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Diagnostic utility of combined ultrasonography and mammography in the evaluation of women with mammographically dense breasts

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KEYWORDS

Breast ultrasonography;
Breast lesion;
Breast cancer.

Abstract *Purpose:* To assess the diagnostic utility and additional cost of combined breast ultrasonography and mammography in the evaluation of asymptomatic women with mammographically dense breasts.

Materials and methods: Of 5108 asymptomatic women, who underwent mammography, 1754 had dense breasts (BI-RADS 3 or 4) and negative mammographic outcome. They were divided in 4 subgroups according to their age (<40 yrs; 40–49 yrs; 50–59 yrs; >59 yrs). Breast ultrasonography was performed immediately after mammography. Lesions detected at ultrasonography were examined cytologically/histologically. Mammograms from women, who were diagnosed carcinoma at ultrasonography, were reviewed by an external radiologist. Costs per diagnosed carcinoma and per examined woman were calculated on the basis of current regional charges. *Results:* Mammographies (5108) were performed, 67 cancers were detected (cancer detection rate 13.1‰); mammography identified 55 carcinomas and ultrasonography performed in women with dense breasts identified 12 cancers (17.9% of all cancers detected, overall cancer detection rate 6.8‰). Ultrasonography identified a benign condition in 1567 out of 1754 women (89.3%) (in 925 absence of focal lesions; 438 simple cysts; 56 ductal ectasia; 148 benign solid lesions); 97 complex cysts, 52 lesions that could not be differentiated as liquid or solid lesions, and 38 solid lesions suspicious for malignancy in the remaining 187 out of 1754 patients (10.7%). Cytology/histology confirmed carcinoma in 12 women (overall biopsy rate 26.2‰, benign biopsy rate 19.4‰). The additional costs were: € 6,123.45 per detected cancer, € 41.89 per examined woman.

Conclusion: Breast ultrasonography immediately after mammography in women with dense breasts is useful to avoid diagnostic delays and inconvenient medico-legal implications even though this procedure involves increased costs.

Sommario *Scopo:* Valutare utilità diagnostica e costi aggiuntivi dell'associazione dell'ecografia mammaria alla mammografia nella valutazione di donne asintomatiche con seno denso. *Materiali e metodi:* Di 5108 donne asintomatiche sottoposte a mammografia, 1754 con

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mammografia negativa e seno denso (BI-RADS 3 o 4) suddivise in 4 gruppi di età (<40; 40–49; 50–59; >59 anni) hanno effettuato immediatamente l'ecografia. Le alterazioni rilevate ecograficamente sono state verificate con esame cito/istologico. Le mammografie dei carcinomi diagnosticati ecograficamente sono state rivalutate da un radiologo esterno. I costi per carcinoma diagnosticato e donna esaminata sono stati calcolati in base alle tariffe regionali.

Risultati: Su 5108 mammografie sono stati riscontrati 67 carcinomi (tasso diagnostico di carcinoma 13,1‰): la mammografia ne ha riconosciuti 55; l'ecografia eseguita nelle donne con seno denso 12 (17,9% del totale, tasso diagnostico globale 6,8‰). L'ecografia ha evidenziato: quadri di benignità in 1567/1754 donne (89,3%) (925 assenza di lesioni focali; 438 cisti semplici; 56 ectasie duttali; 148 lesioni solide benigne); 97 cisti complesse, 52 lesioni che non è stato possibile ulteriormente differenziare in lesioni cistiche o solide e 38 lesioni solide sospette per malignità nelle restanti 187/1754 pazienti (10,7%). L'esame cito/istologico ha confermato la presenza di 12 carcinomi (tasso biotico globale 26,2 ‰ e tasso di biopsie benigne 19,4‰). I costi aggiuntivi sono risultati: € 6123,45 per carcinoma diagnosticato, € 41,89 per donna esaminata.

Conclusione: L'esecuzione immediata dell'ecografia dopo la mammografia in donne con seni densi, seppure non sceva da un aumento dei prezzi complessivi, è utile per evitare ritardi diagnostici e spiacevoli contenziosi medico–legali.

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Introduction

Mammography is the method of choice in the study of breast carcinoma in asymptomatic women over 40 years of age, and it is considered the most sensitive instrumental examination in the early diagnosis of clinically occult carcinoma (90%) [1]. Mammographic sensitivity is highly correlated to the morphological characteristics of the tumor, but also to the patient's age and composition of breast tissue. Sensitivity is therefore higher in the evaluation of breasts consisting mainly of fat tissue (80–98%) as compared to very dense breasts (30–48%) [1–4]. Mammographic density is considered one of the main causes of false negative outcome in mammographic examinations with a reduced sensitivity and a reduced effectiveness of mammographic screening in women under 50 years of age and an increased risk of interval cancer at all ages [3–8].

Breast ultrasonography is a second line diagnostic tool, which is useful in the analysis and characterization of specific areas considered suspicious at clinical or mammographic examination [9–13]. At present breast ultrasonography cannot be considered a valid screening tool due to the lower sensitivity and accuracy in the diagnosis of breast carcinoma as compared to mammography and because of the elevated number of false positive results and subsequent increase in diagnostic procedures [14–19]. Due to improved spatial and contrast resolution of modern equipment [20–24] and as the patient's age has little influence on diagnostic accuracy of ultrasonography, the latter is an important tool in the early detection of mammographically occult malignant lesions in women with mammographic density [25,26]. The aim of this study was to evaluate diagnostic utility of a systematic "real time" combination of breast ultrasonography and mammography in the examination of asymptomatic women with mammographic density but with neither palpable lesion nor suspicion of malignancy at mammography. An additional aim of the study was to evaluate the increased mean cost per patient in connection with this combined procedure.

Materials and methods

From January 2000 to May 2006, 5108 consecutive women (age range 35–82 yrs, mean age 57 yrs) underwent mammography in our radiology department and were prospectively selected among all the asymptomatic women who were referred to our department for a routine breast examination. Ethical approval for the study was granted by the Medical Research Ethics Committee of our university, and informed consent was obtained from all patients.

Mammographic breast density was classified using The American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS) [27] and divided into four morphological categories according to the parenchymal structure (BI-RADS 1: the breast is almost entirely fatty; BI-RADS 2: scattered fibroglandular densities; BI-RADS 3: the breast is heterogeneously dense, and mammographic sensitivity can be reduced; BI-RADS 4: the breast tissue is extremely dense and lesions may not be detected at mammography). The mammograms were divided into 5 diagnostic categories according to the presence of nodular opacities, parenchymal distortions or suspicious microcalcifications (category 1: negative outcome; category 2: benign lesions; category 3: probably benign lesions; category 4: suspicious anomalies; category 5: suspected malignancy).

It was considered that elevated mammographic density (BI-RADS 3 or 4) prevented the mammograms from being safely assigned to the definitive diagnostic categories 1, 2 or 3. With the exception of mammograms presenting suspicious anomalies or malignancies (category 4 or 5), all mammograms showing elevated mammographic density were therefore assigned to category 0 (requiring further diagnostic investigation) and the patients underwent breast ultrasonography.

The study group was furthermore divided into 4 subgroups according to the patients' age (<40 yrs; 40–49 yrs; 50–59 yrs; >59 yrs).

Mammography was performed using dedicated equipment, mammographic cassettes and radiographic films, and standard craniocaudal, mediolateral and oblique projections were taken.

Immediately after the examination, the mammograms were evaluated separately by 2 radiologists, both experts in the field of breast examination (20 and 16 years' experience, respectively).

Ultrasonographic examination was performed by a radiologist with 16 years' experience in the field of breast examination using

Aloka Prosound SSD-5500 and General Electric Voluson 730 Pro, with a linear 10–13 MHz probe. The patients were examined in the supine position with their arms raised above their head. All four quadrants of the breast as well as the nipple were studied, and the examination included classification of the parenchymal structures according to the presence of hypoechoic glandular tissue or hyperechoic fibrous tissue. The lesions were identified due to the presence of nodular masses, posterior shadowing or anomalies/distortions in the breast structure, and they were further characterized by the evaluation of the form, margins, vascularization and changes in the surrounding echostructure.

Whenever a suspicious lesion was identified at ultrasonography, needle aspiration biopsy was performed for cytological examination using a 22-gauge needle, or ultrasound guided biopsy was performed for histological examination using an 18-gauge needle. In these cases the mammograms were retrospectively evaluated by an external radiologist with 21 years' experience in the field of breast examination, and particular attention was paid to the region showing ultrasonographic anomalies. The patients whose cytological or histological examination indicated proliferative lesion or carcinoma were referred to the surgical department for excision. Complex cysts underwent needle aspiration biopsy.

The result of systematic combination of ultrasonography and mammography in women with dense breasts is expressed as the overall cancer detection rate and detection rates related to the 4 age subgroups (the relation between the amount of women with cancer identified at screening and the amount of women who were screened $\times 1000$). Overall biopsy rate was calculated (the relation between the amount of women who underwent invasive procedures and the amount of women who were screened $\times 1000$) and the benign biopsy rate (the relation between women who underwent surgery leading to a benign histological diagnosis and the amount of women who were screened $\times 1000$). The cost per diagnosed carcinoma and per woman was calculated on the basis of the regional costs related to the performed examinations.

Results

In a total of 5108 women, 67 carcinomas were identified resulting in a cancer detection rate of 13.1‰. In 204 mammograms considered suspicious for malignant lesions, 55 carcinomas were detected (patients' age range 43–78 yrs; mean age 65 yrs) showing a mammographic sensitivity

of 82.1% and specificity 97.0%. Eight carcinomas out of 55 (14.5%) identified at mammography were diagnosed in women with elevated breast density (3 cases of BI-RADS 4 and 5 cases of BI-RADS 3). Of the remaining 4904 negative mammograms, 1754 (35.8%) were from women with elevated breast density. These patients immediately underwent ultrasonography.

Ultrasonography permitted diagnosis of further 12 carcinomas (17.9% of all diagnosed carcinomas) with a detection rate of 6.8‰ (12 out of 1754). In the 4 subgroups detection rates were as follows: in the first subgroup (<40 yrs) 10.2‰ (1 carcinoma in 98 patients), in the second subgroup (40–49 yrs) 7.0‰ (6 carcinomas in 852), in the third subgroup (50–59 yrs) 6.5‰ (4 carcinomas in 612), and in the fourth subgroup (>59 yrs) 5.2‰ (1 carcinoma in 192).

At the retrospective study of the mammograms from the patients who were diagnosed carcinoma at ultrasonography, the external reviewer confirmed negative outcome of mammography in 10 out of 12 cases; in 2 cases he found slight alterations, which did not justify suspicion for malignancy (BI-RADS 3). In one patient, the mammogram showed a light distortion of the parenchymal structures, and in the other patient, the mammogram showed an area of asymmetric density, which was present with the same morphology in a previous mammogram.

In the 1754 women with dense breast tissue and negative outcome of mammography, sonography yielded the following outcome (Table 1):

- in 925 cases (52.7%) absence of focal lesions (U1) (Fig. 1);
- in 438 cases (25.0%) simple cysts (U2) (mean dimension 1.7 cm; range 0.3–4.5 cm);
- in 56 cases (3.2%) ductal ectasia (U2);
- in 148 cases (8.4%) 156 benign solid lesions (U2) (mean dimension 1.5 cm; range 0.4–3.6 cm);
- in 97 cases (5.5%) 97 complex cysts (U3); needle aspiration biopsy yielded negative outcome in all cases (C-1 and C-2) (mean dimension 1.8 cm; range 0.9–2.8 cm);
- in 52 cases (3.0%) mainly hypoechoic nodules, but differentiation between complex cysts and solid lesions

Table 1 Outcome of immediate breast ultrasonography and definitive diagnosis

Initial diagnosis ultrasonography	Number of patients	Definitive diagnosis	Total number of patients
Absence of focal lesion	925	Diagnosis unchanged at follow-up	1567
Simple cyst	438		
Ductal ectasia	56		
Benign solid lesion	148		
Complex cyst	97	Cytological analysis negative for malignancy	97
Differential diagnosis: doubt between complex cyst and solid lesion	52	Cytology Liquid cyst	14
		Solid lesion	5
		Cells with nuclear anomalies	3
		Core-biopsy negative for malignancy	30
		Core-biopsy positive for malignancy	29
		No cells with nuclear anomalies	9
Solid lesion suspicious for malignancy	38	Core-biopsy negative for malignancy	38
		Core-biopsy positive for malignancy	
Total number of patients			1754

Fig. 1 (a and b) The breast tissue is extremely dense (BI-RADS 4) and additional diagnostic imaging is required (diagnostic category 0); (c) ultrasonography shows no focal lesions (U1).

Fig. 2 Invasive ductal carcinoma (7 mm). (a and b) Mammography shows extremely dense breast tissue (BI-RADS 4) and additional diagnostic imaging is required (diagnostic category 0); (c) ultrasonography shows a hypoechoic lesion with ill-defined margins and posterior shadowing (9.5 mm); suspicious for malignancy (U4).

was not possible (U3); needle aspiration biopsy was performed in all cases (mean dimension 1.0 cm; range 0.6–1.8 cm). Cytological examination evidenced that 14 lesions contained fluid whereas the remaining 38 were solid. In the 8 cases presenting cellular anomalies (C-3), subsequent core biopsy was negative for malignancy in 5 cases (fibrosis) whereas 2 patients had invasive ductal carcinoma (no special type carcinoma) and 1 had infiltrating lobular carcinoma;

- in 38 (2.2%) lesions suspicious for malignancy at ultrasonography (U4) (mean dimension 1.2 cm; range 0.4–1.7 cm), subsequent core biopsy revealed benign lesions in 29 cases (fibrosis and fibrocystic disease in 15 cases; fibroadenoma in 12 cases, sclerosing adenosis in 1 case and typical ductal hyperplasia in 1 case) and 9 cases of carcinoma (infiltrating ductal carcinoma in 4 cases, infiltrating carcinoma in 3 cases and intraductal carcinoma in 2 cases) (Fig. 2).

Surgical excision of the 9 lesions, which were suspicious for malignancy, confirmed the presence of infiltrating ductal carcinoma in 6 cases (of which one focal lesion associated with ductal carcinoma in situ), 2 cases of intraductal carcinoma, 3 cases of infiltrating lobular carcinoma and 1 case of tubular carcinoma.

Maximum mean diameter of the 12 tumors identified at histological examination was 1 cm (range 0.5–1.5 cm), and mean stage was stage I, pT1NoMx according to the TNM classification.

The most frequently observed ultrasonographic alteration was the presence of focal lesions, which were mainly round (7 lesions, Fig. 3) or irregular (2 lesions, Fig. 4), hypoechoic (9 lesions), with blurred margins (6 lesions, Fig. 5) or irregular margins (3 lesions), and posterior shadowing in 2 cases. In 4 cases power Doppler permitted detection of intense intra- and perilesional vascularization. There were 2 cases of isohypoechoic lesions with blurred margins: in 1 case the core of the lesion was strongly vascularized and in 1 case there was posterior shadowing. One case was considered suspicious for malignancy merely due to the presence of an ill-defined mass with posterior shadowing (Fig. 6). Mean dimension of ultrasonographically diagnosed malignant lesions was 0.9 cm (range 0.4–1.5 cm).

In the 12 women who had breast cancer, ultrasonography evidenced the following additional characteristics: in 5 cases the malignant lesion was associated with ductal ectasia (simple retroareolar in 3 cases; retroareolar and peripheral in 2 cases); in 4 cases the malignant lesion was surrounded by multiple benign solid hypoechoic cystic formations with regular margins which impeded evaluation of the parenchyma; 2 cases presented an elevated amount of fibrous tissue: multiple areas with posterior shadowing. In 1 case ultrasonography diagnosed a deeply located malignant lesion in a very small breast whose dimension impeded an adequate mammographic study.

Mean age of the patients whose malignant lesion was diagnosed only at ultrasonography was 54 years (range 36–72 yrs): 6 were of childbearing age (1 was <40 yrs and 5 were 40–49 yrs) and 6 were in menopause (1 was 40–49 yrs, 4 were 50–59 yrs, 1 was >59 yrs). Only one woman had previously taken hormone replacement therapy, completed 2 years before this study.

Fig. 3 Invasive ductal carcinoma (9 mm). (a) Mammography shows heterogeneously dense breast tissue (BI-RADS 4) and additional diagnostic imaging is required (diagnostic category 0); (b) ultrasonography shows a roundish markedly hypoechoic lesion with microlobulated margins and a small vascular pole (10 mm); suspicious for malignancy (U4).

In total, diagnostic completion using ultrasonography led to 149 fine needle aspiration biopsies, 46 core biopsies and 12 surgical excisions; overall biopsy rate was 46/1754 × 1000 (26.2‰); benign biopsy rate was 34/1754 × 1000 (19.4‰). On the basis of currently calculated cost of the additional procedures performed according to this study protocol (1754 ultrasonographic examinations;

Fig. 4 Invasive ductal carcinoma (5 mm). (a) Mammography shows heterogeneously dense breast tissue (BI-RADS 3) and additional diagnostic imaging is required (diagnostic category 0); (b) ultrasonography shows a mildly hypoechoic irregular lesion with irregular margins and posterior shadowing (6 mm); suspicious for malignancy (U4); (c) ductal dilation in the subareolar area.

149 fine needle aspiration biopsies; 149 cytological analyses; 46 core biopsies; 46 histological analyses; 12 surgical biopsies during hospitalization) the additional cost per diagnosed carcinoma was € 6,218.44 and per woman who underwent the procedure € 42.54 (Table 2). All the women who participated in this study undergo regular mammographic and ultrasonographic follow-up in our department and so far no new case of carcinoma has been diagnosed.

Discussion

According to the recent literature [8,16] mammography has proved to be an excellent tool in the early diagnoses of breast carcinoma, showing an elevated sensitivity (>90% in mainly fatty breasts) and a specificity of (90–95%). However, in daily clinical practice, it can be extremely difficult for the radiologist to identify the usual mammographic signs of malignancy in very dense breasts, with the exception of malignant microcalcifications. Diagnosis of breast carcinoma can therefore be complex and requires multiple imaging modalities thus considerably prolonging the time interval from mammography and final diagnosis of

carcinoma [6,28]. Fibroglandular tissue is radiologically dense and appears lighter or white on the mammogram like a carcinoma, which can thus be masked by the surrounding tissue. At ultrasonography, the echostructure of fibroglandular tissue is mainly hyperechoic whereas carcinoma appears mainly hypoechoic and it is therefore easily differentiated from the surrounding healthy tissue [29].

Some recent studies [25,30] of patient populations who underwent diagnostic examination of the breast have shown the important role of ultrasonography in clinically and mammographically asymptomatic women with dense breasts. In the literature it has been documented that the use of ultrasonography in addition to mammography leads to an increased overall sensitivity in the diagnosis of breast carcinoma from 63% to 95%, to a slightly increased specificity from 89% to 92% [31] and a cancer detection rate varying from 3‰ to 5‰ [8].

The outcome of our study confirmed these figures, as 12 malignant tumors were diagnosed at ultrasonography in 1754 women whose mammography was negative for malignancy, thus reaching an overall cancer detection rate of 6.8‰, which is slightly higher than the rates reported in the literature [1,8,29,31]. This difference could be linked to our particular patient population of women who

Fig. 5 Tubular carcinoma (6 mm). (a and b) Mammography shows extremely dense breast tissue (BI-RADS 4) and additional diagnostic imaging is required (diagnostic category 0); (c) ultrasonography shows an ellipsoid, hypoechoic, taller-than-wide lesion with ill-defined margins, and with a marked vascular pole within and next to the lesion (7 mm); suspicious for malignancy (U4).

spontaneously came to our department requesting a mammographic examination, but also to the synchronous performance of both procedures by a radiologist who is an expert in breast examination.

Diagnostic rate related to the 4 subgroups divided by age (<40 yrs; 40–49 yrs; 50–59 yrs; >59 yrs) was highest in patients <50 where ultrasonography proved most useful detecting malignant lesions in 7 cases out of 950 (7.3‰). However, diagnostic rate related to patients <40 (10.2‰) could be unusually high also due to the limited number of patients in this age group as compared to the other age groups.

At subsequent review of the 12 mammograms from those patients who were diagnosed breast carcinoma at ultrasonography, only 2 mammograms presented minor alterations, which were not significant enough to cause suspicion of malignant lesions. This could from one point of view be put down to the experience of the radiologists who initially read the mammograms, but it is also an indication of the limited effectiveness of mammography in dense breasts.

The mean dimension of the tumors detected at ultrasonography was 0.9 cm (1 cm at subsequent histological examination). If these patients had undergone mammography only, without ultrasonography for diagnostic completion, detection of the malignant lesions would have been delayed, and the increased dimensions of the tumors could have had a serious effect on treatment and survival of the patients and might in some cases have lead to inconvenient medico-legal implications.

In 46 women out of 1754 (2.6%) invasive procedures were performed and in all cases a definitive diagnosis was achieved. Biopsy rate was low but similar to the one reported in the literature [1].

Analysis of the costs shows that ultrasonographic examination leads to a mean increase per diagnosed carcinoma of € 6218.44 against a long-term benefit which is difficult to estimate, as it is not possible to calculate the influence of an early diagnosis on the patient's survival.

Although the additional cost per diagnosed carcinoma is elevated, ultrasonography permitted detection of 17.9% of the carcinomas detected in the entire study population (12 out of 67) and the contribution of this diagnostic examination can therefore not be ignored. In our experience, the only way to limit the number of unnecessary procedures after ultrasonography and thereby reduce the costs is that women at high risk of carcinoma undergo ultrasonography performed by an expert in breast examination.

In addition to our results in terms of figures, it is worth underlining the importance of performing ultrasonography immediately after mammographic evaluation and assessment of mammographic density. Immediate ultrasonographic examination performed by the specialized radiologist who evaluated the mammograms, or by an ultrasonographic operator, also expert in breast examination, with possibility of exchanging points of view, can exclude diagnostic doubts in the same session. Mammographically occult cancers can be detected immediately and diagnostic delay be avoided. Moreover, there is little risk of losing the patient in the intermediate phase

Fig. 6 Invasive ductal carcinoma (7 mm). (a) Mammography shows extremely dense breast tissue (BI-RADS 4) and additional diagnostic imaging is required (diagnostic category 0); (b) ultrasonography shows an ill-defined hypoechoic lesion with irregular margins and posterior US shadowing (6×4 mm); suspicious for malignancy (U4).

between mammography and diagnostic completion by ultrasonography, of losing patients who prefer turning to other institutions for ultrasonographic examination, or losing patients who decide not to undergo ultrasonography. Only ultrasonography immediately after mammography

Table 2 Additional costs per cancer detected and per woman examined according to current regional charges for the different diagnostic procedures

Procedure	Number	Cost per procedure (€)	Total cost (€)
Ultrasonography	1754	35,89	62951,06
Needle aspiration	149	37,18	5539,82
Cytological analysis	149	5,17	770,33
Core biopsy	46	37,18	1710,28
Histological analysis	46	27,17	1249,82
Surgical biopsy during hospitalization	12	200	2400
Total cost			74621,31
Cost per carcinoma detected (12)			6218,44
Cost per woman examined with dense breasts (1754)			42,54
Cost per woman examined (5108)			14,61

yields the opportunity to reach a definitive conclusion using the diagnostic tools available today. In this way it is possible to make a safe diagnosis and avoid the risk of inconvenient medico-legal arguments between the patient and the radiologist who is responsible for the mammographic examination. These comments are referred to a patient population consisting of women who spontaneously came to our institution requesting a mammography, but they may be even more appropriate in a framework of screening where there is greater risk of losing patients in the intermediate phase after mammography. Although systematic ultrasonographic examination of women with radiographically dense breasts (BI-RADS 3 or 4) involves an increased overall cost per woman, it is justified by the possibility of reaching an early diagnosis of tumors not detectable at mammography.

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