrasonography to the model ($p=0.39$).

For the other subgroups of patients no substantial difference in AUC was demonstrated for the models with and without ultrasonography. Furthermore it is shown that there was almost no difference between the performance of the models in patients with or without prior history of breast cancer, or patients with or without dense breast parenchyma.

Table 4: Areas under the ROC curves (AUC) for prediction models by multivariate logistic regression with ultrasonography (variables category 1-4) and without ultrasonography (variables category 1-3) for different clinical characteristics in cases without palpable lumps

Clinical characteristics	N (mal)	AUC cat 1-4	AUC cat1-3	p-value
Premenopausal	1610 (6)	0.978	0.916	0.39
Postmenopausal	1140 (20)	0.970	0.976	0.75
Prior history breast disease	2074 (21)	0.999	0.998	0.45
No prior history breast disease	658 (7)	0.985	0.975	0.44
Dense breast parenchyma	1096 (6)	0.969	0.969	
No dense breast parenchyma	1765 (22)	0.971	0.972	0.96

Discussion

This study shows that diagnostic information from all different stages of the diagnostic work-up contributed in the prediction of breast cancer, including the medical history, clinical examination, mammography and ultrasonography. ROC curve analysis showed that by combining information from all categories an AUC of 0.984 was obtained and a sensitivity of 95% and specificity of 92% could be reached. Furthermore, it was demonstrated that in this study population the performance of additional ultrasonography improved the model's predictive value for breast cancer more or less significantly. This was illustrated by the inclusion of the integrated diagnosis of ultrasonography, mammography and clinical examination as variable in the prediction model. The contribution of the diagnosis of mammography combined with clinical examination was non-significant ($p\text{-value} > 0.15$) and was excluded from the model, which may be explained by the obviously strong interaction with the integrated overall diagnosis.

Based on ROC curve analysis, we showed that breast ultrasonography mainly contributed to the prediction of breast cancer in patients referred for palpable lumps, and to a lesser degree in patients referred with an abnormal screening mammogram and patients referred for other symptomatology. In patients referred for follow up of a prior breast malignancy the increase in AUC was largest, but not statistically significant. This may be explained by the low number of malignancies in this group ($n=8$). However, it should be concluded that there is an important contributing role for breast ultrasonography in the prediction of breast cancer in this group of patients.

A palpable breast lump is a well-established indication for breast ultrasonography^{1,3,5}. Purasiri et al. reported a diagnostic index based on diagnostic scores of clinical examination, mammography, ultrasonography, age and fine needle aspiration cytology in patients with palpable lesions¹². In contrast to our results, their model failed to show any predictive value for ultrasonography in these patients.

Furthermore, Roche et al. reported a scoring system for breast imaging in patients with palpable lumps, but analyzed diagnostic scores of cytology combined with radiology, consisting of the combination of mammography and ultrasonography which makes it impossible to define the role for ultrasonography separately¹³.

In both examples, fine needle aspiration cytology was included in the model as it has become part of the routine diagnostic work-up of palpable breast lesions^{14, 15}. However, our model represents the process of routine diagnostic breast imaging at a radiology department, and therefore only includes clinical examination and radiological imaging.

In order to define more subgroups of patients in whom ultrasonography contributed in the prediction of breast cancer, patients without a palpable lump were studied further. Within the different subgroups of patients as specified in table 4, premenopausal patients had a larger increase in AUC than postmenopausal patients by adding ultrasonography to the model. Although the increase in AUC was not significant, which may be explained by the small number of malignancies in the group of premenopausal women, it should be concluded that ultrasonography does contribute substantially to the prediction of breast cancer in these patients.

The additional predictive value of ultrasonography was not influenced by the presence of dense breast parenchyma or a prior history of breast cancer. This is a notable result as some studies conclude that bilateral whole-breast ultrasonography, when

performed in patients with dense breast tissue, is useful in detecting breast cancer not discovered with mammography or clinical breast examination. However, in these studies the reported cancer detection rate was very low¹⁶⁻²⁰. Possibly, the low number of malignancies in our patient group is an explanation for this finding.

It was surprising that in univariate analysis a positive family history was not related to the presence of breast cancer in this population, despite its well-known role as a risk factor for breast cancer²¹. This may be explained by the composition of our study population, presenting with a higher prevalence of breast cancer than the general population.

Also, several statistically significant variables from univariate analysis did not contribute significantly to the final prediction model and were therefore excluded, e.g. the use of hormones, the reason for referral and the presence of a palpable lump. Apparently, the predictive value of these variables was weakened by the inclusion of other, stronger, variables. Likewise, in univariate analysis all ultrasonographic characteristics were statistically significant, e.g. the shape and the margins of suspect lesions, but in multivariate analysis only the final ultrasonography diagnosis (integrated with mammography and clinical examination), was included. This may be explained by the acquisition of the diagnosis. A 3-point grading scale with increasing suspicion of malignancy was used to define the diagnosis of each modality. As these diagnostic scores integrate all findings of a test, they will actually contain information on the other variables in the analysis as well, leading to the exclusion of other contributing variables from the model. From this result, it can be concluded that this scoring system is very powerful.

Diagnostic algorithms as presented may be helpful in medical decision-making in daily practice, by estimating a patient's probability of having breast cancer. Many methods have already been developed to estimate the risk of breast cancer for women with a given age and risk factors in the general population^{22, 23}. Next to the fact that these models do not include the results of imaging tests, they are not applicable to our outpatient population, because a different distribution of risk factors and breast cancer prevalence would require a different composition of predictive variables. The algorithm presented here is therefore only applicable to a comparable outpatient population referred for breast imaging, having a prevalence of breast cancer of around 6%. We believe this will concern the patient populations of most breast imaging clinics and radiology departments in hospitals in and outside The Netherlands²⁴⁻²⁶.

Nevertheless, the value of this model in clinical practice may be argued. After having performed clinical examination, mammography and ultrasonography the radiologist may not so much be interested in the patient's chance of having breast cancer, but rather in whether the patient should be discharged or referred for additional diagnostic procedures. In order to fill these needs, future research should be aimed at the expansion of the model with variables on pathological tests, such as fine needle aspiration cytology, core needle biopsy and excision surgery.

Meanwhile, the current model demonstrates clearly which variables are most significant in the realization of a final imaging diagnosis. In order to improve the performance of diagnostic breast imaging in radiology departments, a standard registration of these specific variables should be encouraged.

Concluding, the prediction model showed that all stages of the diagnostic imaging work-up for breast disease contributed to the diagnosis of breast cancer. Additional ultrasonography improved the predictive value of the model most significantly in patients referred for a palpable lump. Furthermore, among patients without a palpable lump, ultrasonography contributed most to the diagnosis in the subgroup of premenopausal patients.

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6

COSTS AND EFFECTS OF THE USE OF ULTRASONOGRAPHY IN THE EVALUATION OF PALPABLE BREAST MASSES

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(Submitted)

Abstract

Aim

To study the cost-effectiveness of incorporating ultrasonography in the triple test for evaluating palpable breast masses.

Methods

A decision analytic model was used to compare the conventional strategy of immediate fine needle aspiration cytology (FNAC) following mammography and clinical examination with 3 different experimental strategies of prior ultrasonography.

In strategy 1, a cut-off between benign and probably benign ultrasonography results was used for further referral for FNAC; in strategy 2, this cut-off was shifted to a cut-off between normal and benign results; and in strategy 3, prior ultrasonography was only performed in patients with normal, benign results on mammography and clinical examination, whereas immediate FNAC was performed in patients with suspicious lesions. Empirical data were obtained from a prospective study in 522 breasts with a palpable mass, including 93 malignancies. Outcome variables included the total costs and the expected number of life years. Sensitivity analysis was performed on all parameters in the model.

Results

All strategies reported similar life expectancies, namely 31.0 life years. Cost-minimization demonstrated that experimental strategy-3 was the least expensive strategy (€ 2946). Experimental strategy-2 was the most costly strategy (€ 3475). Compared to the conventional strategy of immediate FNAC (€ 3087), both ultrasonography strategy 1 and 3 were preferred.

Sensitivity analysis showed that the proportion of suspicious or benign FNAC results and the proportion of false-negative ultrasonography results were the most influential variables on the cost outcome of the model.

Conclusion

A reduction in total costs for the diagnosis and treatment of breast cancer can be established when incorporating diagnostic ultrasonography in the triple test for the evaluation of palpable breast masses.

Introduction

Breast cancer is the leading cause of death in women in the Western world and the diagnosis and treatment have become a financial burden to health care services. Many patients are referred by their general practitioner to a hospital setting for diagnostic breast imaging of a palpable breast mass. Routine diagnostic work-up of palpable breast masses includes the performance of clinical examination, mammography and fine needle aspiration cytology (FNAC), combined as the "triple test". Several studies have shown that the triple test is accurate and can replace open surgical biopsy for diagnosis when all 3 components are concordant (all indicating a benign condition or all indicating a malignant condition)^{1,2}.

Additionally, a palpable breast lump has become an important indication for ultrasonographic examination³⁻¹¹. Several prospective studies have demonstrated the diagnostic value of ultrasonography as an adjunct to mammography in these patients and report sensitivities and specificities of 93%-99% and 67%-97% respectively¹²⁻¹⁶. The usefulness of ultrasonography lies in the differentiation between solid and cystic masses. A 100% accuracy in the diagnosis of a cyst can be reached when strict criteria are used, consisting of a round oval shape or gently lobulated, circumscribed margin, anechoic echogenicity and acoustic enhancement⁸. By diagnosing cysts, ultrasonography can reduce the suspicion for breast cancer and save patients from additional pathological examinations, including FNAC. In many cases, the radiologist will perform ultrasonography-guided fine needle aspiration of cystic fluid, but the examination by the pathologist can be spared and will reduce patient charges. Furthermore, ultrasonography may detect abnormalities which are palpable but mammographically occult, e.g. because of radiologically dense breast tissue.

These effects indicate that ultrasonography could be incorporated in the triple test for palpable breast masses. Vetto et al. studied the accuracy of a modified triple test in 55 women younger than 40 years, in which ultrasonography substituted mammography¹⁷. As the sensitivity of mammography is lower in younger patients with dense, glandular breasts, ultrasonography can be performed as initial imaging study in these patients, next to clinical examination. The authors report a high diagnostic accuracy reducing the need for routine open biopsy, resulting in an overall reduction in patient charges. However, when expanding this study to patients older than 40 years, ultrasonography would have to be applied as an adjunct to mammography rather than as a substitute. Furthermore, the costs of performing ultrasonography in all these patients are considerable and the suitability of its application in daily clinical practice will therefore also depend on the cost-effectiveness.

In an earlier prospective study at the radiology department of Maastricht University Hospital, we assessed the diagnostic value of ultrasonography as an adjunct to mammography and clinical examination in the evaluation of 492 patients with 522 palpable breast masses.

The aim of the present study was to assess the cost-effectiveness of incorporating ultrasonography in the triple test for evaluating palpable breast masses. Three different scenarios were studied and in order to compare the associated costs and effects with the routine conventional triple test, a decision analytic model was designed.

Figure 1: decision tree for diagnostic strategies

Legend:

Diagnosis: ultrasonography (US)

Diagnosis FNAC:

Diagnosis (core needle) biopsy:

Diagnosis surgery:

TP:

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1=normal, 2=benign, 3=probably benign, 4=suspect malignant, 5=malignant

1 = normal, 2 = benign, 3 = suspect malignant, 4 = malignant, 0 = indeterminate

1 = normal, 2 = benign, 3 = probably benign, 4 = suspect malignant, 5 = malignant, 0 = indeterminate

$\perp$ = normal, $\angle$ = benign
malignant, benign

malignant, benign
true-positive result malignant

true-positive result, malignant
 true-negative result, benign or normal

true-negative result, benign or normal

false-positive result, benign or no

Methods

Diagnostic strategies

Four different strategies following the performance of mammography and clinical examination in patients with palpable breast masses were compared (table 1). The **conventional strategy** consisted of immediate FNAC after mammography and clinical examination in all patients, according to the triple test. In **experimental strategy-1**, prior ultrasonography was performed in all patients and a cut-off point between benign and probably benign results was used for referral for additional FNAC. Patients were discharged when no abnormality or a cyst was found. When a solid benign structure was detected, such as a fibroadenoma, simple excision was performed. All suspicious findings on ultrasonography were eventually excised; none were discharged. In **experimental strategy-2**, the effect of shifting the cut-off point for referral for FNAC between normal and benign ultrasonography results was studied. Assumptions were similar to those in experimental strategy-1. In **experimental strategy-3**, prior ultrasonography was only performed in patients with normal or benign results on mammography and clinical examination, whereas immediate FNAC was performed in patients with suspicious lesions.

Table 1: Different diagnostic strategies analyzed

Strategy	Sequence of diagnostic procedures		
Conventional	CE+MAM 1,2,3,4,5	FNAC 1,2,3,4,5	
Experimental-1	CE+MAM 1,2,3,4,5	US 1,2	Discharge
		US 3,4,5	FNAC
Experimental-2	CE+MAM 1,2,3,4,5	US 1	Discharge
		US 2,3,4,5	FNAC
Experimental-3	CE+MAM 1,2	US 1,2	Discharge
	CE+MAM 3,4,5	US 3,4,5	FNAC
		FNAC	

Legend: CE= clinical examination, MAM= mammography, US= ultrasonography, FNAC= fine needle aspiration cytology, diagnostic scores: 1= normal, 2= benign, 3= probably benign, 4= suspicious malignant, 5= malignant

As empirical data were not available for all strategies, a decision analytic model was constructed using the computer program Decision Analysis by TreeAge (DATA3.5; TreeAge software, Williamstown, Mass). A short version of the decision tree comparing the strategies (square mode) is shown in figure 1. The model included diagnostic procedures such as ultrasonography, FNAC and histological core needle biopsy; primary therapeutic events such as excision biopsy, surgery, radiotherapy, chemotherapy and hormonal therapy; and treatment of local recurrences, distant recurrences and palliative care at the terminal stage of the disease. Ultrasonography-guided fine needle aspiration of a cyst was regarded as part of diagnostic ultrasonography, unless cytological examination was requested from a pathologist. A distinction was made between surgery of a benign lesion (excision biopsy) or a malignant lesion (curative, malignant surgery).

The routes following FNAC were the same for all strategies; either surgery of a malignant lesion, surgery of a benign lesion or core needle biopsy of a lesion of

uncertain nature was performed. Additionally, in the conventional strategy, a proportion of patients with normal FNAC results underwent further biopsy or surgical excision, in order to rule out a false-negative result while no ultrasonographic confirmation of the diagnosis was available.

In figure 2, the subtree for surgical treatment of malignant breast lesions is shown. Surgery of a mass that was radiologically diagnosed as malignant could reveal a true-positive or false-positive result. Further distinction was made between cases with a bad prognosis leading directly to palliative care, surgery with and without adjuvant chemotherapy and hormonal therapy, and occurrence of a local or systemic recurrence.

Figure 2: subtree for surgery of malignant breast lesions

Legend:

TP: true-positive result, malignant

FP: false-positive result, benign or normal

It was assumed that all malignancies detected by ultrasonography in the experimental strategies were detected by FNAC in the conventional strategy. Consequently, the prevalence of malignancy and the discharge-rate were equal in all strategies.

The outcome of each clinical pathway of the model reflected either the total costs, adding up the costs of all diagnostic and therapeutic medical events, and the average expected number of life years, that was retrieved from the Dutch institute for health statistics and adapted for advanced death by disease.

Data sources

In the prospective clinical study that formed the basis of this decision analysis, 3835 breasts in 2020 patients were examined by both clinical examination, mammography and ultrasonography (methodology as described in chapter 4). From the total study population all cases with a palpable lump were selected ($n=522$ breasts, 492 patients). The mean age of the study population was 49 years (range 17 - 90).

After a follow up of 12 months during which pathology results from core needle biopsies, excision biopsies and other surgical interventions were recorded, a total of 93 malignancies were reported, leading to a prevalence of breast cancer of 19% (93/492) in this population.

The decision model was designed on the level of breasts ($n=522$).

The diagnosis from ultrasonography was integrated with results of mammography and clinical examination and scored on a 5-point grading scale of increasing suspicion for malignancy, as 1 = normal, 2 = benign, 3 = probably benign, 4 = suspect malignant, 5 = malignant, which was adapted from the BI-RADS-lexicon for mammography and under development for ultrasonography^{8, 18}. In accordance with clinical practice, for the definition of positive and negative cases, a cut-off point was used between benign (2) and probably benign (3) results. All patients with palpable masses and positive imaging results were subsequently referred for FNAC.

Furthermore, a combined diagnosis from mammography and clinical examination together and results from core needle biopsy were scored on a similar grading scale. FNAC was recorded on a 4-point grading scale, as 1 = normal, 2 = benign, 3 = suspect malignant / atypia, 4 = malignant, 0 = indeterminate. The presence of malignancy as a result of surgery was registered as a dichotomous variable.

Chance nodes (indicated by a circle) in the model represented the diagnostic or therapeutic actions at different grades on these diagnostic scales (e.g. in experimental strategy-1, FNAC was performed when ultrasonography reported a suspicious diagnosis (score 3, 4 or 5): see figure 1).

Most probabilities required for experimental strategy-1 were retrieved from our clinical study. Data on the other strategies were adapted from these data or composed hypothetically by consulting an expert panel and by using clinical guidelines (table 2). Additionally, for all phases of the model relevant literature was reviewed.

Results of cost calculation studies in our hospital formed the basis of the costs used in the model, complemented with data from the Dutch Health Care Insurance Board¹⁹ and the Dutch pharmacotherapeutic guidelines²⁰. The used costs are integral and include costs for personnel, material, capacity and departmental overhead. Costs were specified in Euros (€), with 1 Euro being equal to 0.85 American dollar (index 2000). In table 3, an overview is given of the different cost components of each cost item in the model. A more detailed calculation of the costs is available from the authors on request.

Palliative care was defined as medical care during the terminal phase of the disease, lasting from the diagnosis of distant, systemic recurrences to the time of death. Data on all medical events during this period were adapted from a study of de Koning et al.^{21, 22}. The probabilities and costs used were updated for the year 2000 according to recent guidelines and experts' opinion.

Due to the health care perspective chosen for this study, direct costs to patients, costs of home care, out of pocket expenses resulting from visits to health care institutions, community care costs, the costs of lost productivity and the impact on the quality of life were not included in this study.

Table 2: Model parameters and range of sensitivity analysis

Parameter / Probability	Chance	Range ¹	Source / reference
Experimental Strategy 1			
Suspicious (3-4-5) US result	0.349	0.314-0.385	Clinical study MUH
Malignant (4) FNAC result after US	0.324	0.267-0.386	Clinical study MUH
TP result surgery after malignant FNAC & US	0.983	0.922-0.999	Clinical study MUH
Benign (2) FNAC result after US	0.439	0.363-0.517	Clinical study MUH
FN result surgery after benign FNAC & US	0.074	0.026-0.162	Clinical study MUH
Malignant (3-4-5) biopsy result after FNAC & US (TP)	0.435	0.333-0.541	Clinical study MUH
Surgery after benign (2) US result	0.126	0.098-0.160	Clinical study MUH
FN result surgery after benign US result	0.023	0.001-0.106	Clinical study MUH
FN result of discharge after normal (1) US result	0.000	0.000-0.050	Clinical study MUH
Malignant (4) FNAC result	0.115	0.058-0.173	Assumption, expert panel
TP result surgery after malignant (4) FNAC	0.983	0.492-1.000	Assumption, expert panel
Benign (2) FNAC result	0.208	0.104-0.312	Assumption, expert panel
FN result surgery after benign (2) FNAC	0.042	0.021-0.063	Assumption, expert panel
Biopsy after probably benign (0-3) FNAC result	0.189	0.095-0.280	Assumption, expert panel
Malignant (3-4-5) biopsy result after FNAC (TP)	0.435	0.218-0.653	Assumption, expert panel
Biopsy after normal (1) FNAC result (TN)	0.300	0.150-0.450	Assumption, expert panel
Surgery after normal (1) FNAC (TN)	0.140	0.070-0.210	Assumption, expert panel
Experimental Strategy 2			
"Suspicious" (2-3-4-5) US result	0.761	0.728-0.791	Clinical study MUH
Malignant (4) FNAC result after US	0.149	0.120-0.181	Adapted from clinical study MU
TP result surgery after malignant FNAC & US	0.983	0.922-0.999	Adapted from clinical study MU
Benign (2) FNAC result after US	0.580	0.534-0.625	Adapted from clinical study MU
FN result surgery after benign FNAC & US	0.107	0.073-0.151	Adapted from clinical study MU
Malignant (3-4-5) biopsy result after FNAC & US (TP)	0.099	0.061-0.150	Adapted from clinical study MU
Surgery after benign (2) US result	0.000	0.000-0.050	Adapted from clinical study MU
FN result surgery after benign US result	0.000	0.000-0.050	Adapted from clinical study MU
FN result of discharge after normal (1) US result	0.000	0.000-0.050	Adapted from clinical study MU
Malignant (4) FNAC result	0.115	0.058-0.173	Assumption, expert panel
TP result surgery after malignant (4) FNAC	0.983	0.492-1.000	Assumption, expert panel
Benign (2) FNAC result	0.208	0.104-0.312	Assumption, expert panel
FN result surgery after benign (2) FNAC	0.042	0.021-0.063	Assumption, expert panel
Biopsy after probably benign (0-3) FNAC result	0.189	0.095-0.280	Assumption, expert panel
Malignant (3-4-5) biopsy result after FNAC (TP)	0.435	0.218-0.653	Assumption, expert panel
Biopsy after normal (1) FNAC result (TN)	0.300	0.150-0.450	Assumption, expert panel
Surgery after normal (1) FNAC (TN)	0.140	0.070-0.210	Assumption, expert panel
Experimental Strategy 3			
Suspicious (3-4-5) CE+MAM result	0.753	0.712-0.784	Clinical study MUH
Suspicious (3-4-5) US result	0.078	0.043-0.128	Adapted from clinical study MU
Malignant (4) FNAC result after US	0.200	0.037-0.507	Adapted from clinical study MU

TP result surgery after malignant FNAC & US	1.000		Adapted from clinical study MU
Benign (2) FNAC result after US	0.500	0.193-0.807	Adapted from clinical study MU
FN result surgery after benign FNAC & US	0.000	0.000-0.050	Adapted from clinical study MU
Malignant (3-4-5) biopsy result after FNAC & US (TP)	0.250	0.001-0.106	Adapted from clinical study MU
Surgery after benign (2) US result	0.109	0.066-0.168	Adapted from clinical study MU
FN result surgery after benign US result	0.000	0.000-0.050	Adapted from clinical study MU
FN result of discharge after normal (1) US result	0.000	0.000-0.050	Adapted from clinical study MU
Malignant (4) FNAC result	0.148	0.119-0.180	Assumption, expert panel
TP result surgery after malignant (4) FNAC	0.983	0.492-1.000	Assumption, expert panel
Benign (2) FNAC result	0.275	0.235-0.318	Assumption, expert panel
FN result surgery after benign (2) FNAC	0.043	0.015-0.097	Assumption, expert panel
Biopsy after probably benign (0-3) FNAC result	0.247	0.204-0.295	Assumption, expert panel
Malignant (3-4-5) biopsy result after FNAC (TP)	0.446	0.341-0.556	Assumption, expert panel
Biopsy after normal (1) FNAC result (TN)	0.298	0.245-0.356	Assumption, expert panel
Surgery after normal (1) FNAC (TN)	0.137	0.091-0.194	Assumption, expert panel
All strategies			
Adjuvant therapy with primary surgery	0.495	0.248-0.743	Assumption, expert panel
Local recurrence after primary surgery	0.100	0.05-0.150	27, 28
Palliative stage after diagnosis	0.010	0.005-0.015	Adapted from 28-30
Palliative stage after adjuvant therapy	0.440	0.220-0.660	Adapted from 28-30
Palliative stage after non-adjuvant therapy	0.220	0.110-0.330	Adapted from 28-30
Palliative stage after local recurrence	0.670	0.335-1.000	Adapted from 28-30
Expected life years			
	Years		
LE Palliative stage after diagnostic test	1.5	0.8-2.3	Adapted from 21, 22
LE Palliative stage after local recurrence	5	2.5-7.5	Adapted from 21, 27, 28
LE Palliative stage after local & distant recurrence	8	4-12	Adapted from 21, 27, 28
LE Disease-free after diagnostic test	32.8	16-49	Average Life Expectancy
LE Disease-free after treatment	32.8	16-49	Average Life Expectancy

¹ Range according to 90% confidence intervals of empirical data or 50-150% of assumed and adapted data

Legend: US= ultrasonography / MUH= Maastricht University Hospital / TP= true-positive result / FN= false-negative result / LE= life expectancy / Diagnosis imaging: 1=normal, 2=benign, 3=probably benign, 4=suspect malignant, 5=malignant / Diagnosis FNAC: 1=normal, 2=benign, 3=suspect malignant, 4=malignant, 0=indeterminate / Diagnosis (core needle) biopsy: 1=normal, 2=benign, 3=probably benign, 4=suspect malignant, 5=malignant, 0=indeterminate / Diagnosis surgery: malignant, benign.

Cost-effectiveness analysis and sensitivity analysis

Baseline cost-effectiveness analysis calculated the total costs and average life expectancy for each strategy. Univariate one-way sensitivity analysis was performed for all parameters in the model, over a range of values according to the 90% confidence interval for empirical data of the clinical study, or from 50% to 150% of the deterministic variables in the model (table 2). The effect on the costs and life expectancy was studied and threshold analysis was performed to identify the values at which the preferred strategy would alter.

Results

Base-case analysis

The results of base-case cost-effectiveness analysis are presented in table 4. In experimental strategy-1, 182 (35%) ultrasonographic examinations resulted in probably benign or malignant results (diagnostic score 3-4-5) and were followed by FNAC, leading to additional costs of € 14,560 ($182 \times € 80$). Furthermore, in 340 cases FNAC was prevented compared to the conventional strategy, saving € 7,140 ($340 \times (€ 101 - € 80)$). One result was false-negative and an additional excision biopsy (€ 1,089) was performed preceding malignant surgery. The associated additional costs of this strategy compared to the conventional strategy were roughly € 8,509. In the conventional strategy, additional costs with respect to the experimental strategy included the confirmation of normal cytology results by core needle biopsy or excision (€ 50,360).

Table 3: Total costs in Euros (€) per item in the model

	Hospital / nursing care	Diagnostic radiology	Diagnostic pathology	Surgery	Radiotherapy	Hormone therapy	Chemotherapy	Specialist controls	TOTAL COSTS IN €
Ultrasonography	0	80	0	0	0	0	0	0	80
FNAC	0	0	101	0	0	0	0	0	101
Core needle biopsy	0	0	211	0	0	0	0	0	211
Excision biopsy	332	0	63	693	0	0	0	0	1,089
Curative surg + adjuvant th	1,329	0	63	875	2,411	611	792	1,491	7,572
Curative surg + no adjuv th	1,329	0	63	875	2,411	0	0	560	5,238
Local recurrence	1,661	236	63	782	986	0	0	653	4,381
Palliative care	15,289	1,316	187	319	877	293	892	567	19,739
Disease-free after surgery	0	655	0	0	0	0	0	0	655
References / sources ¹	1	2	2	2	4	3	3	1,2	

¹Sources: 1 = Dutch Health Care Insurance Board ¹⁹, 2 = Hospital Information System Maastricht University

Hospital, 3 = Farmacotherapeutic Guidelines 2000-2001²⁰, 4 = Dutch Radiotherapy Guidelines for Breast Cancer

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Cost-effectiveness analysis showed that this strategy was less costly than the conventional one (€ 3010 versus € 3087).

Shifting the cut-off to normal (1) and benign (2) ultrasonography results, resulted in 397 referrals (76%) for additional FNAC (experimental strategy-2). This included an increase of 215 FNAC examinations compared to experimental strategy-1 or € 21,715. It was assumed that no extra malignant FNAC results were generated and that most extra cases were diagnosed as benign through surgery and core needle

biopsies. The remaining 125 cases were either discharged or a benign lesion was surgically excised. As a consequence, this experimental strategy was more costly (€ 3475) compared to the conventional strategy.

In experimental strategy-3, 393 cases (75%) with a suspicious abnormality on mammography or clinical examination (diagnostic score 3-4-5) were referred for immediate FNAC. The remaining 129 normal (1) or benign (2) cases underwent prior ultrasonography. It was assumed that no false-negative ultrasonography resulted from this group. The total costs of this strategy were € 2946, which was € 141 less costly than the conventional strategy of immediate FNAC.

Table 4: Results of base-case cost-effectiveness analysis

	Conventional strategy (FNAC)	Experimental strategies (US)		
		1	2	3
No. FNAC performed	522	182	397	403
No. US performed	0	522	522	129
TP US		92	93	3
FP US		90	304	7
TN US		339	125	119
FN US		1	0	0
Costs (€) diagnosis	82	165	294	69
Costs (€) treatment	1472	1412	1748	1444
Costs (€) follow up care	1433	1433	1433	1433
Costs (€) total	3087	3010	3475	2946
LE (years)	31.0	31.0	31.0	31.0
Preferred strategy		US	FNAC	US

Legend: US= ultrasonography / TP US= true-positive US result / FP US= false-positive US result / TN US= true-negative US result / FN US= false-negative US result / LE= life expectancy / costs (€) total= costs of diagnosis+treatment+follow up care after treatment.

The total number of FNAC and ultrasonography examinations performed was highest in experimental strategy-2 (n=919, 522 FNAC and 397 ultrasonography) and lowest in the conventional strategy (n=522, 522 FNAC and 0 ultrasonography). The table also reports the number of positive and negative ultrasonography examinations, indicating the number of cases in which additional action followed, rather than the number of "malignant" diagnoses. It is shown that strategy-3 obtained the lowest number of false-positive and false-negative results.

Furthermore, table 4 shows the costs splitted for diagnosis, treatment and follow up care in these strategies. It is shown that the costs for diagnosis were minimized to an average of € 69 per patient in experimental strategy-3. Experimental strategy-2 was most costly in both diagnosis and treatment. Costs of follow up care for malignancies were equal for all strategies (€ 1433) as well as the average life expectancy (31.0 years).

Overall, the model showed that experimental strategy-3 with selected ultrasonography as additional diagnostic modality, was the cheapest strategy as compared to the conventional strategy and both other experimental strategies.

Sensitivity analysis

One-way sensitivity analysis was performed for all parameters in the model, comparing each experimental strategy with the conventional strategy. The cost rankings for the different strategies remained stable over a range of costs from 50 to 150% of base-case estimates. Furthermore, sensitivity analysis of life expectancy outcome variables showed no impact on the strategy being preferred.

In table 5, all variables that influenced the strategy preferred in the model are reported. These variables mainly influenced the cost outcome of the model, while no impact was demonstrated on the life expectancy. Most important influential variables included the proportion of suspicious and benign FNAC results and the proportion of false-negative ultrasonography results. For experimental strategy-1 nine influential variables were identified, whereas there were only 1 and 2 influential variables in experimental strategies-2 and-3 respectively.

Table 5: Results of sensitivity analysis and threshold analysis

Probability	Chance	Threshold analysis ¹
Experimental strategy 1		
Suspicious (3-4-5) US result	0.349	>0.36
Malignant (4) FNAC result after US	0.324	>0.35
Benign (2) FNAC result after US	0.439	<0.37
FN result surgery after benign FNAC & US	0.074	>0.13
Malignant (3-4-5) biopsy result after FNAC & US (TP)	0.435	>0.48
FN result of discharge after (0-1) US result	0.000	>0.01
Malignant (4) FNAC result ²	0.115	<0.11
Biopsy after probably benign (0-3) FNAC result ²	0.189	<0.17
Malignant (3-4-5) biopsy result after FNAC ²	0.435	<0.39
Experimental strategy 2		
Malignant (4) FNAC result after US	0.149	<0.14
Experimental strategy 3		
FN result of discharge after (0-1) US result	0.000	>0.06
Malignant (4) FNAC result ²	0.148	>0.17

¹ Value of probability at which FNAC would be preferred over US strategy

² Variable from conventional strategy

Discussion

This study showed an overall reduction in costs in two of the three experimental strategies of performing prior ultrasonography in patients presenting with a palpable breast lump, as compared to routine FNAC examination. In the cheapest strategy ultrasonography was performed mainly in patients with a palpable mass without suspicion on mammography and clinical examination.

The reported number of average expected life years was similar in the different strategies (31.0 years). This is explained by the relative short time period in clinical practice between diagnostic imaging and surgical excision leading to the definitive diagnosis. False-negative ultrasonography results could lead to a possible delay of diagnosis, but will be diagnosed shortly after excision biopsy of an assumed benign lesion. It should be noted that a different design of the strategy in which no further

testing would be done, more delay of diagnosis could be expected with a possible loss of life expectancy.

Also, as the number of detected malignancies is expected to be equal in all strategies, the average life expectancy per patient will be similar. As a consequence, this study focused on cost-minimization rather than on cost-effectiveness.

The most important role for ultrasonography in the evaluation of palpable breast masses is in the differentiation between solid and cyst masses. Patients with demonstrated cysts are generally discharged, often after aspiration of the mass, while patients with solid benign masses such as fibroadenoma are mostly referred for surgical excision and patients with suspicious lesions are referred for FNAC.

Experimental strategy-1 and-2 in our model illustrated the effect of changing the cut-off used for referral for additional FNAC. Obviously, strategy-2 resulted in higher expenses for both diagnosis and treatment than strategy-1, as all benign lesions were referred for FNAC and more benign excisions followed as a consequence. Based on lower costs, the conventional strategy was preferred to experimental strategy-2. It may therefore be concluded that diagnostic ultrasonography would have no role in the triple test, when benign imaging results would still be confirmed by FNAC.

Conversely, when only referring suspicious lesions for FNAC, ultrasonography would be a cost-saving strategy (strategy-1). Finally, experimental strategy-3 further reduced costs by only performing ultrasonography in cases without a suspicious mammogram or clinical examination. This finding suggests that there is no role of ultrasonography in the diagnosis of obviously malignant lesions on mammography and clinical examination.

It may be argued that, although FNAC of palpable masses is mostly performed palpation-guided, ultrasonography could be used also as a guiding modality. Diagnostic ultrasonography could then practically be performed during the same visit. However, in the Netherlands, FNAC is performed and examined mostly by pathologists, while diagnostic ultrasonography is performed by radiologists.

Also, in order to diagnose a cyst, the radiologists may aspirate cystic fluid on ultrasonographic guidance, which may easily be sent in for cytological examination by the pathologist. However, this was regarded as a different diagnostic modality in our model with a separate cost price. Experimental strategy-2 showed furthermore, that FNAC examination of all imaging-detected benign lesions, such as cysts, would lead to an unnecessary increase in costs. This suggests that routine cytological examination of all breast fluids is not recommended²³.

Various sources were used for the costs of diagnostic and therapeutic actions in this model. When adjusting the costs for diagnosis and treatment of breast cancer reported by Will et al.²⁴, for the distribution of stages of breast cancer as detected in our prospective study (22% stage I, 40% stage II, 38% stage III, 0% stage IV), this would result in 9333 Canadian \$ (1995) or € 6,813. This amount is comparable with the average costs of curative surgery with and without adjuvant chemotherapy and hormonal therapy found in our study, being € 6405, especially when considered that we excluded the costs of diagnosis and staging from our calculations. Furthermore, Will's calculated costs of treating a local recurrence was 6,405 Canadian \$, or € 4,676 and comparable to the estimated amount of € 4,381 in the current study.

The costs of palliative care were adapted from the study of de Koning et al. in 1990²¹, and were raised by 29% according to the clinical situation in 2000 (from € 15,281 to €

19,739). Other studies in different settings have also calculated these costs, reporting € 15,385²⁴, € 8659²⁵ and € 7049²⁶. The comparison of data between different countries is difficult because of different methodologies regarding length of time for initial and terminal care, different comparator years as well as different health care systems and currencies. Furthermore, a variation of costs results from differences in treatment approaches, the nature of health care systems and the patient populations used in the analysis.

In the present study no discount rates were applied to the costs or life expectancy. The life expectancy and the number of malignancies, and thus the costs of follow up care, were equal in all strategies. Furthermore, most actions were performed within one year, so it was believed that this would not influence our findings. Furthermore, non-medical costs were assumed to be the same for all strategies and were thus excluded from the model. Besides, they are difficult to obtain and their use is controversial²⁴. As sensitivity analysis showed that the costs used in this model had little influence on the results of the analysis and as they are comparable with other studies, we conclude that our cost data are valid.

Variables that influenced the results of the model, as demonstrated by sensitivity analysis, included the proportion of suspicious and benign FNAC results and the proportion of false-negative ultrasonography results. Most of these variables were identified from experimental strategy-1. It may be concluded that the results are applicable to this particular study population, as the values used in experimental strategy-1 for base-case analysis are empirical data from a large prospective study.

A decision analytic model as discussed in this paper may be a valuable tool to guide health policymakers in decisions related to strategies to improve the efficiency of the healthcare system and to make care delivery more efficient and less costly²⁴. On a national or international level, the difference in costs between the strategies analyzed in this study may be regarded as negligible. This would suggest there is no relevant economic difference between performing immediate FNAC or prior ultrasonography in these patients. However, as ultrasonography is being used increasingly in radiological practice in the evaluation of breast masses, there is a need for an efficient and appropriate implementation. Furthermore, patients' preference for non-invasive testing and the emotional reassurance that a visible imaging test can offer above pathological results, indicates a social argument in favor of ultrasonography.

We believe that on the level of local radiology departments, the diagnostic strategies analyzed illustrate a feasible and desirable gain in efficiency of diagnostic breast imaging. It was shown that the costs savings of strategy-3 compared to the conventional strategy included 62% of the costs for diagnostic procedures. However, scheduling additional ultrasonography in patients with a palpable mass would be done most efficiently early in the diagnostic work-up, e.g. at the stage of referral to the radiology department. Therefore, the performance of ultrasonography in all patients with palpable breast masses, as examined in strategy-1, would be more practical in clinical practice than the selection of patients after performance of clinical examination and mammography, as examined in strategy-3, despite the difference in total costs of € 64 per patient and a smaller reduction in diagnostic costs compared to the conventional strategy of € 17.

Concluding, the results of this study indicate that incorporating ultrasonography in the triple test for evaluation of palpable breast masses can result in a reduction of the total costs for the diagnosis and treatment of breast cancer. The least expensive

strategy consisted of prior ultrasonography of lesions without suspicion of breast cancer based on mammography and clinical examination, and immediate FNAC of suspicious lesions. While the cost saving of this selective application of ultrasonography is considerable, logistic and emotional arguments plead for the performance of ultrasonography in the diagnostic work-up of all patients with palpable breast masses.

Furthermore, it should be realized that this model analyzed some hypothetical strategies. This emphasizes the need for more prospective clinical research studying the clinical impact of these strategies, in terms of diagnostic performance as well as in terms of their impact on the efficiency of diagnostic breast imaging planning.

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7

GENERAL DISCUSSION AND CONCLUSIONS

The studies discussed in this thesis have focused on the diagnostic performance of ultrasonography in diagnostic breast imaging.

The first objective of the thesis was to assess the diagnostic value of ultrasonography as an adjunct to mammography and clinical examination in the diagnosis of breast cancer.

The prospective study that was described in chapter 2 demonstrated the relevance of radiological imaging in 1890 patients referred with breast problems, and showed the diagnostic value in addition to results from palpation and age of the patient. However, as mammography and ultrasonography results were only scored as one radiological breast imaging diagnosis, as is usual in clinical practice, it was impossible to study the incremental value of ultrasonography here. Subsequently, our systematic review of all available literature between 1990 and 2000 found little evidence-based support for the well-established role of ultrasonography as an adjunct to mammography in the diagnosis of breast cancer.

In response to this lack of evidence in the literature, the MAMMOED study was performed. It showed, by ROC curve analysis of the imaging diagnoses, that systematic ultrasonography as an adjunct to mammography and clinical examination significantly increased the diagnostic yield in 3835 breasts of 2020 consecutive patients referred for diagnostic breast imaging. Additional ultrasonography detected 8 extra malignancies in this population and correctly "downgraded" 332 cases from a positive to a negative diagnosis.

Furthermore, multivariate logistic regression analysis of diagnostic variables from medical history, clinical examination, mammography and ultrasonography demonstrated that each step in the diagnostic work-up improved the diagnostic value of the prediction model for breast cancer. Adding results of ultrasonography to the other modalities significantly improved the predictive value of the model.

Based on these findings it can be concluded that in an outpatient population referred to a radiology department for diagnostic breast imaging, additional ultrasonography improved the diagnostic yield.

The second objective of this thesis was to study the feasibility of defining subgroups of patients who benefit most from additional ultrasonography. The systematic literature review showed that most publications on the additional diagnostic value of ultrasonography studied a selected study population, e.g. patients with a palpable breast mass or patients referred for biopsy or surgery. Furthermore, several studies, including our prospective study in chapter 2, performed ultrasonography next to mammography on clinical indication only, leading also to a selected study population undergoing both test modalities. Therefore, none of these studies were able to answer the research question posed. This emphasized the need for a prospective study in which systematic ultrasonography is performed in a non-selected consecutive patient population, which was realized in the MAMMOED study. In order to facilitate and optimize the logistic planning of breast imaging early in the diagnostic work-up, it was decided to focus mainly on the reasons for referral when defining subgroups of patients.

Based on the sensitivities, specificities and the p-values resulting from ROC curve analysis of the imaging diagnoses only, additional ultrasonography would be mainly recommended in patients referred for a palpable breast mass or with an abnormal screening mammogram, including 30% of the total study population. The increase in diagnostic yield by adding ultrasonography to mammography and clinical

examination was not statistically significant in patients referred for breast symptomatology and follow up of a prior breast malignancy. Finally, due to the very low prevalence of breast cancer, no ROC curves could be plotted for patients referred for follow up of a prior benign lesion, patients referred for reassurance, or when ultrasonography was performed as screening examination of the contralateral breast. It is suggested that diagnostic breast imaging has limited value in these patients.

Logistic regression analysis of several diagnostic variables from the different modalities confirmed a significant increase in diagnostic yield only in patients referred for a palpable mass.

It should be noted that in both analyses, the largest increase in area under the ROC curve was found for patients referred for follow up of a prior malignancy, although this was not statistically significant. The most plausible explanation for this is the small number of malignancies in this group, and it has to be concluded that despite the lack of statistical significance, there is actually an important role for ultrasonography in these patients. This finding illustrates the relative value of using *p*-values generated from ROC curve analysis in answering this research question.

A consequence of restricting ultrasonography mainly to patients referred for a palpable breast mass based on these analyses is that several malignancies detected by ultrasonography in the other subgroups would have gone undetected. In this respect, it may be argued that additional pathological tests in the diagnostic work-up, like fine needle aspiration cytology (FNAC) in the triple assessment of palpable breast masses¹⁻³ and core needle biopsies in the evaluation of non-palpable mammographic abnormalities⁴⁻⁶, would also lead to the correct diagnosis and make the additional diagnostic information from ultrasonography redundant in these cases.

On the other hand, besides the detection of additional malignancies, ultrasonography also correctly "downgraded" many suspicious diagnoses on mammograms and clinical examination to a benign diagnosis. Especially the diagnosis of (non-palpable) cysts may result in a considerable saving of unnecessary FNAC examinations and biopsies. It has been shown that the psychological stress to women undergoing breast biopsy is high and the cost is considerable⁷, so the role of ultrasonography in reducing the number of negative biopsies is crucial. Additionally, patients' preference for uninvasive and fast diagnostic tests with an immediate, visible result will plead for ultrasonography.

Possibly, a different classification of subgroups of patients based on other characteristics might change the selection of clinical indications for ultrasonography. However, the arguments discussed restrain us from making recommendations on the use of ultrasonography in clinical practice, based on the results from ROC curves and logistic regression analysis alone. We conclude that the selection of subgroups of patients who benefit most from additional ultrasonography should be based on more than just these statistical considerations.

In order to do so, the whole process of medical decision-making should be taken into account, including the performance of additional testing such as by pathology, the efficiency of clinical practice, as well as the associated costs. Decision analytical modeling as presented in chapter 6 is a possible method of analyzing this. In this model, 3 different diagnostic strategies of incorporating ultrasonography in the triple test for the evaluation of palpable breast masses were compared to the routine conventional triple test, consisting of immediate FNAC performance after mammography and clinical examination. This design is corresponding to the third objective of this thesis.

Cost-minimization showed that the least expensive strategy would be to perform immediate FNAC in patients with suspicious lesions on mammograms and clinical examination, and to perform prior ultrasonography in patients without suspicious results. It was concluded that integrating ultrasonography in the triple test would result in a reduction of the total costs for the diagnosis and treatment of breast cancer. These results confirmed the results found by ROC curve and logistic regression analysis and favor the use of additional ultrasonography in patients with a palpable mass.

However, when taking into account the aim for improving the efficiency of diagnostic breast imaging planning in radiology departments, the least expensive strategy was not necessarily the one preferred. As has been mentioned throughout this thesis, it would be more efficient to decide on additional ultrasonography at the stage of referral rather than having to wait first for the results of mammography and clinical examination. This would indicate a preference for experimental strategy-1 instead of strategy-3, despite the additional costs of € 64 per patient. It should be realized that strategy-3 is a hypothetical strategy, which needs to be examined further by prospective clinical research, before being implemented in clinical practice.

Elaborating on these results, future research should be directed on the costs and effects of ultrasonography in the other subgroups of patients discussed in this thesis. Integrating the results from clinical epidemiological methodology, such as ROC curves and logistic regression analysis, with the results from decision analytical modeling will enable us to give recommendations for the use of additional ultrasonography in daily clinical practice.

Furthermore, implementation of these guidelines in clinical practice should be monitored thoroughly. A possible design of monitoring clinical practice in radiology is through a continuous computer registration of procedures and outcomes. This includes a welcome combination of medical research and quality assurance, through analysis of compliance to clinical guidelines and performance of diagnostic imaging tests over time.

Some requirements to guarantee the quality of such a design include the use of standardized and uniform reporting systems, consistent terminology and clear clinical guidelines. Furthermore, a correct set of data has to be registered in order to be able to answer the research questions posed.

The prediction model, which was presented in chapter 5, demonstrated the most important diagnostic variables from medical history, clinical examination, mammography and ultrasonography that predict the presence of breast cancer. Using this model, probability calculation can be done for individual patients by adding up the scores for the outcomes of the different variables. Although the applicability of this diagnostic algorithm in clinical practice may be argued, it demonstrated clearly which variables are most significant in the realization of a final imaging diagnosis. Therefore, these variables would be crucial in a continuous registration of outcomes for quality assurance of diagnostic breast imaging.

One of the requirements for the success of this system of quality assurance is the use of uniform reporting systems and consistent terminology. The different publications analyzed in our systematic literature review used various grading scales and cut-off points for the imaging results (results not shown), which will obviously influence the results in terms of numbers of false-positive results, false-negative results, sensitivities and specificities.

The 5-point grading scale that was used as reporting system for breast imaging in the studies discussed in this thesis was based on the BI-RADS-lexicon for diagnostic mammography⁸. This system has been extensively tested and validated by the American College of Radiology and the similar scoring system for ultrasonography is currently being validated⁹. However, it should be noted that the application of these diagnostic scores in our studies differed slightly from this lexicon.

The cut-off point used to define positive and negative imaging results was defined between benign (score 2) and probably benign (score 3) results. Whereas for normal or suspicious malignant results it is obvious whether to call them positive or negative, for probably benign results it is not. One way of dealing with the difficulty of choosing a cut-off point when comparing different diagnostic methods is by constructing ROC curves that plot the sensitivity against the proportion of false-positive results. If the "cost" of a false-negative result is the same as that of a false-positive result, the best cut-off is that which maximizes the sum of the sensitivity and specificity, which is the point near the top left-hand corner¹⁰. In the ROC curve presented in chapter 4 this method confirmed our choice of a cut-off between benign and probably benign results, representing a sensitivity of 97% and a specificity of 95% for combined ultrasonography, mammography and clinical examination. According to the BI-RADS-lexicon however, probably benign lesions have a high probability of being benign and a short interval follow up of 6 months is suggested for confirmation. However, we reasoned probably benign lesions are more suspected for malignancy than benign lesions and it prevents a number of false-negative results when classifying them as positive.

In chapter 5, the cut-off point chosen on the ROC curve corresponded with a sensitivity of 95% and a specificity of 92%. The sensitivity and specificity resulting from this curve were lower than in chapter 4, while studying the same imaging modalities in the same study population. This is explained by the use of a 3-point grading scale for the diagnostic scores instead of the 5-point grading scale used in chapter 4.

Diagnostic score 0 was used to define indeterminate or uninterpretable results, due to imaging flaws or patient characteristics such as dense breast parenchyma at mammography or mastopathy at clinical examination. According to the BI-RADS lexicon, score 0 rather stands for incomplete assessment and these results should not be included in the data analysis⁸. No consensus exists for the incorporation of indeterminate or uninterpretable results into data assessment.

In chapter 4, a method was chosen that approached clinical implications best, namely by recoding indeterminate clinical examinations like in e.g. mastopathy, as benign (score=2) and indeterminate mammography or ultrasonography results as probably benign (score=3) for analysis. It was believed that additional action would always result from indeterminate mammography or ultrasonography results, whereas this is not required after clinical examination. In chapter 5 however, we focused on the prevalence of breast cancer in each category and recoded indeterminate and normal scores into one group, benign and probably benign scores in another, and suspicious malignant and malignant scores in a third group.

Additionally, we have tested other ways of handling indeterminate results, e.g. by recoding them as a separate level of suspicion for breast cancer or deleting them completely from analysis (results not shown) and conclude that, although there were small differences between the outcomes, the method chosen did not influence our

overall conclusions. More research would be needed on the impact of handling indeterminate results on the outcome of diagnostic imaging.

Defining the reference standard in diagnostic imaging research is a difficult methodological issue. The ultimate "gold" standard would include pathology results of all patients, but it would be impossible and unethical to take a pathology specimen in patients in whom no abnormality was detected.

A possible "silver" reference standard would be to apply active surveillance and subject all patients to repeat imaging testing after a specified follow up period. However, in our opinion this would also be ethically unjustified in patients with negative imaging results. Furthermore, this procedure would interfere with common clinical practice and would introduce bias as imaging tests function as reference standard for themselves. The reference standard that we have used in our studies could be defined as "bronze": positive cases were confirmed by pathology whereas a 12 month passive follow up period was applied in patients with negative imaging results. This may induce a form of verification bias as more positive results than negative cases may be verified, and may lead to an overestimation of sensitivity and an underestimation of specificity¹¹. However, as the pathology registration system used is of high quality and covers all examinations of all pathology laboratories in The Netherlands, we are confident that subsequent malignancies diagnosed elsewhere would not go unnoticed. Furthermore, the duration of our follow up period is believed to be long enough to maximize the chance of detecting malignancies that were actually missed and to minimize the chance of finding newly developed cancers. We therefore believe that for our study purposes in this clinical situation, our reference standard used was as "gold" as possible.

Summarizing, the conclusions of the studies discussed in this thesis are:

- Radiological imaging tests have large diagnostic value in the diagnosis of breast cancer in addition to results of palpation and age of the patient (chapter 2).
- Based on the literature between 1990 and 2000, little evidence-based support is available to confirm the well-recognized value of ultrasonography as an adjunct to mammography and clinical examination (chapter 3).
- Systematic application of ultrasonography as an adjunct to mammography and clinical examination in 3835 cases significantly improved the diagnostic yield (chapter 4).
- The most important diagnostic variables predicting the presence of breast cancer include: age, menopause, specific breast symptoms, diagnosis of clinical examination, mammographic calcifications and the integrated diagnosis resulting from ultrasonography, mammography and clinical examination. The "worst-case" scenario consisted of postmenopausal women older than 50 years, having specific breast symptoms such as skin retraction or nipple discharge, a suspicious clinical examination, suspicious calcifications on the mammogram and a suspicious final diagnosis of clinical examination, mammography and ultrasonography together, resulting in a probability of breast cancer of 0.997 (chapter 5).
- Incorporating ultrasonography in the triple test for the evaluation of palpable breast masses can result in a reduction of the total costs for the diagnosis and treatment of breast cancer (chapter 6).
- Quality assurance of diagnostic imaging could be combined with clinical research by continuous monitoring of compliance to clinical guidelines and test performance (discussion).

- Integrating the results from clinical epidemiological methodology, such as ROC curves and logistic regression analysis, with the results from decision analytical modeling is required to define subgroups of patients who benefit most from additional ultrasonography and will enable us to give recommendations for its use in daily clinical practice (discussion).
- Based on ROC curve analysis, logistic regression analysis and decision analytical modeling, it is suggested that ultrasonography is indicated as an adjunct to mammography and clinical examination in the evaluation of palpable breast masses (chapter 4, 5, 6 + discussion).

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8

SUMMARY
SAMENVATTING
DANKWOORD
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Summary

Routine diagnostic breast imaging in the radiology departments of a hospital consists of clinical examination, mammography, and ultrasonography when indicated. This thesis focuses on the diagnostic performance of breast imaging in diagnosing breast cancer and more specifically on the role of ultrasonography herein.

Chapter 2 discusses a prospective study that was performed in 1994, assessing the diagnostic performance of breast imaging in a non-screening population. A consecutive set of 1944 breast examinations in 1890 patients was studied, consisting of palpation and mammography, supplemented with ultrasonography when clinically indicated. In total, 3816 breasts were examined. Pathology results after a follow up of one year were used as reference standard for the presence of breast cancer and demonstrated 118 malignancies in 115 patients (6.1% prevalence).

With a cut-off point between benign and probably benign results, a sensitivity of 89% and a specificity of 98% was found for radiological breast imaging. There were 13 false-negative and 69 false-positive results. Logistic regression and ROC curve analysis demonstrated that adding the imaging results to the information available from palpation and the age of the patient significantly improved the diagnostic performance. Combining all information a sensitivity of 100% could be reached hypothetically, with a specificity of around 60%.

This study concludes that radiological breast imaging has an important role in the diagnosis of breast cancer in daily clinical practice. The results on the prevalence of breast cancer and the performance of breast imaging were comparable to other studies in national and international radiology departments.

In this study, additional ultrasonography was performed in 28% of all patients referred for diagnostic breast imaging. Current practice shows that the use of ultrasonography is increasing, reporting over 35% of patients undergoing ultrasonography as an adjunct to mammography in 1999. This is partly the result of the wider availability and accessibility, the broadening clinical indications and the belief of physicians that is less likely to be blamed for doing more testing than for doing too little. However, this practice leads to the question what the diagnostic performance is of additional ultrasonography and whether ultrasonography could be restricted to subgroups of patients who benefit most.

The study discussed in chapter 2 was not able to answer these questions. First, as ultrasonography was performed on clinical indication, as decided by the individual radiologist, the study population who had undergone breast ultrasonography was a selected one. Secondly, one definitive radiological diagnosis was given, in which mammography results were integrated with ultrasonography results. This made it impossible to analyze the impact of incremental ultrasonography.

Following, in chapter 3 a systematic literature review was performed in which all publications in MEDLINE and EMBASE between 1990 and 2000, assessing the role of ultrasonography as an adjunct to mammography, were analyzed. Diagnostic odds ratios for mammography and ultrasonography were calculated as a combined measure for sensitivity and specificity and were compared between the different studies. 22 studies were included, showing a large variety of indications for ultrasonography and variations in the diagnostic performance of mammography and ultrasonography. The study showed that little evidence-based support was available for the well-recognized value of ultrasonography as an adjunct to mammography in

clinical practice. The method of selecting the study population and the method of ultrasonography interpretation, with or without prior knowledge of mammography results, strongly influenced the performance of mammography and ultrasonography relative to each other.

These results emphasized the need for a prospective study in which systematic ultrasonography is performed in a non-selected consecutive patient population to identify the subgroups of patients in which the highest diagnostic yield would be obtained. In order to facilitate and optimize the logistic planning of breast imaging early in the diagnostic work-up, it was decided to focus mainly on the reasons of referral when defining subgroups of patients.

In chapter 4, the results are presented of a large prospective study, named the MAMMOED study (MAMmacarcinoom-studie Maastricht: Optimalisatie Echografische Diagnostiek) that was performed at Maastricht University Hospital between October 1999 and August 2000, as part of the Cost Containment Research Program of the Dutch Health Care Insurance Board. Aims of the study were to assess the diagnostic value of ultrasonography as an adjunct to mammography and clinical examination in the detection of breast cancer and the feasibility of selecting subgroups of patients who benefit most.

In 3835 breasts in 2020 consecutive patients referred for breast imaging, bilateral clinical examination, mammography and ultrasonography were performed. Pathology results from biopsy or surgical excision during 12 months follow up were used as gold standard for the presence of breast cancer and reported 129 malignancies in 127 patients (6.3% prevalence).

Breast ultrasonography detected 8 extra malignancies and correctly downgraded 332 positive results on mammography and clinical examination to a negative final diagnosis.

ROC curve analysis showed that there was a significant improvement in diagnostic value by adding ultrasonography to mammography and clinical examination. Subgroups of patients were defined according to indication for referral and age. The diagnostic yield improved significantly in patients referred for palpable breast masses, especially in patients younger than 50 years old, or patients referred from the national breast cancer screening program. The increase in area under the ROC curve was not statistically significant in patients referred for breast symptomatology and follow up of a prior breast malignancy. Due to the small numbers and low prevalence of breast cancer, the diagnostic benefit remained undefined for patients referred for follow up of a prior benign lesion, patients referred for reassurance, or when ultrasonography was performed as screening examination of the contralateral breast.

The study concluded that systematic application of ultrasonography significantly improved the overall diagnostic yield, and that the diagnostic value increased most significantly in patients with palpable breast masses and patients referred with abnormal screening mammograms.

In the diagnostic work-up for breast disease, all information on the lesions and abnormalities found by the different tests is combined with the knowledge of patient characteristics from medical history into one overall diagnosis indicating the suspicion of breast cancer. The contribution of each diagnostic test in defining the overall diagnosis was studied by multivariate logistic regression analysis and reported in chapter 5. Additionally, the contribution of additional ultrasonography in the prediction of breast cancer was studied for different patient populations. Patient data

of the MAMMOED study were used and diagnostic variables were included from medical history, clinical examination, mammography and ultrasonography.

A prediction model for breast cancer was presented, which included the variables: age, menopause, specific breast symptoms, diagnosis of clinical examination, mammographic calcifications and the integrated diagnosis resulting from ultrasonography, mammography and clinical examination. Using this model, the probability of breast cancer can be calculated for individual patients by combining the results of the different diagnostic tests. The "worst-case" scenario consisted of postmenopausal women older than 50 years, having specific breast symptoms such as skin retraction or nipple discharge, a suspicious clinical examination, suspicious calcifications on the mammogram and a suspicious final diagnosis of clinical examination, mammography and ultrasonography together, resulting in a probability of breast cancer of 0.997.

ROC curve analysis of the generated probabilities for each category of variables, showed that each step in the diagnostic work-up improved the diagnostic value of the prediction model for breast cancer. Adding results of ultrasonography to the other modalities significantly improved the predictive value of the model. Using all available information a sensitivity of 95% and specificity of 92% could be reached.

Stratified analysis according to reason for referral showed that additional ultrasonography significantly improved the predictive value of the model in patients referred for palpable masses ($p=0.04$). Among patients without a palpable lump, ultrasonography contributed most to the diagnosis in the subgroup of premenopausal patients ($p=0.39$).

It was concluded that, although the value of this prediction model in clinical practice may be argued, the model demonstrated a set of diagnostic variables, which are most important in the composition of a final imaging diagnosis.

In order to study the costs and effects of the use of additional ultrasonography in the evaluation of palpable breast masses, a decision analytical model was presented in chapter 6.

The model was based on the subgroup of patients from the MAMMOED study presenting with a palpable mass ($n=522$, 93 malignancies). Routine diagnostic work-up of palpable breast masses includes the performance of clinical examination, mammography and fine needle aspiration cytology (FNAC), combined as the "triple test".

In this model, 3 different diagnostic strategies of incorporating ultrasonography in the triple test were compared to the routine conventional triple test. In strategy 1, a cut-off between benign and probably benign ultrasonography results was used for further referral for FNAC; in strategy 2, this cut-off was shifted to a cut-off between normal and benign results; and in strategy 3, prior ultrasonography was only performed in patients with normal, benign results on mammography and clinical examination, whereas immediate FNAC was performed in patients with suspicious lesions. Outcome variables included the total costs of strategies and the expected number of life years.

All strategies reported similar life expectancies, namely 31.0 life years. Cost-minimization demonstrated that experimental strategy-3 was the least expensive strategy (€ 2946). Experimental strategy-2 was the most costly strategy (€ 3475). Compared to the conventional strategy of immediate FNAC (€ 3010), both ultrasonography strategy 1 and 3 were preferred.

The study concluded that a reduction of the total costs for the diagnosis and treatment of breast cancer could be achieved by integrating ultrasonography in the triple test.

These results confirmed the results found by ROC curve and logistic regression analysis and favor the use of additional ultrasonography in patients with a palpable mass.

The overall conclusion of this thesis was that systematic application of ultrasonography as an adjunct to mammography and clinical examination significantly improved the diagnostic performance. Integrating the results from clinical epidemiological methodology, such as ROC curves and logistic regression analysis, with the results from decision analytical modeling indicated that in patients with palpable breast masses additional ultrasonography results in more accurate diagnosis at lesser costs.

Samenvatting

Het gangbare beeldvormende onderzoek van de mamma bestaat op de meeste radiologie afdelingen uit klinisch onderzoek en diagnostische mammografie, hetgeen kan worden aangevuld met echografisch onderzoek wanneer geïndiceerd. Dit proefschrift concentreert zich op het vermogen van deze onderzoeken om borstkanker te diagnosticeren en in het bijzonder de rol van de echografie hierbij.

Hoofdstuk 2 beschrijft een prospectieve studie uit 1994 naar het diagnostisch vermogen van beeldvormend onderzoek van de mammae in een poliklinische patiëntenpopulatie. Bij 1944 opeenvolgende diagnostische onderzoeken bij 1890 patiënten werden 3816 mammae onderzocht met behulp van palpatie en mammografie, aangevuld met echografie wanneer klinisch geïndiceerd.

Als gouden standaard voor de aanwezigheid van borstkanker werden de beschikbare pathologie uitslagen gedurende één jaar follow up gebruikt. Er werden 118 maligniteiten gevonden bij 115 patiënten ($115/1890 = 6,1\%$ prevalentie). Bij een afkappunt tussen benigne en waarschijnlijk benigne testresultaten had het radiologisch beeldvormend onderzoek een sensitiviteit en specificiteit van respectievelijk 89% en 98%. Er werden 13 foutnegatieve en 69 foutpositieve resultaten gevonden.

Met behulp van logistische regressie en ROC curve analyse werd voorts aangetoond dat het diagnostisch vermogen significant verbeterde wanneer testresultaten van beeldvormend onderzoek werden toegevoegd aan resultaten van palpatie en leeftijd. Hypothetisch kon een sensitiviteit van 100% worden behaald bij een specificiteit van 60%, wanneer alle informatie werd gecombineerd. Er werd geconcludeerd dat radiologisch beeldvormend onderzoek een belangrijke rol speelt bij de diagnose van borstkanker in de dagelijkse praktijk.

De resultaten van dit onderzoek en de prevalentie van borstkanker waren vergelijkbaar met die uit andere studies door nationale en internationale radiologie groepen. Aanvullend echografisch onderzoek werd bij 28% van de patiëntenpopulatie uitgevoerd. De huidige praktijk laat echter zien dat deze toepassing van echografie is toegenomen; in 1999 werd op de afdeling radiologie van het Academisch Ziekenhuis Maastricht bij meer dan 35% van de patiënten die doorverwezen werd voor diagnostisch beeldvormend onderzoek van de mamma ook een echografie uitgevoerd. Gedeeltelijk is dit het resultaat van de toegenomen beschikbaarheid en toegankelijkheid van echografie, de verbrede klinische indicaties en het geloof van artsen dat het uitvoeren van teveel testen hen minder snel wordt kwalijk genomen dan het uitvoeren van te weinig testen. Desalniettemin leidt dit tot de vraag wat het diagnostisch vermogen is van aanvullende echografie in deze patiëntenpopulatie en of echografie beperkt kan worden tot subgroepen patiënten die het meeste baat hebben bij dit onderzoek.

De studie die in hoofdstuk 2 werd beschreven, kon deze vragen niet beantwoorden. Ten eerste werd de echografie hier op klinische indicatie uitgevoerd, zoals bepaald door de individuele radioloog, waardoor de groep patiënten die een echografie ondergingen een sterk geselecteerde populatie was.

Ten tweede werd één definitieve radiologische diagnose gesteld, waarin de testresultaten van mammografie geïntegreerd werden met die van de echografie. Dit maakt het onmogelijk om de invloed van aanvullende echografie te bestuderen.

Vervolgens werd in hoofdstuk 3 een systematisch literatuuronderzoek besproken, waarin alle publicaties uit MEDLINE en EMBASE tussen 1990 en 2000 over de rol van

echografie als aanvulling op mammografie werden geanalyseerd. Als gecombineerde maat voor de sensitiviteit en specificiteit werden diagnostische odds ratios berekend voor mammografie en echografie en vergeleken tussen de verschillende studies. In totaal werden 22 studies in het onderzoek meegenomen en lieten een grote verscheidenheid zien in gebruikte indicaties voor echografie en diagnostisch vermogen van mammografie en echografie.

De studie liet zien dat er maar weinig literatuur voorhanden is, die de reeds lang geaccepteerde waarde van echografie als aanvulling op mammografie in de klinische praktijk onderbouwt. In de geanalyseerde publicaties had de methode om de patiëntenpopulatie te selecteren en de methode van echografie beoordeling, namelijk met of zonder voorkennis van de resultaten van mammografie, een grote invloed op de prestatie van mammografie en echografie ten opzichte van elkaar.

De resultaten van dit literatuuronderzoek benadrukten de behoefte aan een prospectief onderzoek waarin systematische echografie wordt uitgevoerd in een niet-geselecteerde patiëntenpopulatie, teneinde subgroepen patiënten te identificeren met de grootste diagnostische opbrengst. Om de logistische planning van beeldvormend onderzoek van de mamma op de radiologie afdeling te kunnen vergemakkelijken en te optimaliseren, werd besloten om de subgroepen patiënten voornamelijk in te delen volgens de verwijfsreden.

In hoofdstuk 4 van dit proefschrift werden de resultaten gepresenteerd van een grote prospectieve studie, de MAMMOED studie genoemd, (MAMmacarcinoom-studie Maastricht: Optimalisatie Echografische Diagnostiek). Deze studie werd uitgevoerd in het Academisch Ziekenhuis Maastricht tussen oktober 1999 en oktober 2001 en maakt deel uit van het Doelmatigheidsonderzoek programma van het College voor Zorgverzekeraars.

Doelen van de studie waren het bepalen van de diagnostische waarde van echografie als aanvulling op mammografie en klinisch onderzoek in het diagnosticeren van borstkanker en de mogelijkheid om subgroepen patiënten te selecteren bij wie aanvullende echografie het meeste baat heeft.

In 3835 mammae van 2020 opeenvolgende poliklinische patiënten die door huisarts of specialist doorverwezen werden voor diagnostisch beeldvormend onderzoek, werd bilateraal klinisch onderzoek, mammografie en echografie uitgevoerd. Alle onderzoeken werden gescoord op een 5-punts schaal met oplopende graad van verdenking op borstkanker: 1= normaal, 2= benigne, 3= onzeker benigne, 4= verdacht maligne, 5= maligne.

De pathologie uitslagen van biopsieën en chirurgische excisies gedurende 12 maanden follow up werden gebruikt als gouden standaard voor de aanwezigheid van borstkanker. In totaal werden 129 maligniteiten gevonden in 127 patiënten ($127/2020=6,3\%$ prevalentie).

Echografisch onderzoek detecteerde 8 extra maligniteiten en zorgde voor een correcte aanpassing van 332 verdachte diagnoses op mammografie en klinisch onderzoek in een negatieve einddiagnose. ROC curve analyse liet zien dat er een significante verbetering was van de diagnose, wanneer resultaten van echografie werden toegevoegd aan die van mammografie en klinisch onderzoek. Er werden subgroepen patiënten gedefinieerd volgens de verwijfsreden en leeftijd. Aanvullend echografisch onderzoek vergrootte de diagnostische opbrengst statistisch significant bij patiënten die doorverwezen werden vanwege een palpabele afwijking, vooral wanneer ouder dan 50 jaar en patiënten die werden doorverwezen vanuit het nationaal bevolkingsonderzoek voor borstkanker.

De toename in oppervlakte onder de ROC curve was niet statistisch significant voor patiënten die doorverwezen werden vanwege andere symptomatologie, zoals pijn of tepelvloed, of vanwege follow up van een eerdere maligniteit in de mamma. Tenslotte bleef, vanwege de kleine aantallen en de lage prevalentie borstkanker, de waarde van aanvullende echografie onduidelijk voor patiënten die doorverwezen werden vanwege een eerdere benigne afwijking, ter geruststelling, of wanneer een screeningsechografie werd uitgevoerd van de tegengestelde mamma.

De studie concludeerde dat systematische toepassing van aanvullende echografie in deze patiëntenpopulatie de uiteindelijke diagnostische opbrengst verbeterde, en dat dit effect het duidelijkst was voor patiënten die verwezen werden met een palpabele afwijking of met een afwijkend screeningsmammogram vanuit het bevolkingsonderzoek.

In de diagnostische work-up voor borstafwijkingen worden alle resultaten van de verschillende onderzoeken gecombineerd met patiëntkarakteristieken vanuit de anamnese tot een einddiagnose en graad van verdenking op borstkanker. De bijdrage van elke diagnostische test in de totstandkoming van deze einddiagnose werd bestudeerd met behulp van logistische regressie analyse en werd besproken in hoofdstuk 5. Tevens werd hier de bijdrage van echografie in de voorspelling van de aanwezigheid van borstkanker voor verschillende patiëntenpopulaties bestudeerd. Hiertoe werden van de patiënten uit de MAMMOED studie verschillende diagnostische variabelen uit de anamnese, klinisch onderzoek, mammografie en echografie gebruikt.

In een voorspellend model voor de aanwezigheid van borstkanker werden de volgende variabelen opgenomen: leeftijd, menopauze, specifieke borstklachten, diagnose uit klinisch onderzoek, mammografisch aangetoond kalk en de geïntegreerde einddiagnose van echografie, mammografie en klinisch onderzoek. Met behulp van dit model kan de waarschijnlijkheid op borstkanker worden geschat voor individuele patiënten door de testresultaten van de verschillende diagnostische onderzoeken te combineren. Het slechtste scenario bestond uit postmenopausale vrouwen ouder dan 50 jaar, met specifieke borstklachten, zoals huidintrekking of tepelvloed, een verdacht klinisch onderzoek, verdacht kalk op het mammogram en een verdachte einddiagnose van klinisch onderzoek, mammografie en echografie samen, en resulteerde in een geschatte kans op borstkanker van 0.997.

ROC curve analyse van de gegenereerde kansen voor elke categorie variabelen liet zien dat elke stap in de diagnostische work-up de voorspellende waarde van het model verbeterde. Het model verbeterde sterk wanneer de resultaten van echografie werden toegevoegd aan de resultaten van de andere modaliteiten. Wanneer alle informatie werd gebruikt, kon een sensitiviteit en specificiteit van respectievelijk 95% en 92% behaald worden.

Gestratificeerde analyse naar verwijsreden liet zien dat aanvullende echografie de voorspellende waarde van het model vooral verbeterde in patiënten die verwezen werden voor een palpabele afwijking ($p=0.04$). Bij patiënten zonder een palpabele afwijking, droeg echografie het meest bij aan de diagnose in de groep premenopausale patiënten ($p=0.39$).

Er werd geconcludeerd dat dit voorspellende model, alhoewel de waarde ervan voor de klinische praktijk kan worden betwist, een set diagnostische variabelen presenteert die belangrijk is bij de samenstelling van een beeldvormende einddiagnose.

Vervolgens werd in hoofdstuk 6 een besliskundig model gepresenteerd, dat de kosten en effecten bestudeert van de toepassing van aanvullende echografie bij de evaluatie van palpabele borstafwijkingen. Dit besliskundig model werd gebaseerd op de groep patiënten uit de MAMMOED studie die een palpabele afwijking hadden ($n=522$, 93 maligniteiten). Het gangbare beeldvormend onderzoek bij palpabele afwijkingen bestaat uit klinisch onderzoek, diagnostische mammografie en dunne naald cytologie (FNAC), samen de "triple test" genoemd. In dit besliskundige model werden 3 verschillende diagnostische strategieën waarbij echografisch onderzoek werd geïntegreerd in de triple test, vergeleken met deze routine conventionele methode. In strategie 1 werd een afkappunt tussen benigne en waarschijnlijk benigne echografie uitslagen gebruikt voor verdere doorverwijzing voor FNAC; in strategie 2 werd dit afkappunt verlegd tussen normale en benigne uitslagen; en in strategie 3 werd aanvullende echografie alleen uitgevoerd bij patiënten met normale, benigne resultaten op mammografie en klinisch onderzoek, terwijl directe FNAC uitgevoerd werd in patiënten met verdachte laesies. De uitkomstmaten waren de totale kosten van de strategieën en het verwachte aantal levensjaren.

Alle strategieën hadden een gemiddelde levensverwachting van 31,0 jaar. Kostenminimalisatie liet zien dat experimentele strategie 3 de goedkoopste was (€ 2946). Experimentele strategie 2 was de duurste strategie (€ 3475). Vergeleken met de conventionele strategie van directe FNAC (€ 3010), ging de voorkeur uit naar echografie strategieën 1 en 3.

De studie concludeerde dat een reductie van de totale kosten van de diagnose en behandeling van borstkanker bewerkstelligd kan worden wanneer echografie in de triple test zou worden opgenomen.

Deze resultaten bevestigden de resultaten van de ROC curve en logistische regressie analyse en moedigen het gebruik van echografie in patiënten met een palpabele afwijking aan.

Uit de resultaten van de verschillende studies die beschreven worden in dit proefschrift kan geconcludeerd worden dat systematische toepassing van echografie als aanvulling op mammografie en klinisch onderzoek in een poliklinische patiëntenpopulatie de diagnostische opbrengst significant verbeterde.

Het combineren van de resultaten van klinisch epidemiologische methodologie, zoals ROC curves en logistische regressie analyse, met de resultaten van besliskundig modelleren, wijzen erop dat het gebruik van aanvullende echografie bij patiënten met een palpabele afwijking een meer nauwkeurige diagnose kan bewerkstelligen tegen lagere kosten.

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Curriculum Vitae

Karin Flobbe werd geboren op 23 september 1972 in Wemeldinge (Zld).

Van 1984 – 1990 doorliep zij het Atheneum aan het Titus Brandsmacollege te Dordrecht.

Daarna studeerde ze aan de Faculteit Gezondheidswetenschappen van de Rijksuniversiteit Limburg (huidige Universiteit Maastricht) waar zij in december 1995 haar doctoraal diploma Biologische Gezondheidkunde behaalde.

Tijdens deze studie doorliep zij wetenschapsstages aan het Department of Infectious Diseases van de Universiteit van Oxford te Engeland (januari – juli 1994, o.l.v. Prof dr Dominic Kwiatkowski), en bij het Medical Research Council in Gambia in West-Afrika (augustus 1994 – februari 1995, o.l.v. Prof dr Geoff A.T. Targett).

Na haar afstuderen werkte zij vervolgens 2,5 jaar als wetenschappelijk onderzoeker aan het Departement Community Health van de Universiteit van Pretoria in Zuid-Afrika (1996 – 1998, o.l.v. Prof dr Carel B. IJsselmuiden).

Vanaf november 1998 is zij werkzaam als wetenschappelijk onderzoeker aan de afdeling Radiologie van het Academisch Ziekenhuis Maastricht, o.l.v. Prof dr Jos M.A. van Engelshoven, alwaar ze in oktober 1999 haar promotieonderzoek binnen de MAMMOED studie begon. Na het voltooien van dit proefschrift zal ze zich als post-doc op deze afdeling blijven bezighouden met de opzet en uitvoering van diverse wetenschappelijke onderzoeksprojecten naar diagnostische testen.

Karin Flobbe was born on September 23rd, 1972 in Wemeldinge (Zld.) From 1984 – 1990 she attended secondary education at the Titus Brandsmacollege in Dordrecht.

Consequently, she studied at the Faculty of Health Sciences at the Rijksuniversiteit Limburg (currently Maastricht University) and obtained her MSc in Biological Health Sciences in December 1995.

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