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Do non-specific minimal signs in a biennial mammographic breast cancer screening programme need further diagnostic assessment?

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Abstract. Mammographic features such as small vague densities, indefinable microcalcifications, subtle architectural distortions, alone or in combination, are non-specific appearances for breast cancer. These features sometimes precede malignancy and a decisive strategy on how to deal with non-specific minimal signs in a breast cancer screening programme is therefore desirable. After studying the prevalence of these signs in a Dutch Breast Cancer Screening Centre and estimating the risk of participants with these signs acquiring breast cancer within 2 years, we have developed such a strategy. Non-specific minimal signs were seen on the mammograms of 53 of 500 (10.6%) participants, aged 50–70 years, in this programme. After retrospective analysis of the mammograms of 254 patients with screen-detected or interval carcinoma, non-specific minimal signs were detected in 77 cases. Combining the incidence of breast cancer with the difference between the expected number of non-specific minimal signs in the screening programme and its actual occurrence in previous mammograms of patients with breast cancer, the risk of cancer in women with these signs, additional to that of screened women in general (additional risk), is calculated as being 0.5%. Invasive breast cancer in women with previously detected non-specific minimal signs demonstrated a favourable stage at diagnosis (axillary metastasis in 23% *vs* 37% in cancers without these previous signs, $p \leqslant 0.05$). Our strategy for follow-up in case of non-specific minimal signs remains unchanged because of the low additional risk and favourable staging, and is restricted to an invitation for the next screening round in 2 years time.

Introduction

The value of mammography in decreasing breast cancer mortality has been proven [1–3]. Interpretation of screening mammograms can sometimes be difficult. In some cases non-specific minimal signs such as small vague densities, a few clustered indefinable microcalcifications, subtle architectural distortions or combinations of these findings can be confusing, even for experienced screening radiologists. These signs are not specific for either malignant or benign lesions and often remain unchanged or disappear with time. As these signs sometimes precede malignancy, as well as representing benign lesions, it is difficult to decide how to manage a case with a non-specific minimal sign.

These signs are sometimes only detected during follow-up or review of a case. The study of these signs on screening mammography is considered to be important [4] and may help to improve the sensitivity for malignancy. At present the prevalence and significance of these signs in breast cancer screening are not known.

In the first part of this study, the prevalence of non-specific minimal signs was assessed in screened women aged 50–70 years. In the second part, the risk of breast cancer developing within 2 years was retrospectively estimated in participants showing these signs on a previous screening mammogram. Based on these results, we evaluated the current method of managing non-specific minimal signs in mammographic screening and defined our future strategy.

Materials and methods

In most districts in The Netherlands, women of 50–70 years of age are invited biennially for mammographic screening in mobile units. Medio-lateral oblique and cranio-caudal views are obtained in the first screening round. Only oblique mammograms are performed at subsequent screening visits unless there is a change when compared with

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previous films. The radiographers have been trained to compare mammograms and immediately perform additional views at their own discretion. The number of women referred for further assessment after double-reading by accredited specialized screening radiologists is therefore relatively low. The screening is free and the overall attendance rate is nearly 80% [5]. More than 400 000 women were screened in 1993 in The Netherlands, resulting in the detection of breast cancer in 1754 (0.65%) new participants and in 463 women (0.37%) during subsequent rounds [5].

In this study, one or more of the three following features seen on single or multiple views [6], were regarded as non-specific minimal signs: (1) a vague density with an incomplete sharp border, with density comparable to glandular tissue and a diameter between 5 and 30 mm; (2) a few (less than 6) clustered indefinable microcalcifications; (3) subtle architectural distortions, including asymmetry of glandular tissue.

In the first part of this study two experienced screening radiologists (JH and DD) and one senior resident (RM) evaluated the prevalence of these signs on one or two view mammography in a group of 502 consecutive participants from the screening program of the Arnhem district in 1995. Consensus about the absence or presence of these signs was reached after discussion amongst the readers in each case. Two cases were excluded from this study because of architectural distortion due to previous surgery.

In the second part of the study, mammograms of 254 patients with breast carcinomas diagnosed during the period 1989–1993, who had previously attended one or more screening visits in Arnhem or Nijmegen, were compared. Carcinomas were detected in a subsequent screening round (screen-detected carcinomas) in 165 patients, and the diagnosis was made in the period between two consecutive screening rounds (interval carcinoma) in 89 cases. Tumour size, histological type and the presence of axillary metastatic lymph nodes for cancers with and without non-specific minimal signs, as retrospectively identified on mammography performed prior to the one at which the diagnosis was suspected, were compared. The characteristics of these signs were recorded. Four patients with technically inadequate mammograms were excluded. Significance testing for the difference between distributions was done using the χ^2 test.

Results

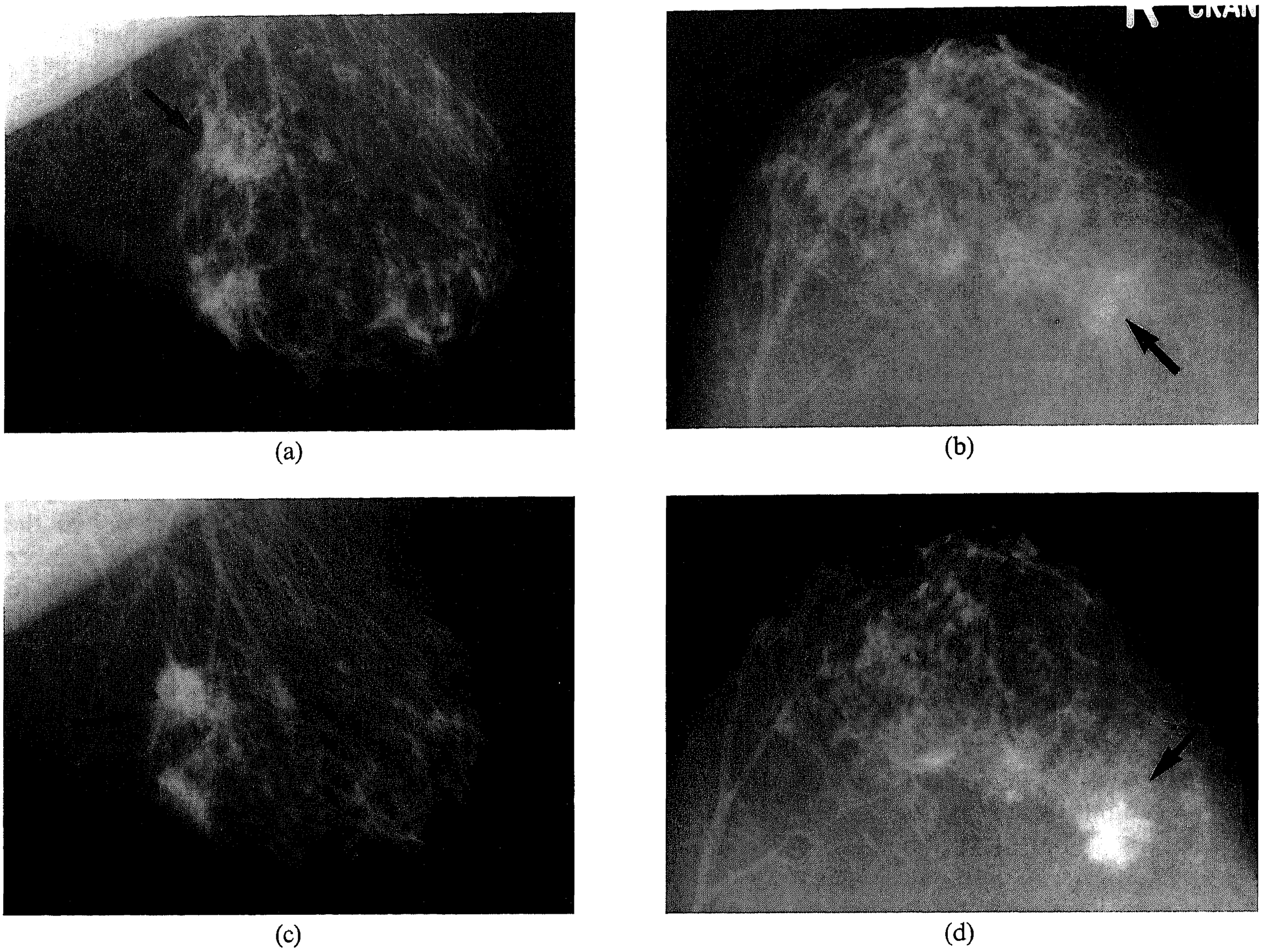
In the first part of the study minimal signs were detected on the mammograms of 53 of 500 ($10.6\% \pm 1.4\%$) participants in the screening. 38 (71.7%) of these 53 participants showed one or two non-specific densities (Figure 1); eight (15.1%) asymmetrical glandular tissue; four (7.6%) subtle architectural distortions and three (5.7%) non-specific microcalcifications (Figure 2).

The characteristics of 254 tumours are shown in Table 1. The size of tumours with and without previous non-specific minimal signs were no different while tumours after screening error were larger (Table 1). Since a number of the women with interval carcinomas were seen in their local hospital by a surgeon who did not regularly report results to the screening programme, the percentages of interval carcinomas, screening errors and tumours radiographically occult at diagnosis (Table 1) are not representative of the screening population. A large number of cases came from the Arnhem district just after they started the screening programme in 1989, when the number of detected *in situ* carcinomas was lower than in recent years (12.0% in 1995 and 17.6% in 1994) (Table 1). Non-specific minimal signs were present on 77 (36%) and absent on 138 (64%) correctly judged previous mammograms (Table 1). There were no differences in histology between tumours with and without these signs on a previous mammogram ($p \leqslant 0.05$) (Table 2).

The characteristics of non-specific minimal signs are shown in Table 3. 18 of 77 patients (23%) with breast cancer who previously presented with these signs had axillary lymph node metastases, compared with 51 of 138 patients (37%) without previous minimal signs (Table 4). According to a Fischer exact χ^2 test, the risk for axillary metastases in participants who developed invasive breast cancer was significantly lower in those with previous minimal signs compared with those without previous minimal signs ($p \leqslant 0.05$). This favourable staging of tumours with previous minimal signs is due to the majority of these tumours, found on screening, showing axillary metastases in only 15% (Table 4).

Discussion

Non-specific minimal signs were present in approximately 10% of a normal screening population of women between 50 and 70 years of age. About 10 000 participants in a population of 100 000 women would be expected to show these signs. Based on the underlying incidence of breast cancer in The Netherlands [7], 255 per 100 000 women would be expected to develop breast cancer within 2 years of participating in the screening programme. Nowadays about three-quarters of these 255 patients will be screen-detected and one-quarter will be interval carcinomas. Assuming that 37% of the screening detected and 29% of the interval carcinomas in women with a correctly judged previous screening mammogram would be preceded by a non-specific minimal sign, about 90



(a) (b) (c) (d)

Figure 1. (a) Oblique and (b) cranio-caudal mammograms with a vague density. (c) Oblique and (d) cranio-caudal mammograms of the same breast 2 years later with suspicious density, histologically proven invasive carcinoma.

Table 1. Characteristics of 254 breast cancers

	Classification of previous mammogram				
	Total (%)	Screening error or technically imperfect film (%)	Non-specific sign present (%)	Non-specific sign absent (%)	Interval cancer occult at diagnosis (%)
Number:					
Interval cancer	89 (100%)	7 (8%)	24 (27%)	49 (55%)	9 (10%)
Screen-detected cancer	165 (100%)	23 (14%)	53 (32%)	89 (54%)	—
Histological type:					
Ductal *in situ*	25 (100%)	—	11 (44%)	14 (56%)	—
Ductal invasive	188 (100%)	25 (13%)	54 (29%)	107 (57%)	2 (1%)
Lobular invasive	21 (100%)	3 (14%)	4 (19%)	12 (57%)	2 (10%)
Other	15 (100%)	2 (13%)	8 (53%)	5 (33%)	—
Unknown	5 (100%)	—	—	—	5 (100%)
Tumour diameter at histology:					
⩽10 mm	68 (100%)	5 (7%)	25 (37%)	38 (56%)	—
10–20 mm	118 (100%)	8 (7%)	40 (34%)	68 (58%)	2 (2%)
>20 mm	63 (100%)	17 (27%)	12 (19%)	32 (51%)	2 (2%)
Unknown	5 (100%)	—	—	—	5 (100%)
Total number	254 (100%)	30 (12%)	77 (30%)	138 (54%)	9 (4%)

of the 255 cancers would have previously demonstrated such a sign. About 10000 out of 100000 screened women will therefore show these signs, of which 90 would be expected to be diagnosed as having cancer within 2 years. This represents a 0.90% chance of developing breast cancer within

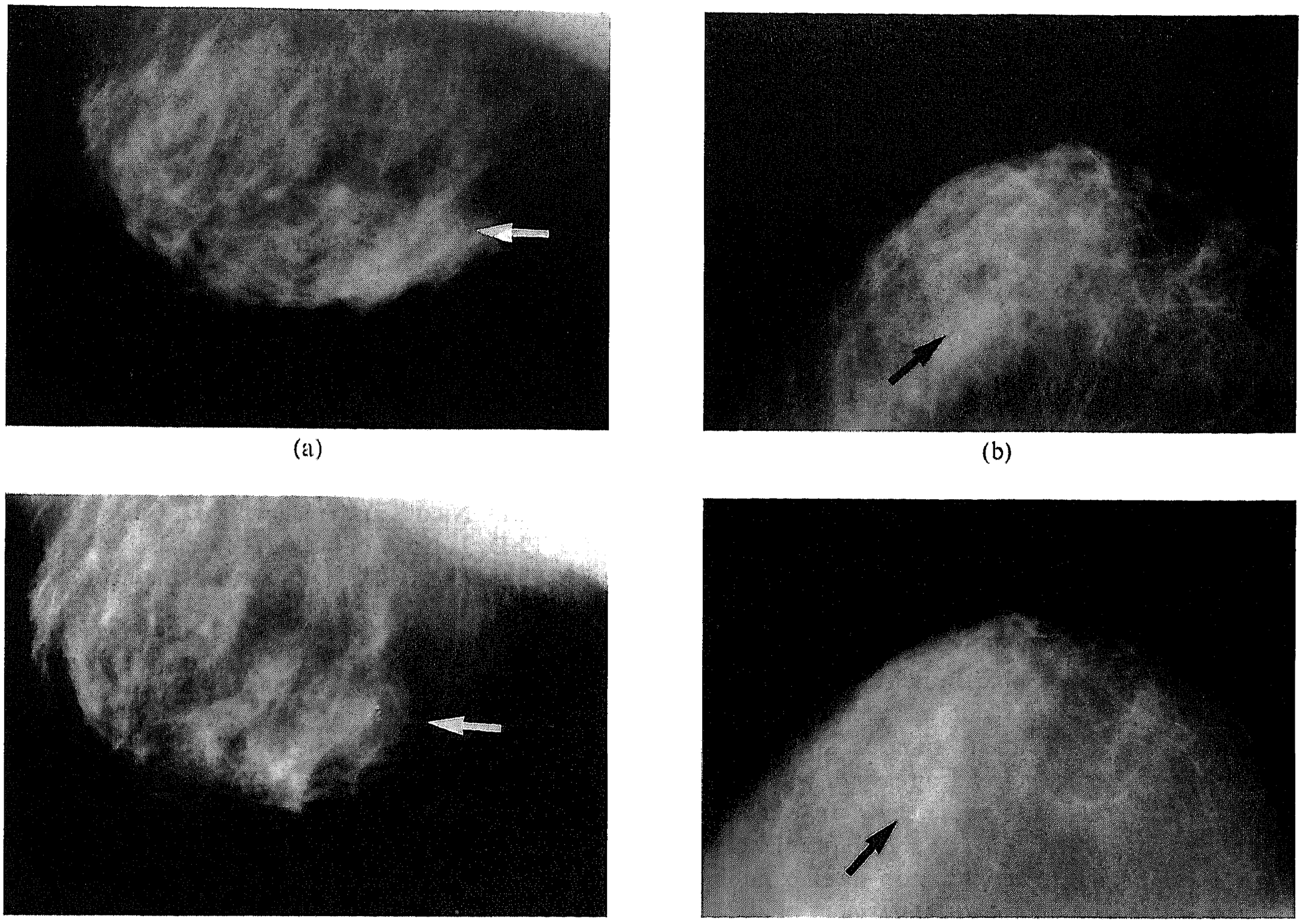


Figure 2. (a) Oblique and (b) cranio-caudal mammograms of a patient with non-specific microcalcifications. (c) Oblique and (d) cranio-caudal mammograms of the same breast 2 years later with increased microcalcifications in an area with histologically proven distrophic calcified fibroadenoma.

Table 2. Presence of non-specific minimal signs on correctly judged previous mammograms of 215 tumours according to histological type

Histological type	Minimal sign present on mammography	Minimal sign absent on mammography
Ductal	54 (70%)	107 (78%)
Lobular	4 (5%)	12 (9%)
Mucinous	4 (5%)	0
Papillary	1 (1%)	0
Tubular	3 (4%)	5 (4%)
Ductal carcinoma *in situ*	11 (14%)	14 (10%)
Total	77 (100%)	138 (100%)

Table 3. Characteristics of non-specific minimal signs on the previous mammogram in breast cancers

	Screening detected cancers	Interval cancers	Total no. of cancers
Density	24	15	39 (51%)
Microcalcifications	19	0	19 (25%)
Density and microcalcifications	5	8	13 (17%)
Architectural distortion	3	0	3 (4%)
Density and architectural distortion	2	1	3 (4%)
Total	53	24	77 (100%)

2 years after the detection of a non-specific minimal sign. Since 0.37% cancers are found during biennial follow-up screening in women, the additional [5] risk of developing breast cancer for women with non-specific minimal signs is about 0.5% when compared with screened women in general.

There are differing opinions on how to deal with such an additional risk. Kopans [8] advocates

Table 4. Presence of axillary metastases in mammographically detected tumours with and without non-specific minimal signs on the correctly-judged previous mammogram

	Tumours without previous non-specific minimal signs		Tumours with previous non-specific specific minimal signs	
	Screen-detected	Interval	Screen-detected	Interval
Axillary metastases absent	59 (66%)	28 (57%)	45 (85%)	14 (58%)
Axillary metastases present	30 (34%)	21 (43%)	8 (15%)	10 (42%)
Tumour diameter				
⩽10 mm	22 (25%)	16 (33%)	18 (34%)	7 (29%)
10–20 mm	47 (53%)	21 (43%)	24 (45%)	16 (67%)
>20 mm	20 (22%)	12 (24%)	11 (21%)	1 (4%)
Total number	89 (100%)	49 (100%)	53 (100%)	24 (100%)

that false negatives are not acceptable and that all non-specific minimal signs need immediate further diagnostic assesment; such as ultrasound, MRI or needle core biopsy [9, 10]. Sickles [11] found that only 0.5% of 3184 biopsies taken from non-palpable mammographically detected but probably benign lesions turned out to be malignant. The tumour size and actual tumour stage at the moment of detection are also relevant when deciding how to deal with these signs. In our study, there was no difference in size and favorable staging for tumours with previous non-specific minimal signs. Immediate diagnostic assessment of all these signs in a screening programme would lead to a large number of false positives and result in unnecessary emotional distress and physical discomfort in a large number of women. Diagnostic evaluation of all these signs would increase our recall rate about eightfold, from 1.3% after the first screening round and 0.65% after following rounds [5] to about 10% overall. According to a nationally agreed consensus the positive predictive value of the screening programme should be, for cost-effective reasons, over 30% in the first round and over 50% during following rounds [12].

Follow-up of women with non-specific minimal signs in our district is therefore restricted to an invitation for the next screening-round. Considering the relatively low additional risk of 0.5% for participants in the screening with non-specific minimal signs of developing breast cancer and the favourable stage of disease in these breast cancers, regular follow-up in the next screening round seems to be a reasonable option.

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