Chapter 2
Screening of Breast Cancer

Per Skaane

2.1 Introduction

The widespread use of screening mammography has been the mainstay of breast cancer prevention in Western countries for the past 20–30 years. Breast cancer screening has already proved effective in reducing the rate of mortality from this disease, and many experts consider mammographic screening to be one of the major medical successes of recent decades. Screening for breast cancer is nowadays performed in many countries where the disease is common, and its benefits are generally accepted.

The use of screening mammography is based on the assumption that breast cancer is a progressive disease, and consequently its earlier detection and diagnosis will lead to an improved prognosis for the affected women. Breast cancers should be detected in their preclinical stage as early-stage cancers, i.e. still presenting as ductal carcinoma *in situ* (DCIS) or as invasive cancer measuring less than 15 mm in diameter. Furthermore, it is important not only to detect the small cancers, but especially to diagnose the small invasive cancers that manifest with mammographic features known to have a worse prognosis, such as malignancies associated with casting-type calcifications. Improved mammographic techniques and the implementation of advanced digital applications may further optimize the conditions for detecting early-stage breast cancers.

During the past few years, there has been a hot public debate on the effect of mammographic screening on mortality. Although the results of randomized controlled trials led an international expert group (International Agency for Research on Cancer, IARC 2002) to conclude that there was a mortality rate reduction of 25%, opponents of screening have repeatedly published critical reports that occasionally ignore the scientific evidence. The establishment of guidelines for mammographic screening is a difficult and controversial task, and even evidence-based analyses from 'neutral' public and federal agencies (Petitti et al. 2010) are published with recommendations based on subjectively selected material with dubious or mislead-

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ing conclusions (Kopans 2010). The European Guidelines recommend population-based biennial mammographic screening for the age group 50–69 years (Perry et al. 2006). Several countries, however, have extended this age range to include younger age groups and also those aged up to 74 years. The debate as to the target age groups and the screening intervals will most likely continue for some years.

A further hot topic recently has been the adverse effects of breast cancer screening. It is important to be aware that these side-effects are inherent in screening in general, and that the numbers of false-positives and overdiagnoses with overtreatment should be kept to a minimum. The natural history of DCIS is poorly understood, and it is suggested that not all DCIS cases will progress to invasive cancer. The implementation of mammographic screening has resulted in a significant rise in the number of diagnosed cancers, and in particular the rise in the number of DCIS diagnoses has been a cause of concern from the aspect of overdiagnosis.

The introduction of new imaging techniques, including digital mammography, computer-aided detection (CAD), MRI and advanced biopsy techniques such as vacuum-assisted biopsy, has led to an increase in the detection of microcalcifications and DCIS. It is important to keep in mind the potentially adverse effects of breast cancer screening as regards overdiagnosis and overtreatment when new screening techniques and modalities are introduced (Hall 2010).

2.2 The Beginnings of Mammographic Screening

On the basis of his examinations of mastectomy specimens, a German surgeon in Berlin, Albert Salomon, published the first description of the value of radiography in the study of breast cancer in 1913 (Gold et al. 1990). Important studies involving mammography were carried out in the US by Warren in the early 1930s. However, it was not until 1958 that a study relating to the use of mammography for screening purposes was published (Gershon-Cohen and Ingleby 1958), with a follow-up in 1961. The authors concluded that the periodic mammography of women over 40 years of age would prove beneficial in reducing the rate of mortality from breast cancer (Gershon-Cohen et al. 1961).

It soon became obvious that prospective randomized trials would be necessary to prove the efficacy of mammographic screening. The first randomized controlled trial (RCT), the HIP (Health Insurance Plan) study, performed in the state of New York from 1963 to 1967, demonstrated that such screening resulted in a significant reduction in the breast cancer mortality rate (Shapiro et al. 1971). The success of the HIP study initiated the Breast Cancer Detection Demonstration Project (BCDDP), which began in 1973. In this study, designed to demonstrate the usefulness of mammographic screening in women aged from 35 to 74 years, one-third of the detected cancers were non-infiltrating or smaller than 10 mm (Baker 1982). The results of the BCDDP left some open questions, however, since no control group was included in this study.

The earliest case-control mammographic screening study in Europe started in the region of Florence in Italy in 1970 (Palli et al. 1986), and was followed by two Dutch case-control studies, the DOM project in Utrecht in 1974 (Collette et al. 1984) and

the Nijmegen project in 1975 (Verbeek et al. 1984). The Edinburgh trial commenced in 1978 (Roberts et al. 1990). The programme 'Europe Against Cancer', launched in 1986, had the aim of introducing systematic screening for breast cancer for women in the age range 50–69 years (de Waard et al. 1994; Moral Aldaz et al. 1994).

2.3 Randomized Controlled Trials

RCTs of breast cancer screening are of the utmost importance since their results furnish the scientific basis for the widespread use of organized mammographic service screening today. In these trials, the participating women are divided into two groups: One group is offered mammographic screening, and the other group serves as control group. It is important to bear in mind that RCTs in fact underestimate the potential benefit from mammographic screening since the intervention group in fact includes women invited to screening, but who do not actually attend the screening programme. Many women choose not to participate in the screening programme (non-compliance). On the other hand, many women allocated to the unscreened control group may seek mammography outside the programme (contamination). In the evaluation of RCTs, such non-compliance and contamination are not taken into account. Consequently, the real benefit of periodic mammographic screening is underestimated.

Furthermore, it is important to be aware of the very different study designs of the various RCTs that have been carried out. The ages of the target groups and the screening intervals varied among the RCTs, and some RCTs were performed with the use of single-view mammography (MLO projection only) whereas others involved two-view (CC and MLO projections) mammography. Clinical breast examinations were included in the three Anglo-American trials (the HIP trial, the Canadian National Breast Screening Study [CNBSS], and the Edinburgh trial), whereas the four Swedish RCTs were designed to evaluate the value of mammography alone (Table 2.1).

Table 2.1 The randomized controlled trials of breast cancer screening

Trial	Start (year)	Age (years)	Intervention	Population		RR	RR (95% CI)
				Study	Control		
HIP[a]	1963	40–64	M+CE	31,000	31,000	0.78	0.61–1.00
Malmo[b]	1976	45–69	M	20,695	20,783	0.81	0.62–1.07
Two county[c]	1977	40–74	M	77,080	55,985	0.68	0.59–0.80
Edinburgh	1978	45–64	M+CE	28,628	26,026	0.78	0.62–1.02
Canadian[d]	1980	40–59	M+CE	44,925	44,910	1.02	0.84–2.21
Stockholm	1981	40–64	M	38,525	20,651	0.90	0.53–1.22
Gothenburg	1982	39–59	M	20,724	28,809	0.78	0.54–1.37

M mammography, *CE* clinical breast examination, *RR* relative risk
[a] *HIP* Health Insurance Plan of Greater New York, USA
[b] Malmo mammographic screening trial (MMST) I and II
[c] Two-County (WE) trial: Ostergotland and Kopparberg
[d] Canadian National Breast Screening Study (CNBSS) 1 (40–49 years) and 2 (50–59 years)

The first of the seven RCTs was the HIP trial in Greater New York in the 1960s (Shapiro et al. 1971, 1982). This study was followed by three RCTs in the 1970s: the Swedish Malmo Mammographic Screening Trial (MMST) in 1976 (Andersson et al. 1988), the Swedish Two County trial (actually including two different trials, the Kopparberg trial and the Ostergotland trial) in 1977 (Tabar et al. 1985), and the Edinburgh trial in 1978 (Roberts et al. 1990). These were followed in the 1980s by the CNBSS trial (Miller et al. 1992a, b), the Stockholm trial in 1981 (Frisell et al. 1991), and the Gothenburg trial in 1982 (Bjurstam et al. 2003). The CNBSS included the CNBSS 1 (age group 40–49 years) (Miller et al. 1992a) and the CNBSS 2 (age group 50–59 years) (Miller et al. 1992b). The MMST also consisted of two studies, the MMST I and the MMST II.

The RCTs have given rise to rather conflicting results, which may explain the still ongoing debate regarding the efficacy of mammographic screening. However, it should be of no surprise that the results are conflicting, in view of the very different designs of these trials. A number of expert consensus conferences and meta-analyses have been conducted in efforts to draw overall conclusions from the RCTs. One international expert group concluded from the results of the RCTs that the breast cancer mortality rate for the age group 50–69 years was reduced by 25% by screening mammography alone (IARC 2002). The long-term follow-up of Swedish RCTs confirmed a significant mortality reduction in consequence of mammographic screening (Nystrom et al. 2002; Tabar et al. 2003).

2.4   Organized Mammographic Service Screening

The success of the Swedish RCTs stimulated the introduction of organized service screening mammography in many European countries. Unlike the RCTs, which were performed primarily as clinical research studies, service screening is a public health initiative.

The Swedish counties successively implemented mammographic screening, but it was not until 1997 that mammographic screening was carried out nationwide, when the last county (Gotland) started its programme. Sweden does not have a centralized programme, as the target age groups and the screening intervals vary from county to county. The screening programme in England started in 1988 for the age group 50–64 years, with the use of single-view mammography and a screening interval of 3 years, but the programme was modified by 2005 to cover the age group 50–70 years and the use of two-view mammography. The Netherlands began mammographic screening in 1989 for the age group 50–69 years, with a screening interval of 2 years, but extended the programme to the age group 50–75 years by 1998. The Icelandic breast cancer screening programme was nationwide in 1989. Spain has a decentralized screening programme with different target groups in the individual regions, similarly as in Sweden. Norway started a national mammographic screening programme in 1995, but it was not until 2004 that it became nationwide. The largest population-based mammographic screening programme in Europe is

that in Germany, which extends to 10.4 million women in the target group aged 50–69 years. It is a centralized nationwide programme similarly to that in Norway. Most European countries have started or are planning to implement mammographic screening programmes.

The benefit in mortality reduction for women attending mammographic service screening has been estimated to be 35–40% (IARC 2002; Olsen et al. 2005; Gabe et al. 2007). Regular mammographic screening has even been shown to achieve a 63% reduction in mortality from breast cancer among the participating women in two Swedish counties (Tabar et al. 2001). A collaborative evaluation of the impact of organized mammographic service screening in seven Swedish counties revealed a 40–45% reduction in breast cancer mortality among the women screened (Duffy et al. 2002).

In light of the success of the RCTs and the evaluations of service screening programmes, the European Parliamentary Group on Breast Cancer (EPGBC) agreed on certain resolutions: 'The resolutions call for every woman in Europe to have access to the same first-class early detection, diagnosis, treatment, and aftercare, irrespective of where she lives, her social status, and her level of education. Women between the ages of 50 and 69 must have the right to attend high-quality mammographic screening at two-year intervals in dedicated and certified centres paid for by health insurance schemes'. The best way to guarantee the success of organized service screening programmes is to implement ongoing quality assurance and to achieve performance indicators according to the European Guidelines (Perry et al. 2006).

2.5   Mammographic Diagnosis of Early-Stage Breast Cancer

Breast cancer is believed to evolve from an intraductal preinvasive precursor, DCIS. Little is known as to how long DCIS needs to develop into invasive cancer, whether low-grade DCIS mainly evolves into low-grade invasive cancer or whether the high-grade precursor develops into high-grade invasive cancer. Some *in situ* cancers obviously do not develop into invasive cancers at all. In general, however, we do know from earlier studies that breast cancer is a progressive disease and that survival depends considerably on the stage at diagnosis, including the tumour size and the axillary lymph node status, and on the treatment (Tabar et al. 2004).

The RCTs and the evaluation of organized service screening programmes have demonstrated a significant decrease in breast cancer mortality rate as a result of early diagnosis. To achieve this mortality reduction, the goal of mammographic screening should be to detect preclinical DCIS and invasive cancers measuring less than 15 mm in diameter which are lymph node-negative. The important performance indicators of the European Guidelines prescribe that, for subsequent regular screening examinations, the proportion of invasive screen-detected cancers less than 15 mm in size should be at least 50% and the proportion of screen-detected invasive cancers less than 10 mm should be at least 30% (Perry et al. 2006).

2.5.1 Ductal Carcinoma In Situ (DCIS)

DCIS has been variously subgrouped in the past, but basically all classifications divide the lesions into low-grade and high-grade DCIS. The most commonly used classification today is the Van Nuys grading 1–3. Van Nuys grade 1 is a non-high nuclear grade without comedo-type necrosis; grade 2 is a non-high nuclear grade with comedo-type necrosis; and Van Nuys grade 3 is a high nuclear grade with or without comedo-type necrosis (Silverstein et al. 1996). The great challenge for the radiologist when detecting calcifications without an associated mass in mammographic screening is to make a suggestion concerning the grading of the DCIS and to carefully analyse the mammograms, including microfocus magnification images, in order to evaluate the extent of the cancer. Predicting the extent of DCIS may be extremely difficult and often impossible, especially if the DCIS presents not as a small cluster, but rather with a segmental distribution. Additionally, it must be borne in mind that areas of DCIS may not present with calcifications at all. Establishment of the grading and extent is important in order for the surgeon to achieve tumour-free margins for breast-conserving treatment. The combination of the data on the grading, the extent, and the margins (the Van Nuys prognostic index) may serve as a guideline for treatment, allowing a scientifically based discussion for shared decision-making (Silverstein et al. 1996).

On mammography, DCIS usually presents as microcalcifications. The mammographic findings on DCIS may reflect the breast anatomy and its pathological changes, and therefore the mammographic features may often correlate with the histology when microcalcifications are demonstrated. Thus, the mammographic findings may often indicate the grading of a DCIS.

Fine amorphous ('powdery') microcalcifications are often found in low-grade (grade 1) DCIS (Tabar et al. 2008), within the terminal ductal lobular units (TDLUs). Occasionally, these calcifications in low-grade DCIS are manifested as 'cotton ball-like calcifications', presenting as multiple clusters (Tabar et al. 2008). Powdery microcalcifications may be seen in a variety of benign conditions besides low-grade DCIS.

'Crushed stone-like calcifications' are the most frequent malignant calcifications observed in mammographic screening (Tabar et al. 2008). Similarly as for the 'powdery cotton ball-like calcifications' (Fig. 2.1), the origin of these pleomorphic or heterogeneous calcifications is the TDLUs. The TDLUs are also the origin of several benign pathological processes, and even a thorough analysis of the pleomorphic calcifications may not permit a differentiation between a benign and a malignant process. The differential diagnosis of these calcifications is a challenge since the more common fibrocystic changes and fibroadenomas also originate in the TDLUs and may present with clusters of similar calcifications (Tabar et al. 2008). Furthermore, pleomorphic or heterogeneous calcifications are to be seen not only in intermediate (grade 2) DCIS, but also in early-stage grade 3 DCIS.

The casting (or linear branching) type calcifications are typically observed in high-grade (grade 3) DCIS. In mammographic screening it is important to diagnose cancers manifesting as casting-type calcifications at an early stage, since these cancers have a much poorer prognosis than cancer of comparable size that is without such calcifications (Tabar et al. 2004). There are two mammographic presentations

Fig. 2.1 Mammographic screening. Microfocus magnification view of the left breast. A cluster of 'powdery' calcifications was detected in this 60-year-old woman (*arrow*). Histology revealed a 15 mm DCIS of grade 2. These fine microcalcifications would most likely have been missed in dense breast parenchyma
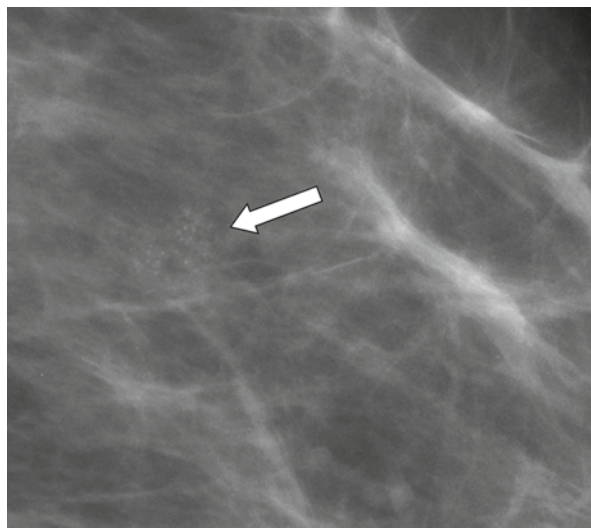

of casting-type calcifications: the fragmented casting type and the dotted casting type (Tabar et al. 2007). High-grade (grade 3) DCIS may exhibit extensive intraluminal necrosis and calcifications which manifest on mammography as fragmented branching calcifications, initially often with an irregular contour. As the debris becomes more extensively calcified, the calcifications seen on mammography attain a smoother outline and a more homogeneous density (Tabar et al. 2007). The dotted casting-type calcifications are usually seen in the micropapillary growth pattern of DCIS.

DCIS often presents with 'typical' microcalcifications in the more advanced cases. Unfortunately, in the very early stage, when the DCIS is confined to a small area, the calcifications are frequently rather non-specific and differentiation from benign microcalcifications may be difficult or impossible (Fig. 2.2). Thus, size is a major determinant of the mammographic features of DCIS, as shown in a large study from the UK breast cancer screening programme (the Sloane project), when 'only' 50% of the cases of high-grade DCIS measuring less than 10 mm presented with casting-type calcifications (Evans et al. 2010). Misinterpretation of calcifications in early-stage high-grade DCIS as benign may result in advanced interval cancer or next screening round cancer (Fig. 2.2).

High-grade DCIS may occasionally present as a localized or asymmetric density without calcifications. Such non-specific densities pose a diagnostic challenge since the additional mammographic views and ultrasonographic images may also be 'normal'.

The diagnostic work-up of microcalcifications in general includes microfocus magnification views. In cases with typical casting-type calcifications, magnification views are often unnecessary for the diagnosis itself. For an exact characterization of smaller calcifications, however, magnification views are mandatory for the further analysis, and even the use of digital mammographic electronic zooming will not always be sufficient for appropriate analysis. Fine 'powdery' microcalcifications may
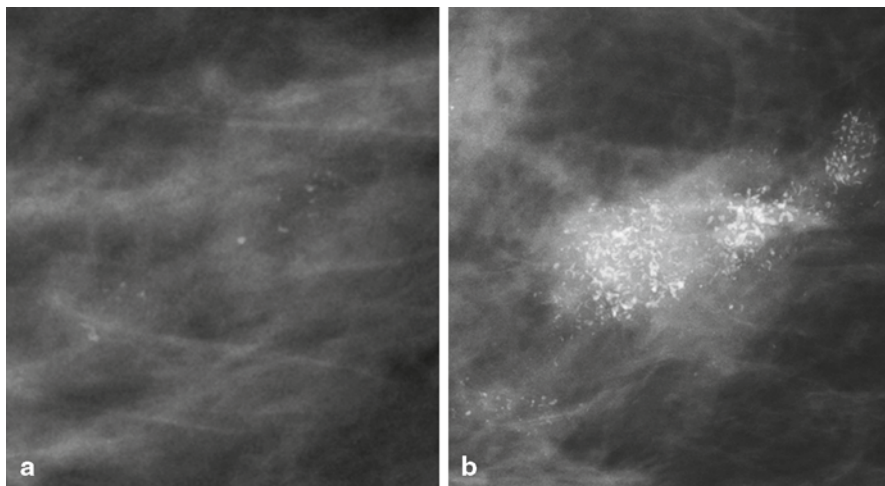
Fig. 2.2 Mammographic screening. **a** Mammography, magnification view, 13.06.2007. The calcifications in the right breast were misinterpreted as benign by both radiologists at double reading. **b** Mammography, magnification view, 18.05.2009. Extensive calcifications of casting-type and associated density. Histology revealed DCIS of grade 3 (extent 50 mm) with multiple foci of microinvasive ductal cancer measuring less than 1 mm

even be difficult to identify in microfocus magnification views from women with very dense breast parenchyma. Ultrasonography as an adjunct to mammography is usually recommended in most cases of suspicious calcifications. Ultrasonography may demonstrate a mass associated with the calcifications, thereby indicating that an invasive component is present rather than a pure DCIS. Furthermore, if the cluster of calcifications can be identified on ultrasonography (Fig. 2.3), the subsequent
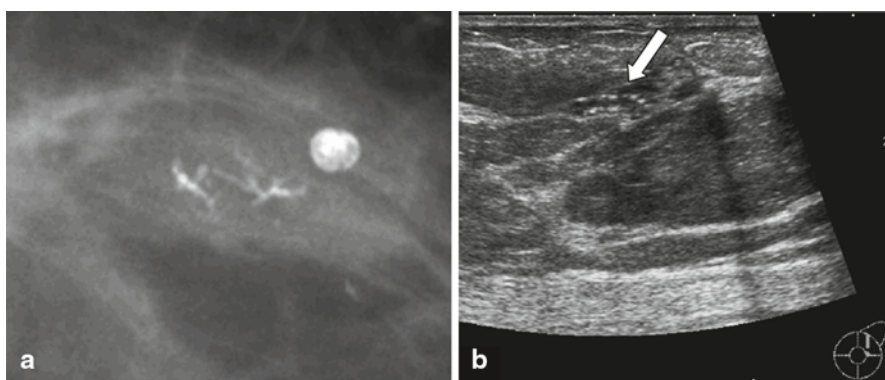
Fig. 2.3 Mammographic screening. **a** Microfocus magnification view of the upper-outer quadrant of the left breast reveals a small cluster of typical casting-type calcifications. **b** Targeted ultrasonography shows the calcifications as small punctate white spots (*arrow*). Ultrasound-guided needle biopsy confirmed DCIS of grade 3

needle biopsy can be performed under ultrasonographic guidance which is faster and more convenient for the patients than stereotactic biopsy.

2.5.2   Early Invasive Breast Cancer

In consequence of the possibility of considerable overlap, the mammographic findings in cases of invasive breast cancer rarely suggest a specific type of invasive cancer, and a specific diagnosis requires histologic examination. The mammographic findings in invasive breast cancer are often divided into primary, secondary and 'indirect' signs. The secondary signs include skin thickening and skin and nipple retraction, and axillary lymph node metastases are usually associated with advanced breast cancer.

Most invasive cancers present with primary signs, including microcalcifications or a mass. The BI-RADS lexicon should be utilized for further characterization when these primary signs of cancer are detected.

Breast cancers manifesting with 'indirect' signs are a serious challenge in mammographic screening. The indirect mammographic signs include developing density, asymmetric density, architectural distortion, and (rarely) a single dilated duct. Unless a previous biopsy or excision has been carried out and distortion has consequently been explained by scar tissue resulting from the previous biopsy, distortion always requires a careful assessment and histological biopsy. It is not possible by means of mammography to differentiate a benign radial scar from an early cancer. An asymptomatic asymmetric density without suspicious mammographic features is in general regarded as a normal variation of the distribution of fibroglandular tissue. When combined with suspicious mammographic features, including microcalcifications or distortion, however, an asymmetric density is highly suggestive of malignancy and requires biopsy.

The detection of early, subtle mammographic findings that may be indicative of malignancy requires an optimum reading environment and a systematic search for abnormalities (Fig. 2.4). For full-field digital mammography (FFDM) with soft-copy reading, an optimum hanging protocol is important. This systematic search for subtle findings in an optimum reading environment and with the use of optimum hanging protocols in soft-copy reading is of especial importance when batch reading is performed. The findings in current screening examinations should always be compared with earlier mammographic images, if available, and even comparison with older priors may occasionally be helpful. The BI-RADS lexicon does not include 'stability descriptors', but the demonstration of slowly increasing masses and asymmetric densities may be the first and very important sign of malignancy.

Batch reading is the common procedure for the interpretation of mammographic examinations in population-based screening programmes. Motorized alternators provide optimum viewing conditions for batch reading using screen-film mammography (SFM). Hand-held viewers with slight magnification are helpful for the detection of small abnormalities, and especially fine amorphous microcalcifications. Following
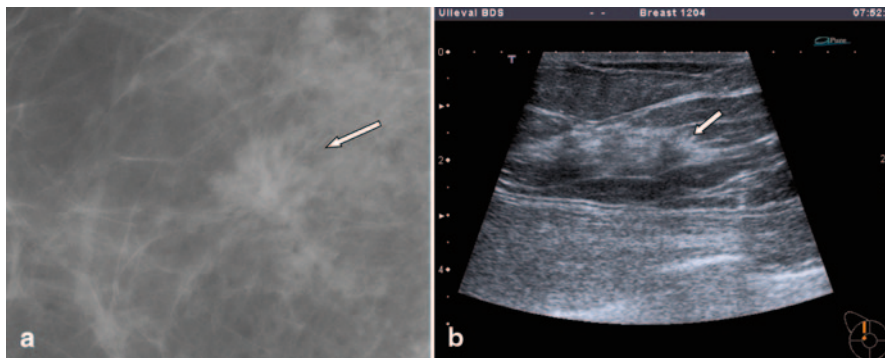
Fig. 2.4 Mammographic screening. A 50-year-old asymptomatic woman with fatty breasts. **a** Microfocus magnification view shows an ill-defined low-density mass with some fine spiculations (*arrow*). Discordant interpretation at double reading. This low-density mass would easily have been missed in dense breast parenchyma. **b** Targeted ultrasonography confirms a small irregular hypoechoic tumour surrounded by an echogenic 'halo' (*arrow*). Histology revealed an invasive ductal carcinoma with a diameter of 9 mm
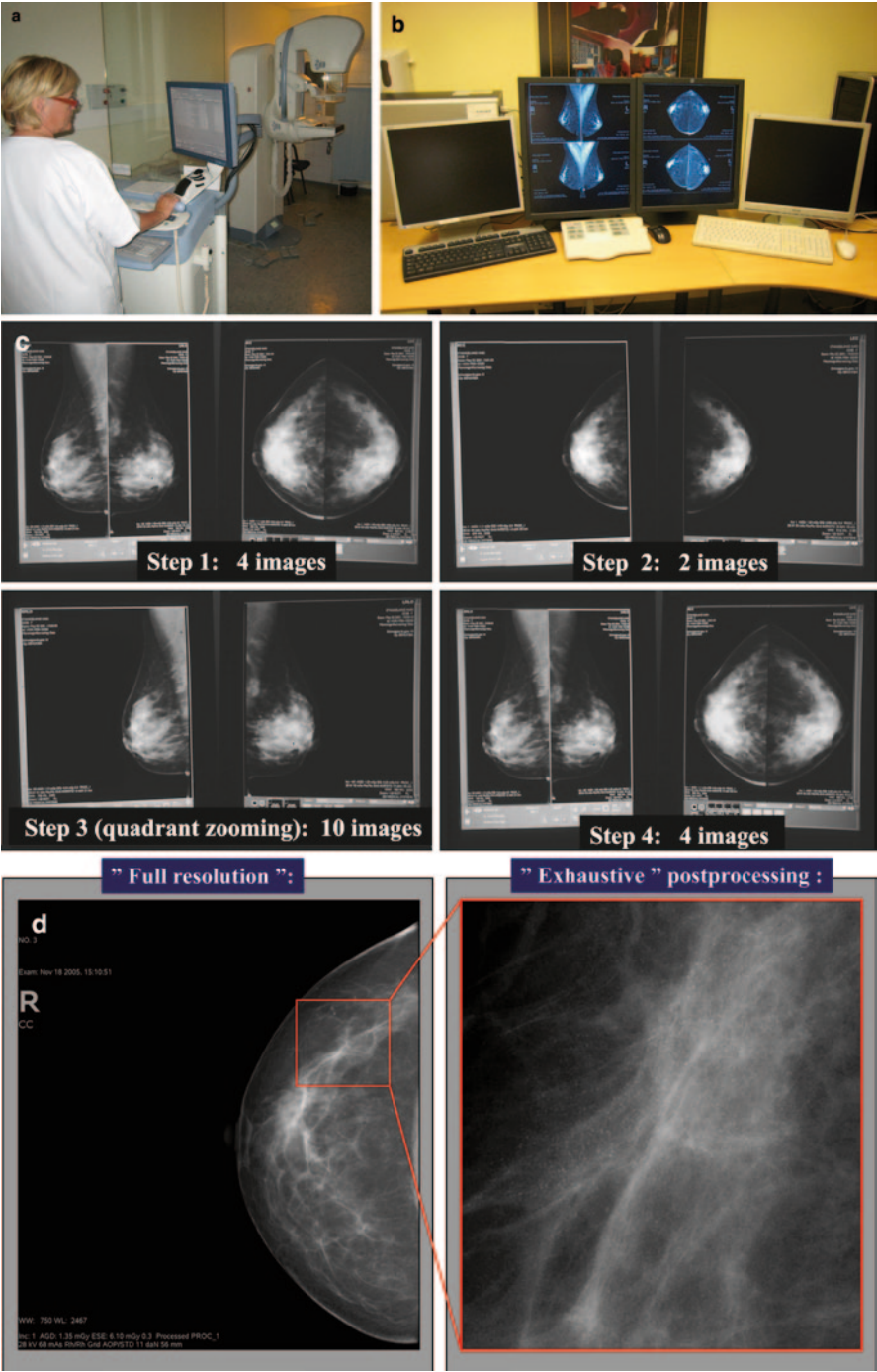
the introduction of digital mammography with soft-copy interpretation, batch reading has become a great challenge. Systematic 'quadrant zooming' is often included in the hanging protocol in order to avoid the use of an electronic 'magnifying glass' (Fig. 2.5a–d). For digital soft-copy reading, it is important to use the simple hanging protocols systematically, as otherwise subtle abnormalities may easily be missed.

2.6   Digital Mammography in Breast Cancer Screening

FFDM offers several potential benefits in organized mammographic screening: the elimination of 'technical failure' recalls; a reduction of the glandular dose in the range 15–35%; a higher work-flow; the simplified archival, retrieval, and transmission of images; the simpler implementation of CAD; and the potential for telemammography, teleconsultations, and screening programme reorganizations.

   A decade ago, there was great concern about the diagnostic performance of FFDM regarding the lower spatial resolution and the use of soft-copy reading. How-

Fig. 2.5 a Digital mammographic equipment. The screen at the acquisition station enables the radiographer to perform an immediate check on the positioning of the woman. Full-field digital mammography eliminates recalls due to technical failure or poor positioning. **b** Work-station for full-field digital mammography with two high-resolution monitors. The screen on the left provides the patient list, while the screen on the right serves for on-line reporting. **c** Hanging protocol for digital soft-copy reading. The systematic use of the protocol assists the work of the radiologist in the darkened room. During batch reading, radiologists read 60–80 examinations (each including four standard images) per hour. **d** Soft-copy reading provides post-processing with electronic zooming for a more detailed analysis of microcalcifications that may prevent unnecessary recalls

Step 1:   4 images

Step 2:   2 images

Step 3 (quadrant zooming):   10 images

Step 4:   4 images

" Full resolution ":

" Exhaustive " postprocessing :

ever, FFDM has been shown to be equivalent or superior to SFM in the diagnosis of microcalcifications (Fischer et al. 2002; Skaane et al. 2005). It should be kept in mind that the true flexibility and benefit of digital technology are realized primarily in a soft-copy display of the images and consequently in soft-copy reading.

The studies to date in which the techniques of SFM and FFDM in breast cancer screening were compared (Lewin et al. 2001; Skaane et al. 2003; Skaane and Skjennald 2004; Pisano et al. 2005; Heddson et al. 2007; Del Turco et al. 2007; Vigeland et al. 2008; Vinnicombe et al. 2009; Sala et al. 2009; Karssemeijer et al. 2009; Hambly et al. 2009; Lipasti et al. 2010; Juel et al. 2010) have yielded divergent and rather conflicting results (Table 2.2). A lower cancer detection rate with FFDM was reported only in the first two published 'pioneering' studies; all subsequent studies have indicated a higher cancer detection rate with FFDM (Table 2.2), but this has mostly been associated with a higher recall rate. The positive predictive value based

Table 2.2 Studies comparing screen-film mammography (SFM) and full-field digital mammography (FFDM) in breast cancer screening: Year of publication, number of examinations, recall rate, cancer detection rate (including invasive cancers and DCIS), and positive predictive value PPV_1 (percentage of cancer among women recalled for diagnostic work-up)

Study	Publ. (year)	Examinations (n)		Recall rate (%)		Ca. detection rate (%)		PPV_1 (%)	
		SFM	FFDM	SFM	FFDM	SFM	FFDM	SFM	FFDM
Co-Ma[a]	2001	6,736	6,736	14.9 * 11.8		0.49	0.40	3.3	3.4
Oslo I[b]	2003	3,683	3,683	3.5 * 4.6		0.71	0.54	20.2	11.8
Oslo II[c]	2004	16,985	6,944	2.5 * 4.2		0.38 * 0.59		15.1	13.9
DMIST[d]	2005	42,555	42,555	8.6	8.6	0.41	0.44	4.7	5.1
Helsingborg[e]	2007	25,901	9,841	1.4 * 1.0		0.31 * 0.49		21.8 * 47.1	
Florence[f]	2007	14,385	14,385	3.5 * 4.3		0.58	0.72	14.7	15.9
Vestfold County[g]	2008	324,763	18,239	4.2	4.1	0.65	0.77	15.1 * 18.5	
CELBSS[h]	2009	31,720	8,478	4.4	4.8	0.65	0.68	14.6	14.3
Barcelona[i]	2009	12,958	6,074	5.5 * 4.2		0.42	0.41	7.5 * 9.7	
DSPP[j]	2009	311,082	56,518	1.3 * 2.2		0.52	0.56	39.5 * 25.6	
INBSP[k]	2009	153,619	35,204	3.1 * 4.0		0.52 * 0.63		16.7	15.7
Helsinki[l]	2010	27,593	23,440	1.6	1.7	0.41 * 0.62		25.6 * 36.4	
Sogn & Fjordane[m]	2010	7,442	6,932	2.3	2.4	0.39	0.48	16.7	19.6

* Difference statistically significant (p<0.05)
[a] Prospective study (Colorado-Massachusetts trial): Paired study design
[b] Prospective study (Norway): Paired study design
[c] Prospective study (Norway): Randomized trial
[d] Prospective study (Digital Mammographic Imaging Screening Trial): Paired design
[e] Retrospective study (Sweden): Allocation by time
[f] Retrospective study (Italy): Concurrent cohorts
[g] Retrospective study (Norway): SFM historic control from 18 counties
[h] Retrospective study (Central East London Breast Screening Service): Allocation by area
[i] Retrospective study (Spain): Allocation by time
[j] Retrospective study (Digital Screening Project Preventicon): Random allocation
[k] Retrospective study (Irish National Breast Screening Program): Random allocation
[l] Retrospective study (Southern Finland): Allocation by time (CR technology)
[m] Retrospective study (Norway): Allocation by time

Table 2.3 Ductal carcinoma *in situ* (DCIS) in studies comparing screen-film mammography (SFM) and full-field digital mammography (FFDM): number of examinations, age group of study population, DCIS detection rate, proportion of DCIS among total number of cancers at FFDM, and significance (p value) of DCIS detection between the two imaging techniques. Studies with no specification of DCIS or a small number of DCIS are not included

Study	Examinations (n)		Age group (years)	DCIS rate (%)		Proportion of DCIS at FFDM (%)	p value SFM vs. FFDM
	SFM	FFDM		SFM	FFDM		
Oslo II	16,985	6,944	45–69	0.12	0.16	*26.8*	p=0.551
DMIST[a]	42,760	42,760	47–62	0.12	0.14	*33.2*	p=0.393
Florence[b]	14,385	14,385	50–69	0.12	0.26	*27.9*	p=0.007
Vestfold[c]	324,763	18,239	50–69	0.11	0.21	*27.1*	p < 0.001
DSPP[d]	311,082	56,518	50–75	0.08	0.13	*23.3*	p < 0.001
INBSP	153,619	35,204	50–64	0.09	0.13	*20.8*	p=0.072

[a] Cancers diagnosed within 455 days after imaging
[b] Numbers given for cancers presenting as clustered microcalcifications
[c] Prevalent screening rounds; SFM is mean value of merged data from 18 counties
[d] CAD used for FFDM only

on recalls was found to be significantly higher for FFDM in only 5 of the 13 studies (Skaane 2009). An important finding from these comparative studies has been the high rate of detection of DCIS with FFDM. This confirms the conclusion from phantom and experimental clinical studies that FFDM is superior to SFM for the detection of microcalcifications (Table 2.3).

2.7 Screening of Women at High Risk, Including Those with Dense Breast Parenchyma

Breast cancer incidence is lower for women in their thirties than among women aged 40–49 years, and mammographic screening has not been advised for women below the age of 40. Screening for women in their thirties should be carried out only if they are at very high risk of the development of breast cancer. Women at extremely high risk include those with hereditary gene mutations BRCA1 and BRCA2, who have been recommended to undergo screening at a 5- to 10-year younger age than that at which a first-degree relative initially presented with breast cancer. Major US medical organizations recommend screening every 1–2 years, beginning at the age of 40. These women, as well as many women in older age groups attending a screening programme, often have dense breast parenchyma (BI-RADS density 3 or 4).

Although mammography is a widely accepted modality for breast cancer screening, its limitations in women with dense breast parenchyma are well known. Screening studies on women at high risk, including mammography, ultrasonography and MRI, have demonstrated that mammography has much lower sensitivity than that of MRI. Two such studies reported a sensitivity of only 33% for mammography,

as compared with 80–91% for MRI (Kriege et al. 2004; Kuhl et al. 2005). Furthermore, it is well known that ultrasonography as an adjunct to mammography may reveal many cancers missed on mammography in women with dense breast parenchyma. The low sensitivity of mammography in women with dense breast parenchyma has raised the question in several countries of whether other screening modalities should be offered to women at high risk, either as an adjunct or as an alternative to mammography. Attention has mainly focused on MRI and ultrasonography.

2.7.1 MRI Screening

MRI has very high sensitivity for invasive breast cancer, and the high sensitivity does not depend on the density of the breast parenchyma. Together with the lack of radiation, this imaging modality has been recommended in several countries for the screening of women at high risk. A problem has been the low specificity of MRI. For many years, MRI was suggested to have low sensitivity for DCIS, but a recent report concluded that MRI may be comparable or even superior to mammography for the detection of DCIS (Kuhl et al. 2007).

In our institution, we still add one MLO view of each breast to the MRI in the screening of women with BRCA1 and BRCA2 mutations since we believe that MRI does not have a high sensitivity for all forms of DCIS, and will probably miss several, especially low-grade DCIS lesions. Ultrasonography as a screening modality is not necessary when MRI is used. When a tumour is detected on MRI screening, 'post-MRI second-look ultrasonography' should be carried out and, in the event of a positive ultrasonographic result, the biopsy can be performed under ultrasonographic guidance (Fig. 2.6). If ultrasonographic identification does not succeed, an MRI-guided vacuum-assisted biopsy should be carried out on suspicious lesions.

In some Western European countries and in North America, MRI is increasingly offered to women at very high risk of developing breast cancers. The studies so far
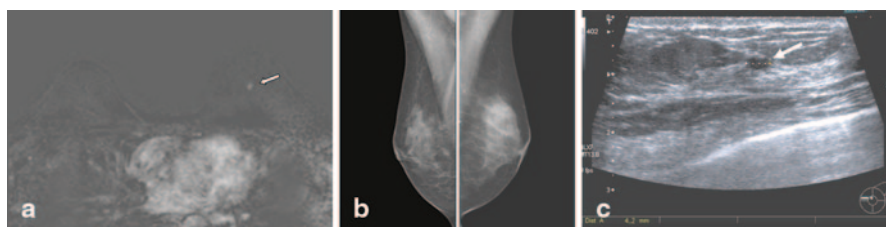
Fig. 2.6 A high-risk woman with hereditary BRCA1 gene mutation. **a** MRI screening. A small tumour is shown in the left breast (*arrow*). **b** Screening mammography (same day as MRI; single MLO view only) shows dense breast parenchyma. Normal mammographic findings in both breasts. **c** 'Post-MRI second-look ultrasonography' shows a small hypoechoic tumour with irregular contour ('microlobulated') suspicious for cancer. Largest diameter on ultrasonography 4.2 mm. Histology revealed a 5 mm invasive ductal carcinoma

have clearly demonstrated the superior sensitivity of MRI for the detection of small breast cancers in these women (Kriege et al. 2004; Kuhl et al. 2005). However, no MRI studies on the screening of high-risk women have so far have used mortality as end-point. Prospective studies should be encouraged to document whether the increased detection of small preclinical cancers in these high-risk women is of benefit since many of the women with hereditary gene mutations BRCA1 and BRCA2 will suffer not only from breast cancer, but also from ovarian cancer. The clinical use of MRI is discussed in more detail in another chapter of this book.

2.7.2   Ultrasonographic Screening

Ultrasonography has for a long time been an important adjunct to mammography in women with dense breast parenchyma, both in those with clinical symptoms (a palpable lump) and indeterminate or negative mammographic finding, and also in asymptomatic women. Most breast tumours manifest on ultrasonography as hypoechoic ('dark') tumours, which are easily depicted in the echogenic ('white') tissue of women with mammographically dense breasts. The specificity of ultrasonography is rather low, as the differentiation of a benign from a malignant tumour is often difficult or even impossible.

Screening by a physician with a hand-held ultrasonographic device may increase the cancer detection yield. Studies have shown that the rate of cancer detection in women with mammography-negative dense breasts may increase significantly if high-resolution ultrasonography is used (Buchberger et al. 2000; Kolb et al. 2002; Corsetti et al. 2008). However, ultrasonography has several disadvantages as a screening tool: First, bilateral whole breast screening with a hand-held transducer is very time-consuming: a mean examination time of 19 minutes was reported in a large multicentre study (Berg et al. 2008). Second, interobserver variability is a well-known challenge in ultrasonography. Third, due to the low specificity, a large number of false-positive findings are reported in ultrasonographic screening, and such low positive predictive values may be unacceptable for a population-based screening programme. Fourth, the reproducibility of abnormal findings on hand-held ultrasonography is limited in many cases and follow-up may be a problem.

Automated whole breast volume ultrasonographic scanning (ABVS) systems now commercially available may offer important advances for screening as compared with hand-held equipment: the examination can be carried out by trained technologists; the images are standardized and reproducible, and follow-up is therefore easier; the images can be interpreted in batch reading; and the interpretation time seems to be shorter for radiologists than with hand-held devices. This means the more efficient use of time by the radiologists interpreting the examinations; and the standardized images could make double reading in batch mode possible, as for screening mammography, and it would be possible to interpret the two imaging modalities combined.
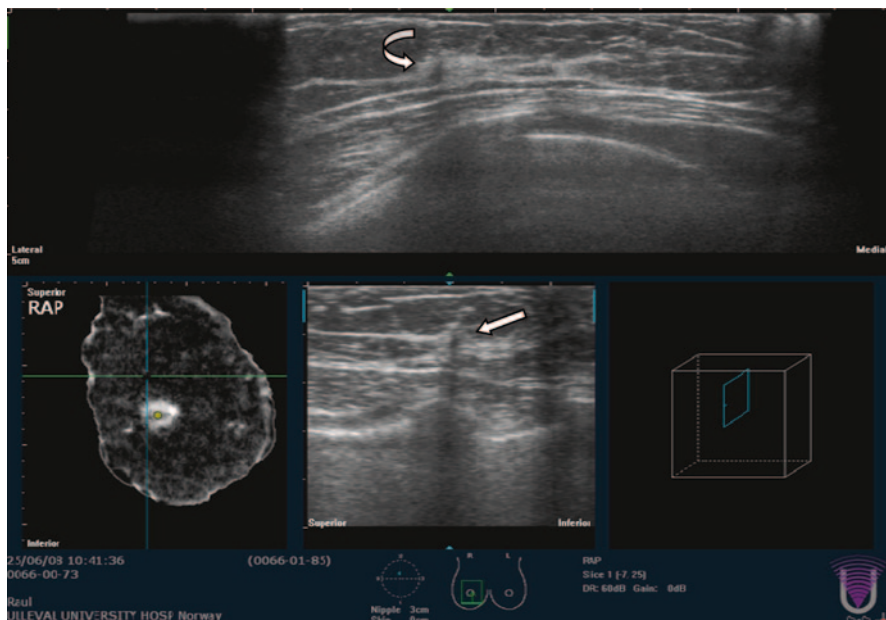
Fig. 2.7 Automated breast volume scanning (ABVS). A high-risk woman attending for screening. ABVS shows a small malignant tumour in the upper-outer quadrant of the right breast. *Top*: transverse plane (*curved arrow*). *Bottom*: reconstructed sagittal plane (*arrow*). Histology revealed a 4 mm invasive ductal carcinoma

Few studies have been carried out so far with automated whole breast ultrasonographic scanning in women with dense breast parenchyma. One study reported good agreement, with high kappa values, between hand-held ultrasonographic equipment and ABVS as regards the BI-RADS classification, and all cancers included in this small study were found with the ABVS (Wenkel et al. 2008). In a larger prospective study, the number of breast cancers detected was double when ABVS plus mammography was used as compared with mammography alone in women with dense breast (BI-RADS 3 and 4) parenchyma (Kelly et al. 2010). The additional detection of small invasive cancers may be of importance when this new technology is considered for screening (Fig. 2.7). However, prospective trials are needed before ultrasonography can be implemented in screening programmes (Kopans 2004).

2.8   Advanced Digital Applications for Screening

Digital mammography offers several potential benefits in mammography screening as mentioned above, but two important inherent limitations of mammography still remain despite the introduction of digital technology. First, the low accuracy due to perception and interpretation errors in women with dense breast parenchyma. The

obscuring effect of overlying and underlying dense tissue remains a huge problem, even for digital mammography with its higher contrast resolution. Second, the non-specific features of small early-stage breast cancers ('minimal sign lesions'), which are either easily missed (overlooked) or misinterpreted in the reading session. Interobserver variability is a huge challenge as concerns minimal sign lesions.

Two digital techniques have been introduced to help overcome these limitations of mammography: CAD and digital breast tomosynthesis (DBT).

2.8.1 Computer-Aided Detection (CAD)

The success of screening mammography depends on the detection of small and subtle lesions. Mammographic film reading is a demanding task, and the perception of these small features is a great challenge. Radiologists differ substantially in their interpretation of screening mammography. CAD is designed to help radiologists increase the cancer detection rate by reducing the number of false-negatives (missed cancers), and to decrease the interobserver variability, which is a serious problem in mammographic screening. Perception errors may pose great difficulty in digital soft-copy reading in batch mode, when a large number of images are interpreted in a darkened room.

Studies on screening mammography have shown that CAD may increase the cancer detection rate significantly, and that a single reader with CAD input has a cancer detection rate comparable to that of double reading (Freer and Ulissey 2001; Gilbert et al. 2008). Single reading is standard practice in the United States and CAD has been widely adopted to improve reader performance. In the European population-based mammographic screening programmes, double reading is recommended in the European guidelines. Moreover, there is no reimbursement for the use of CAD in European countries. For these reasons, CAD has generally not been implemented in the European screening programmes. However, even in screening programmes involving the use of double reading, cancers can be missed by both readers, but correctly marked by CAD (Skaane et al. 2007). CAD undoubtedly has the potential to help radiologists increase the cancer detection rate by reducing the number of missed cancers (Fig. 2.8). A strong reason why CAD has not been implemented in mammographic screening so far is the fear of a higher number of false-positive recalls (Fig. 2.8). Prospective studies are encouraged in order to evaluate the impact of CAD in organized mammographic screening programmes.

2.8.2 Tomosynthesis

Advances in digital mammography have led to the development of DBT. This technique provides thin tomographic images of the breast and may reduce the obscuring effect of overlying and underlying tissue. DBT may have a potential in mammo-
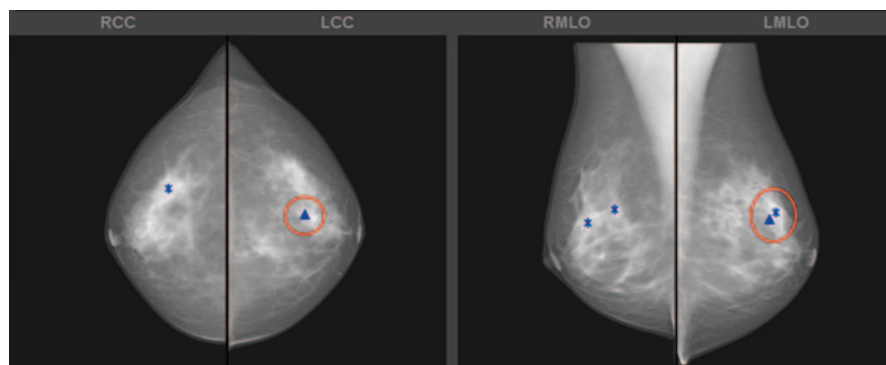
Fig. 2.8 Full-field digital mammographic screening. Both independent readers missed the suspicious lesion in the left breast. Retrospective stand-alone CAD analysis of the screening examination shows true positive CAD marks (the *triangle* indicates calcifications and the *asterisk* indicates a suspicious density) in the left breast (*circles*). The woman presented with screening-detected cancer (invasive ductal carcinoma and DCIS of grade 3) in the next screening round 2 years later. Note the false-positive CAD marks in the right breast

graphic screening, either in a combined mode (FFDM plus DBT) or by replacing the conventional 2D images.

Most of the relatively few studies published on DBT so far have been carried out in an experimental clinical setting. The preliminary results have demonstrated that DBT has the potential to increase both the sensitivity and the specificity in mammographic screening (Andersson et al. 2008; Good et al. 2008; Gur et al. 2009). The early experience indicates that DBT may be of especial importance for the detection of small spiculated masses and distortions. Microcalcifications are well revealed. Prospective studies in a screening setting are needed to establish whether this new technology has the potential to increase the sensitivity and/or the specificity in breast cancer screening, and whether DBT should be used in a combined mode or replace (in one or two views) conventional 2D mammograms.

2.9 Adverse Effects of Breast Cancer Screening

The adverse effects of mammographic screening include the examination itself (the discomfort caused by the compression and the radiation dose), false-positive interpretations with unnecessary recalls and assessments, false-negative interpretation and cancers manifesting as interval cancers or next round cancers, overdiagnosis ('overdetection') and overtreatment. The most important of these adverse effects and a hot topic for several years is overdiagnosis (and consequently overtreatment). Overdiagnosis is defined as the diagnosis of a breast cancer that would not have presented clinically within the lifetime of the patient if she had not attended the screening program. Overdiagnosis is one of the downsides of a screening programme,

and applies both to low-grade DCIS and perhaps to some small grade 1 invasive cancers.

Overdiagnosis is likely to be driven by the radiologist's fear of missing a cancer and the potential litigation, but also by new technological developments, including digital mammography, CAD, improved biopsy techniques (vacuum-assisted biopsy) and MRI (Warren and Eleti 2006). Comparative studies of SFM and FFDM in breast cancer screening have revealed a significantly higher detection rate for DCIS in programmes where FFDM is used (Table 2.3).

Quantifying the problem of overdiagnosis is a great challenge, and widely differing estimates have appeared in the literature. It has been estimated that 4% of the cases of diagnosed DCIS at incidence screening are non-progressive and that a woman attending an incidence screening round has a 166 times higher probability of having a progressive DCIS or invasive cancer diagnosed than of having a non-progressive DCIS detected (Yen et al. 2003). A recently published study concluded that between 2 and 2.5 lives are saved for every overdiagnosed case, and consequently the benefit of mammographic screening in terms of lives saved is greater in absolute terms than the harm in terms of overdiagnosis (Duffy et al. 2010). Nevertheless, when new advanced technologies are incorporated in breast cancer screening programmes, it is important to be aware that radiologists are faced with the challenge of 'increasingly detecting and performing percutaneous biopsies on borderline, preinvasive, or low-grade cancers that were heretofore rarely identified and that may never progress to meaningful disease' (Hall 2010).

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