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Original Paper

The Visibility of Cancer on Earlier Mammograms in a Population-based Screening Programme

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The aim of this study was to examine how frequently the later-round screen-detected and interval breast cancers were visible in earlier screening mammograms by retrospective review and to compare their radiological and clinicopathological features with those diagnosed by primary screening. In a population-based mammography screening programme 63 731 women aged 50–59 years were invited and 56 158 examinations were carried out in the period 1987–1992 in the Tampere area in Finland. A total of 276 breast cancers were detected, of which 131 were diagnosed on later screening rounds or were interval cancers. A retrospective review of previous screening mammograms was carried out in 130 cases by the radiologist who diagnosed the breast cancer and thus knew the exact location of the tumour, no blinded review was carried out. 43 (33%) cancers were visible, 84 (65%) were not visible and 3 (2%) not included on the mammogram in a retrospective review. Later round screen-detected cancers were statistically significantly more often visible in earlier screening mammograms (43%) than interval cancers (19%) ($P = 0.002$). Tumours missed by screening mammography but which were visible on retrospective review were often histologically well-differentiated and were more often diagnosed in the subsequent screening round than by clinical diagnosis as interval cancers. If all retrospectively visible interval cancers had been diagnosed by screening 19% (10/54) of the interval cancers could have been avoided. If all retrospectively visible cancers had been diagnosed at the time of false-negative screening or assessment 65% (84/130) of all patients would have benefitted from an earlier diagnosis compared with the actual figure of 31% (41/130). © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

SCREENING FOR breast cancer has been shown to reduce breast cancer mortality rates in women aged over 50 years [1–4]. Biannual population based screening with two-view double reading mammography was started in Finland in January 1987 for women aged 50–59 years. The effect this had on mortality has been published in detail elsewhere [4, 5]. Good sensitivity and specificity of the screening programme is a necessary condition for an effective programme. The reasons for a false-negative screening test depend on the density of breast parenchyma, histology and size of the tumour and experience and skill of the radiologist [6]. Positioning of the breast, quality of the mammogram and other technical considerations may also significantly affect the sensitivity of the

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screening. Some breast cancers are visible in earlier mammograms on retrospective review [7–11]. In this study we estimated how many screening and interval cancers could have been detected at the earlier screening round by improved interpretation of the mammogram and whether there are any radiological or clinical differences between retrospectively visible and invisible cancers.

MATERIALS AND METHODS

The study material originates from the mammographically screened women in Tampere and its surroundings (about 400 000 inhabitants) in the period 1987–1992 (Table 1). Women were individually identified by personal identification number and invited for screening at 2-year intervals. A craniocaudal and medio-lateral oblique two-view mammogram was used. Two radiologists interpreted mammograms and one of them carried out further examinations. Assessment involved a combination of further imaging, physical examination and fine needle aspiration biopsy. Screening units referred patients with suspicious lesions to operation directly without consultation with the family doctor or general practitioner. Hospitals sent clinical and histopathological data on operated tumours to the screening units.

In this study, cancers diagnosed at screening, between screens, and among non-attenders were checked by linkage of the screening data to the Finnish Cancer Registry. Therefore, the study material includes all new breast cancer cases in the screened age groups. A woman was classified as a non-attender if she had not responded to the invitation for the screening round preceding the diagnosis of breast cancer. Cancers diagnosed between two consecutive screening rounds were considered as interval cancers.

All the radiologists involved in this study were experienced in clinical mammography work. Most of them attended intensive screening mammography education courses before the programme began. The radiologist who diagnosed the breast cancer in or outside of the screening, reviewed initial screening mammograms together with the subsequent mammograms and recorded radiological data concerning the visibility and size of the tumour.

No blinded review of mammograms was carried out. The tumour was regarded as visible in retrospect if there were any, even minimal, abnormalities in the location where cancer was later detected. All types of densities, even benign looking tumour masses, structural distortions and microcalcifications were regarded as abnormalities. The radiological signs and tumour characteristics were analysed from the mammogram taken at the time the tumour was diagnosed. To confirm further the validity of the patient data, all medical records were retrospectively reviewed by a senior radiologist and oncologist.

Table 1. *Population based mammography screening results in the Tampere screening programme* 1987–1992

	n	%
Invited	63 731	
Screened	56 158	88*
Recalled	2269	4.00†
Open surgical biopsies	441	0.79†
Benign	218	0.39†
First primaries	213	0.38†
First round cancers	136	0.24†
Second round cancers	52	0.09†
Third round cancers	25	0.04†
Recurrences	9‡	0.02†
Interval cancers	54	0.10†
Cancers among non-responders	9	0.02†
All cancers	276	0.49†

*% among those invited. †% among those screened. ‡excluded from the study material.

Clinical and histopathological data were recorded from patient files of the University Hospital of Tampere or Tampere City Hospital, where all the patients were treated and followed up. Clinicopathological characterisation of tumours used TNM and histopathology classification according to the WHO scheme. All cytological samples were taken using fine needle aspiration technique by mammographic, ultrasonographic or palpation guidance. Cross-tabulations were made by SPSS for Windows 95 software and statistical significance was based on two-tailed Fisher's exact test using the approximation of Woolf for the differences and Chi-squared test for trends.

RESULTS

The study included 64 000 invitations of women with 88% attendance (Table 1). 276 women had histologically verified breast cancer. Among them were 77 cancers diagnosed in the second or third screening rounds and 54 between two screening rounds (interval cancers). One cancer was found in the second screening round but the woman had not attended the screening in the first round. The positive predictive value of screening mammography was 9% (213/2269). The recommended screening interval was 2 years. The most common interval for the screen-detected cases was 23–25

Table 2. *Distribution of tumours by retrospective review and screening status in the Tampere screening programme* 1987–1992

	Screening status at diagnosis		
	2nd+3rd round *n* (%)	Interval *n* (%)	Total *n* (%)
Tumour visible in earlier mammograms	33 (43)	10 (19)	43 (33)
Radiologically measured size			
1–8 mm	24	2	26
10–15 mm	4	2	6
Not measurable	5	6	11
Tumour not included in the mammogram	2 (3)	1 (2)	3 (2)
Tumour not visible in earlier mammograms	41 (54)	43 (80)	84 (65)
Total	76 (100)	54 (100)	130 (100)

Table 3. *Radiological differences between retrospectively visible and invisible carcinomas by mammography in the Tampere screening programme* 1987–1992

	Visible in retrospect			Not visible in retrospect			Total
Main mammography finding	Screened *n*	Interval *n*	All *n* (%)	Screened *n*	Interval *n*	All *n* (%)	*n* (%)
Mass only	28	5	33 (77)	22	16	38 (45)	71 (56)
Microcalcifications only	3	0	3 (7)	11	1	12 (14)	15 (12)
Mass and microcalcification	2	1	3 (7)	5	2	7 (8)	10 (8)
Other*	0	0	0 (0)	3	4	7 (8)	7 (6)
Unknown	0	4	4 (9)	0	20	20 (24)	24 (19)
Total	33	10	43 (100)	41	43	84 (100)	127† (100)

*Other mammography findings include asymmetry, architectural distortion and skin retraction. †Three cancers were not included on the mammogram.

months (35 out of 77 cases), (range 12–68 months; mean 24.4 months). Of 54 interval cancers, 17 (31%) appeared within 12 months of the previous screening, 15 (28%) within 12–18 months, 16 (30%) within 18–24 months and six (11%) more than 24 months after the previous screening round (mean interval 16.8 months; range 2–43 months).

In 130 cases a retrospective review of earlier mammograms was carried out (Table 2). Of these 76 were screen-detected and 54 were interval cancers. In retrospective analysis screen-detected cancers were significantly ($P = 0.002$) more often visible in earlier mammograms (43%) than interval cancers (19%) (Table 2). In earlier screening mammograms tumour size was measurable in 28 screen-detected cases (37%) and in four of these the size exceeded 10 mm (Table 2). Corresponding figures among interval cancers were four (7%) and 2 cases were larger than 10 mm. The size of the retrospectively visible tumour was not measurable in the earlier mammogram in 11 cases because of the unspecific appearance of the tumour. Tumour mass as a basis of diagnosis was often visible in the previous mammogram, whereas microcalcifications were often not visible. Primary screen-detected cancers showed microcalcifications significantly more frequently (21/74, 28%) than interval cancers (4/53, 8%) ($P = 0.003$), (Table 3).

There were no major differences in the histological types between the retrospectively visible and invisible cancers. Most of the tumours (73%) were ductal invasive cancers (Table 4). Histological grade was significantly lower in the retrospectively visible cancers ($P = 0.02$), among which grade 1–2 tumours were common. Post-surgical stage was also more favourable, but not significantly lower, among the patients with retrospectively visible tumours (Table 4).

Table 4. *Differences between retrospectively visible and invisible tumours in tumour size, postsurgical stage, histological type and grade in the Tampere mammography programme* 1987–1992

Tumour characteristics	Visible in retrospect			Not visible in retrospect			Total
	Screened *n*	Interval *n*	All *n* (%)	Screened *n*	Interval *n*	All *n* (%)	*n* (%)
Tumour size measured from histological specimen							
1–9 mm	8	0	8 (33)	10	5	15 (31)	23 (32)
10–19 mm	8	1	9 (38)	10	10	20 (42)	29 (40)
20–39 mm	3	3	6 (25)	3	7	10 (21)	16 (22)
≥40 mm	0	1	1 (4)	1	2	3 (6)	4 (6)
Total	19	5	24 (100)	24	24	48 (100)	72 (100)
Postsurgical stage							
1	26	3	29 (78)	25	20	45 (69)	74 (73)
2	3	4	7 (19)	9	8	17 (26)	24 (24)
3	0	1	1 (3)	2	1	3 (5)	4 (4)
Total	29	8	37 (100)	36	29	65 (100)	102 (100)
Histological type							
Tis	2	0	2 (5)	6	4	10 (12)	12 (10)
Invasive lobular	5	1	6 (14)	2	3	5 (6)	11 (9)
Invasive ductal	21	8	29 (67)	31	31	62 (76)	91 (73)
Other	5	1	6 (14)	2	3	5 (6)	11 (9)
Total	33	10	43 (100)	41	41	82 (100)	125 (100)
Histological grade							
1	15	2	17 (63)	12	10	22 (37)	39 (45)
2	6	2	8 (30)	12	14	26 (44)	34 (39)
3	1	1	2 (7)	6	5	11 (19)	13 (15)
Total	22	5	27 (100)	30	29	59 (100)	86 (100)

Altogether 10 of 54 (19%) interval cancers were visible by retrospective review. Therefore, 19% of the interval cancers could have been avoided if all the visible interval cancers had been detected at a previous screening round. Had all the retrospectively visible cancers diagnosed at the time of false-negative screening or assessment, 65% (84/130) of all patients would have benefitted from a more early diagnosis compared with the actual figure of 32% (41/130).

There were 11 cancer patients for whom further examinations were performed in an earlier screening round without detecting the malignant lesion. Eight of these cancers were found in the next screening round and three as interval cancers before the next round. In two screen-detected cancer cases, recall imaging in the earlier screening round was performed to investigate a different lesion that later appeared to be malignant microcalcifications and tumour density. In six screen-detected and three interval cancer cases diagnostic imaging was performed to investigate the same lesion which later was confirmed to be cancer, i.e. correct diagnosis at screening mammography but incorrect diagnosis at diagnostic imaging. In two screening cases and one interval case microcalcifications were falsely interpreted to be benign after microfocus magnification mammograms. In four screening cases and two interval cases asymmetric density was falsely interpreted as benign.

DISCUSSION

We estimated the proportion of false-negative interpretation of screening mammograms in a well defined target population subjected to an organised screening programme with an average interval of 2 years between the screening rounds. In Finland, decisions on health services are made by individual municipalities with state subsidies. There was some variation in the intervals between the screening rounds because not all municipalities included in our study followed the recommendations and there were also some long intervals between screening and detecting the interval cancer. However, we called these cases screening or interval carcinomas, because these women had participated in screening whenever it was organised. All cancers in second or third screening round were identified as well as all interval cases up to the last round. The coverage was assessed by linkage to the Finnish Cancer Registry, which is nationwide and has virtually complete coverage [12].

Non-specific minimal signs of breast cancer in mammograms are common and sometimes these signs can only be detected during follow-up or review of cases [13]. In published reports the proportion of cancers visible in earlier mammograms varies between 22 and 75% [7–11, 14–15] depending on the definition of the retrospective visibility of the tumour, i.e. whether based on the opinion of one or several radiologists [7, 10, 11, 14], on the technical quality of the screen [11], on the interval between the mammograms [16] and on whether earlier mammograms were interpreted blindly (without knowledge that carcinoma was subsequently detected) or retrospectively (with the mammogram showing the carcinoma available for comparison) [7, 9, 15, 16]. We found 33% (43 patients) of the tumours to be retrospectively visible in an earlier mammogram, which is within the range of earlier publications. Eleven (26%) of them had had further diagnostic assessment in an earlier screening round with a false-negative result. Of these, two were false-negative at screening, i.e. screening led to assessment of a different lesion than the one which later appeared to be cancer and nine were false-negative at assessment, i.e. assessment with false-negative result referred to the same lesion that later appeared to be cancer.

We found 33 (43%) of 76 screen-detected cancers to be visible in earlier screening mammograms. If we define these as false-negative, there were 24 (31%) false-negatives at screening and 9 (12%) false-negatives at assessment. Jones and colleagues [7] found 25 (19%) false-negatives at screening and 5 (4%) at assessment out of 133 screen detected cancers. The higher proportion in our study may depend on the non-blinded study design and complete follow-up of the total population.

Most (79%) of the interval cancers were invisible retrospectively and some of them were very fast growing with high malignant potential. Our results were consistent with previous studies [14–16]. Retrospectively visible carcinomas had lower tumour grade and more favourable tumour stage than retrospectively invisible carcinomas. Retrospectively visible carcinomas were less aggressive than invisible ones and most of them (33 out of 43) were found in the next screening round and were small (28 were $\leq$15 mm tumours). Screen-detected cancers were more often visible in earlier mammograms on retrospective interpretation than interval cancers, even though the time interval was longer for screen-detected cancers. The tumour size in earlier mammograms was measurable less often in the interval than in the screen-detected cancers i.e. their tumour borders were indistinct and unspecific. Most cancers which were interpreted to be visible by retrospective review were tumour masses without microcalcifications. Such tumours are difficult to detect, especially if the breast parenchyma is dense [6].

Out of the 130 tumours only 41 (31%) were screen detected tumours not visible on earlier mammograms and, therefore, in fact detected early. All the other 89 (68%) tumours were late detected as they were either interval cancers or screen-detected cancers visible on earlier mammograms (with 3 exceptions where the tumour was not included in the mammogram). Had all the 43 visible interval and screen-detected cancers been detected by the previous screening the proportion with early detection would have been substantially higher (65% instead of 32%). If all retrospectively visible interval cancers had been diagnosed by screening, 19% of the interval cancers could have been avoided. However, non-specific minimal signs of breast cancer in mammogram are common and sometimes these signs can only be detected during follow-up or review of cases. In our cases all, even minimal and unspecific densities in the earlier mammograms were noted as visible tumour in the reviewing.

When screening mammograms are calculated, visibility of breast cancer in earlier screening mammograms may be a favourable prognostic sign because such tumours are relatively low grade and, therefore, slow growing with low malignant potential. In fact this is what one would expect, since only slow growing cancers would have been sufficiently large to have been visible at previous screening mammography.

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