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Use of previous screening mammograms to identify features indicating cases that would have a possible gain in prognosis following earlier detection

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Abstract

False-negative screening mammograms generally refer to breast cancers that were overlooked or misinterpreted at screening. An important question is whether earlier detection could have made a difference in the prognosis of the women concerned. We reviewed screening and diagnostic mammograms of 234 screen-detected and interval cancer cases (aged 44–84 years) diagnosed between 1991 and 1996 in the Nijmegen breast cancer screening programme. A lesion was visible on 117 (50%) of the screening mammograms prior to the diagnosis of breast cancer. Fifty-one out of the 117 cancers had poor prognostic characteristics at diagnosis (i.e. N+ and/or T2+) and could potentially have benefited from an earlier diagnosis ('possible gain'). The 'possible gain' cases were more often characterised by architectural distortion (29 vs. 10%; $P=0.01$) or a high-density mass (25 vs. 13%; $P=0.06$) on the mammogram prior to diagnosis than the 58 'no gain' cases. Our study shows that architectural distortion and non-spiculated high-density masses on the mammogram prior to diagnosis are associated with a possible gain in prognosis. Earlier detection of the carcinomas preceded by these signs may well have an impact on breast cancer mortality and thus warrant extra attention in radiological practice.

Keywords: Breast cancer; Mammography; Screening; Interval cancer

1. Introduction

Despite recent debate, screening for breast cancer by mammography is an accepted means of secondary prevention to reduce mortality from this disease [1]. Since the effect on breast cancer mortality will only become apparent in the long-term, monitoring the performance and early outcomes is essential in the early phases of a screening programme [2]. An important indicator in this respect is the number of interval cancers, i.e. cancers diagnosed after a negative screening examination, but before the next examination [3,4].

Radiological review of interval cancers has shown that an often considerable proportion, ranging from 4 to 56%, has been overlooked or misinterpreted at screening [3,5–12]. Learning about the characteristics of these cases can help to improve radiologists' performance and, thereby, overall performance of the screening programme [13,14]. In addition, rereading exercises should be extended to include screen-detected cancers, since detection at screening does not necessarily imply that these cancers could not have been detected earlier [5,15–22]. Estimates of the percentage of screen-detected cancers where a lesion was visible on the previous screening mammogram have ranged from as low as 5% [17] to as high as 67% [22].

In the current study, we performed an informed review of all screening and diagnostic mammograms of 234 screen-detected and interval cancer cases diagnosed

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between 1991 and 1996 in the Nijmegen breast cancer screening programme. Our aim was to estimate the proportion of false-negative screening examinations where earlier detection could have had an impact on prognosis for the women concerned ('potential gain').

2. Patients and methods

The population-based screening programme for breast cancer in Nijmegen, a city in the Netherlands of approximately 150 000 inhabitants, was introduced in 1975. Some 30 000 women aged 35 years and older are invited biennially by personal invitation. Women older than 65 years were invited from 1977 onwards. Since 1989, the age group invited for screening in Nijmegen is consistent with national screening policy (target population: 50–69 years until 1997; 50–74 years thereafter). Two-view mammography was employed as the screening test at the initial screens. At subsequent screens, only the mediolateral oblique view was taken. However, because of on-site processing, the radiographer could decide that a second craniocaudal view was necessary based on prespecified criteria. Most of the films (more than 90%) were read by two radiologists, who decided whether referral was necessary. The results of the first nine rounds of the Nijmegen programme have been published in detail elsewhere [23].

Between 1991 and 1996, 259 women were diagnosed with breast cancer either at screening (screen-detected cancers) or within 24 months from a negative screening (interval cancers). We excluded 25 women from the current study because they did not attend screening prior to diagnosis ($n=11$), or they were diagnosed with lobular carcinoma *in situ* ($n=6$) or their screening or diagnostic mammograms were not available for review ($n=8$). All screen-detected cases in the study had to have participated in at least two screening rounds. The screening examination on the basis of which they were diagnosed was regarded as their diagnostic mammogram. The remaining data-set consisted of 234 breast cancer cases (aged 44–84 years at diagnosis) of which 142 were screen-detected and 92 were interval cancers.

All diagnostic mammograms and all mammograms of the screening round prior to diagnosis were reviewed (non-blinded) by a radiologist and a radiographer. Previous mammograms were classified as either 'lesion visible' or 'no lesion visible'. Furthermore, data on radiological features, technical quality, positioning aspects and mammographic breast pattern were collected during the review. Pathobiological aspects of the tumour and relevant patient characteristics (such as age at diagnosis, menopausal status and family history) were obtained through linkage of the data-set with the screening register and hospital records.

In a second step, cancers where a lesion was visible on the previous screening mammogram were further classified according to the possibility that earlier detection, i.e. detection as a consequence of the preceding mammogram, could have influenced the prognosis for the women concerned (see Table 1). The category 'possible gain' represents women with a poor prognosis at diagnosis (N+ and/or T2+). In the category 'no gain', women had a good prognosis at diagnosis (N- and <T2). Women for whom no data were available on either size or nodal status at diagnosis were classified as 'gain undefined'.

We performed descriptive analyses comparing differences in the characteristics between groups using frequency tabulations. Statistical significance of differences was assessed with the Chi-square test or Fisher's exact test from the Statistical Analysis System (SAS) software package.

3. Results

A lesion was present on 50% (117 out of 234) of the screening mammograms prior to the diagnosis of breast cancer (Table 1). There was no difference in this respect between screen-detected and interval cancer cases (53 vs. 47%, $P=0.28$). Out of 117 cancers with a visible lesion, 51 cancers were attributed a possible prognostic gain (T2+ and/or N+ at diagnosis). The proportion of cases that could possibly have benefited from earlier diagnosis was higher among interval cancers than screen-detected cases (57 vs. 36%; $P=0.09$).

Table 1
Classification of screening mammograms prior to diagnosis in 234 patients with breast cancer

	Classification of previous screening mammogram			Classification according to potential gain where lesion is visible		
	Number of cases	No lesion visible	Lesion visible	No gain	Possible gain	Undefined
Total	234 (100%)	117 (50%)	117 (50%)	58 (50%)	51 (44%)	8 (6%)
Screen-detected	142 (100%)	67 (47%)	75 (53%)	42 (56%)	27 (36%)	6 (8%)
Interval cancer	92 (100%)	50 (54%)	42 (46%)	16 (38%)	24 (57%)	2 (5%)

No gain = women with a good prognosis at diagnosis (N- and <T2) and a visible lesion on the screening mammogram prior to diagnosis. Possible gain = women with a poor prognosis at diagnosis (N+ and/or T2+) and a visible lesion on the screening mammogram prior to diagnosis. Undefined = women for whom no data were available on either size or nodal status at diagnosis.

Table 2
Patient characteristics and characteristics of the tumour at diagnosis in the three study groups

	Lesion visible		No lesion visible
	Possible gain ($n=51$) *n* (%)	No gain ($n=58$) *n* (%)	($n=117$) *n* (%)
Age at diagnosis (years)			
<50	3 (6)	3 (5)	20 (17)
50–59	17 (33)	22 (38)	36 (31)
60–69	20 (39)	23 (40)	44 (38)
70+	11 (22)	10 (17)	17 (14)
Menopausal status			
Premenopausal	33 (65)	40 (69)	48 (41)
Postmenopausal	18 (35)	18 (31)	69 (59)
Mammographic density (% of the breast) on the mammogram prior to diagnosis			
<5%	1 (2)	2 (3)	4 (3)
5–25%	30 (59)	38 (66)	67 (57)
26–75%	20 (39)	16 (28)	43 (37)
>75%	0 (0)	2 (3)	3 (3)
Positive family history?			
Yes	5 (10)	14 (24)	21 (18)
No	45 (88)	44 (76)	95 (81)
Information not available	1 (2)	0 (0)	1 (1)
Tumour size at diagnosis			
Size unknown	0 (0)	0 (0)	1 (1)
DCIS	0 (0)	4 (7)	17 (15)
⩽2 cm (<T2)	25 (49)	54 (93)	71 (61)
>2 cm (T2+)	26 (51)	0 (0)	28 (24)
Lymph node status			
Not investigated	0 (0)	4 (7)	22 (19)
Negative (N−)	11 (22)	54 (93)	70 (60)
Positive (N+)	40 (78)	0 (0)	25 (21)

DCIS, ductal carcinoma *in situ*.

In Table 2, we present characteristics of the patients and their tumours at diagnosis in the three study groups: 'possible gain' cases, 'no gain' cases and cases where no lesion was visible on the screening mammogram prior to diagnosis. There were no differences between the groups in age at diagnosis and mammographic breast pattern on the screening mammogram prior to diagnosis. Patients with no visible lesion on the previous mammogram were more often postmenopausal than the 'possible gain' group (59 vs. 35%; $P=0.01$) or 'no gain' patients (59 vs. 31%; $P=0.001$). The 'Possible gain' patient group had a low percentage of patients with a positive family history of breast cancer compared with the 'no gain' group (10 vs. 24%; $P=0.08$). The distribution of tumour size and lymph node status in the 'possible gain' and 'no gain' cases reflects the classification requirements for these groups.

Comparison of the technical and positioning aspects of the screening mammogram prior to diagnosis showed essentially no differences between the three study groups (data not shown). Overall, very few mammograms were characterised as inadequate from the technical or positioning point of view.

Table 3 compares radiological characteristics of the screening mammogram prior to diagnosis where a lesion was visible. Differences in main radiological signs between the 'possible gain' and 'no gain' groups were found in the presence of architectural distortion (29 vs. 10%; $P=0.01$) and the relative absence of cases with only microcalcifications (8 vs. 17%; $P=0.14$). Approximately half of the 'possible gain' cases were characterised by a 'density without microcalcifications'. This characteristic was more common among interval cancer than screen-detected cases (67 vs. 41% of screen-detected cases; $P=0.06$; data not shown).

A spiculated margin was noted in 8 cancers, all screen-detected, from the 'no gain' group that presented as a density on the previous mammogram. This feature was less common in the 'possible gain' group, although this difference was not statistically significant (7 vs. 21%; $P=0.17$). Overall, most tumour densities in the 'possible gain' and 'no gain' groups presented with an 'indistinct' or 'obscured' margin on the mammogram prior to diagnosis (75 vs. 59%; $P=0.17$). Cancer densities in the 'possible gain' group were more often characterised as high-density than 'no gain' cancer densities (25 vs. 13%; $P=0.06$).

Table 3
Radiological characteristics of the mammogram prior to diagnosis for women who possibly could have benefited from earlier detection (possible gain) and women who could not have benefited from earlier detection (no gain)

	Possible gain ($n=51$) n (%)	No gain ($n=58$) n (%)
Main suspicious sign on mammogram prior to diagnosis		
Density without microcalcifications	27 (53)	37 (64)
Density with microcalcifications	1 (2)	2 (4)
Only microcalcifications	4 (8)	10 (17)
Architectural distortion	15 (29)	6 (10)
Asymmetric breast tissue	4 (8)	3 (5)
Additional suspicious features on mammogram prior to diagnosis		
No additional suspicious features	42 (82)	52 (90)
Additional suspicious features[a]	9 (18)	6 (10)
Tumour margin (in case of density)		
Spiculated	2 (7)	8 (21)
Indistinct/obscured	21 (75)	23 (59)
Partly circumscribed	0 (0)	1 (2)
Circumscribed	3 (11)	3 (8)
Microlobulated	2 (7)	4 (10)
Density of tumour (in case of density)		
High-density	7 (25)	5 (13)
Isodense	19 (68)	34 (87)
Unclassifiable	2 (7)	0 (0)

[a] Such as nipple/skin retraction, skin thickening, axillary adenopathy.

Table 4 shows the histological type of the cancers in the three study groups. The proportion of invasive ductal carcinomas is lowest in the 'no gain' group (50 vs. 69% in 'possible gain' group; $P=0.05$, 50 vs. 64% in 'no lesion visible' group; $P=0.07$ respectively. Invasive lobular carcinomas are often associated with a visible lesion on the mammogram prior to diagnosis (24/35), but their presence does not differ between the 'possible gain' and 'no gain' groups (25 vs. 19%; $P=0.41$). Tubular carcinomas are more often found in the 'no gain' group than in the two other groups (21 vs. 2% in the 'possible gain' group; $P=0.003$, 21 vs. 5% in the 'no lesion visible' group; $P=0.001$ respectively).

4. Discussion

Among the factors limiting the efficacy of mammographic screening, delay in the detection of breast cancer due to false-negative mammograms is of crucial importance [8]. On the other hand, it is essential to realise that not all women with cancers that are potentially detectable in retrospect would have benefited from earlier detection in terms of improved prognosis. For instance, ductal carcinoma *in situ* or slow-growing invasive tumours may still present in a favourable stage even though the diagnosis was delayed [16,25].

In the last decade, many studies have tried to classify and describe characteristics of cancers that could have been detected at screening. Most studies focused on the review of interval cancers [3,7,9–11,13,24], but several studies also recognised the importance of rereading screen-detected or 'incident round' cancers, usually considered to be 'true-positive' [5,15–17,19–21].

In most review studies, researchers have attempted to distinguish between lesions that were overlooked or misinterpreted and lesions where the mammogram showed minimal or unusual lesion characteristics, the so-called 'minimal signs' [5,9,10,12,13,20,21,24]. We believe that this distinction is arbitrary to some extent and essentially a subjective undertaking. The key issue is whether or not a lesion was visible on the screening mammogram prior to diagnosis and, if so, whether or not earlier detection could have made a difference in prognosis for the women concerned ('possible gain').

In our study, a lesion was present on the previous mammogram in approximately half of the interval cancer cases as well as the screen-detected cancer cases. The proportion of cancers visible on previous mammograms

Table 4
Histological type of the cancers in the three study groups

Histological type	Lesion visible		No lesion visible ($n=117$)
	Possible gain ($n=51$) n (%)	No gain ($n=58$) n (%)	n (%)
Ductal carcinoma *in situ*	0 (0)	4 (7)	17 (15)
Invasive ductal carcinoma	35 (69)	29 (50)	75 (64)
Invasive lobular carcinoma	13 (25)	11 (19)	11 (9)
Tubular carcinoma	1 (2)	12 (21)	6 (5)
Other histological types	2 (4)	2 (3)	8 (7)

in other studies varies from 4 [11] to 75% [26] and was generally reported to be higher among screen-detected than interval cancer cases [16,17,21,27]. This wide range illustrates that the review procedures used (e.g. blinded vs. informed review, one or more radiologists involved in the review) and the definition of a 'visible lesion' in these studies are not standardised and cannot easily be compared.

Interval cancers were more often classified as 'possible gain' than screen-detected cancers. This can be explained by a higher growth rate for interval cancers [25] as well as a higher probability for these lesions to become palpable in the interval between screening examinations. Both are features associated with more advanced cancers. The higher proportion of tumour densities without microcalcifications is also consistent with the more aggressive nature of interval cancers.

The most distinguishing radiological sign on the mammogram prior to diagnosis for 'possible gain' cases was the presence of architectural distortion. Several groups have also reported architectural distortion as a characteristic of 'missed' cancers [7,11,12,19,20]. This subtle feature may be a 'precursor sign' for invasive lobular or ductal carcinoma, usually with diffuse tumour growth [20,27,28]. The fact that in our study 17% of the cases presenting as 'density without microcalcifications' on the diagnostic mammogram, were preceded by 'architectural distortion' on the previous mammogram (data not shown) strengthens this hypothesis. Earlier detection of invasive lobular and ductal carcinoma, predominantly the pleomorphic and intermediate grade types, may well have an impact on mortality. The finding that high-density masses are associated with a possible gain is as expected and will also contribute to a decrease in breast cancer mortality.

Our study shows that ductal carcinoma *in situ* (usually characterised by microcalcifications) and tubular carcinomas (typically characterised by a spiculated margin) are more often found in the 'no gain' group. This is consistent with length-biased sampling, where at screening one is more likely to detect impalpable, slower-growing lesions with a relatively good prognosis [12,25,29]. Detection of these cancers will only have a limited impact on breast cancer mortality.

To our knowledge, no other study combined radiological review with pathohistological data on prognosis, although the concept has been previously proposed [17]. A recent study from the United Kingdom did identify 'risk groups' based on tumour characteristics at diagnosis, but reported this information separate from their classification of detectability of a lesion on the previous screening mammogram. However, the authors reported that at screening, as at diagnosis, there was little difference in mammographic appearance between cancers in the different risk groups. They were therefore unable to identify any specific lesions particularly indicative of a subsequent poor prognosis [29].

The vast majority (>90%) of the cases in our study were classified as adequate from the technical and positioning point of view. We were also unable to identify patient characteristics that would be helpful in defining a subgroup of women requiring extra attention when interpreting the screening mammograms. Future studies should focus, possibly with the help of computer-aided detection systems [22], on identifying in more detail radiological patterns that can distinguish cancer cases with 'possible gain' from 'no gain'. Application of this type of knowledge in screening practice is possible through training of radiologists in the detection, as well as interpretation, of subtle mammographic signs [13,20] and should contribute towards a decrease in breast cancer mortality.

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