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Delayed Diagnosis and Large Size of Breast Cancer After a False Negative Mammogram

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The aim of this prospective, multicentre study was to investigate the effects of a false negative mammogram on treatment delay and tumour size. Among 306 consecutive women with histologically diagnosed, invasive breast cancer, the frequency of a false negative mammogram was small (13%) among women aged over 50 years, but 35% among those aged 50 or younger ($P < 0.0001$). Forty-five per cent of the women with a false negative mammogram had a longer than 2-month and 29% a longer than 6-month interval from mammography to surgery as compared with only 2 and 0% of women, respectively, who had a true positive mammogram ($P < 0.0001$ for both). Women with a false negative mammogram and a longer than 2-month interval to surgery had larger primary tumour size (60 versus 26% pT2-4, $P = 0.005$) and more often positive axillary nodes (60% versus 32% pN +, $P = 0.03$) at the time of surgery than those with a shorter delay. We conclude that a false negative mammogram is common in women younger than 50, and may lead to treatment delay and advanced clinical stage.

Key words: breast neoplasms, breast diseases, mammography
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INTRODUCTION

MAMMOGRAPHY IS an important and widely accepted method used to diagnose non-palpable breast cancer. It has also been regarded as an essential part of the preoperative examination of women with a palpable mass, even when cancer is obvious, in order to evaluate both the ipsilateral and the contralateral breast for clinically occult lesions [1].

There is some evidence that a false negative mammogram in a patient with breast cancer may result in treatment delay [2], but the frequency and consequences of such a delay are unsettled. In the present study, we investigated sensitivity of mammography in detecting cancer in women with a breast mass and/or breast symptoms, and examined treatment delay and size of cancer in women with a false negative mammogram.

PATIENTS AND METHODS

Patients

The study is based on 502 women with histologically confirmed breast cancer who were admitted to an oncological department in three university hospitals in Finland. The patients were investigated in 1992, except for 155 women, who belonged to a pilot study carried out in one of the departments (Turku) during 1 January 1991 to 1 October 1991, and who were also included. The cases are consecutive, and all women with breast cancer attending these departments during the study periods were included in the study.

Nationwide mammography screening for breast cancer has been carried out in Finland since 1987, and cases where breast cancer was detected in such screening ($n = 132$) were excluded from further analysis. In addition, cases where cancer was found incidentally by the medical personnel and not by the woman herself ($n = 37$), where mammography had not been performed before surgery ($n = 19$), and where cancer was entirely intraductal without an invasive component ($n = 8$) were also excluded, which left 306 women with self-suspected invasive cancer in the final analysis.

The patients were interviewed by an oncologist, and the time of the first appearance of the breast tumour and/or other signs or breast symptoms were recorded on a data collection form at the time of the patient's first visit to the department. In addition, the time of the first visit to a medical doctor due to the present breast disease, possible subsequent visits, time of the first and later mammograms and surgery, and size and histological type of cancer were recorded. The principal sign or symptom was a breast tumour in 236 (77%), pain or other abnormal sensations in the breast in 39 (13%), skin dimpling in 9 (3%), other skin changes in 5 (2%), nipple discharge in 7 (2%), axillary tumour in 5 (2%), backpain in 1, and unknown in 4 (1%). Mammography findings, whether positive or probably positive (class IV–V) for the presence of cancer, indecisive (class III), or negative (class I or II), were extracted from the case records. Both lesions that were stated to be benign in the radiologist's report and lesions that were invisible were considered to be false negative findings for cancer. No attempt was made to reinterpret the mammogram retrospectively. Fifty-seven per cent of the patients reported that the radiologist had performed palpation of the breasts

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Table 1. Preoperative mammography results among 306 women with histologically confirmed breast cancer at surgery

Mammography result	Age ≤ 50 years n (%)	Age > 50 years n (%)	P
Malignant or probably malignant (class IV/V)	72 (58)	152 (84)*	
Indecisive (class III)	9 (7)	7 (4)	
Benign (class I/II)	43 (35)	23 (13)	< 0.0001

*Sensitivity of mammography to diagnose cancer: total positive/(total positive + false negative) × 100, i.e. (72 + 152)/72 + 152 + 43 + 23) × 100 = 77%.

in conjunction with mammography, and ultrasonography was performed in 54% of the patients at the time of mammography.

Clinical staging was done according to the UICC TNM classification [3]. There were 156 pT1, 117 pT2, 16 pT3, 14 pT4 and 2 pTX carcinomas in the series (1 case was primary breast sarcoma), and axillary nodal metastases (pN +) were present in 152 (50%) carcinomas (pN0, $n = 145$; pNX, $n = 8$). Distant metastases at the time of the diagnosis were found in 13 (4%) cases. Ninety (30%) carcinomas belonged to the postsurgical stage I, 169 (57%) to II, 24 (8%) to III, and 13 (4%) to IV. This stage distribution is similar to that found in unselected urban female population in Finland [4], although stage I breast cancer is slightly underpresented.

Statistical analysis

Frequency tables were analysed with the chi squared test or Fisher's exact *t*-test. The chi squared test for trend was used for ordinal variables. The distributions of time intervals from the date of mammography to surgery were analysed using Kruskal-Wallis's analysis of variance. All *P* values are two-sided.

RESULTS

Mammography correctly detected cancer in 224 (73%) of the 306 cases (true positives), was indecisive in 16 (5%) and false negative in 66 (22%). The rates of false negative findings in different hospitals were 18, 22 and 24% ($P = 0.77$). There was no difference in the primary tumour size (pT1 versus pT2 versus pT3–4, $P = 0.56$), axillary nodal status (pN1 versus pN+, $P = 0.45$), or postsurgical stage (stage I versus II versus III and IV, $P = 0.53$) between the true positive (class IV–V) and false negative (class I–II) cases.

A false negative mammogram was more common in women who were 50 years or younger than in those aged over 50 at the time of the diagnosis (35 versus 13%, respectively, $P < 0.0001$, Table 1). Tumours of lobular ($n = 43$) or one of the specialised types of histology (mucinous, $n = 7$; tubular, $n = 6$; medullary, $n = 4$; cribriform, $n = 3$; or papillary, $n = 2$) tended to be more often falsely negative or indecisive in mammography (23/65, 35%) than those of the ductal type (58/240, 24%, $P = 0.07$). There was no difference in the reported frequency of breast palpation performed by the radiologist between those who had a false negative mammogram (54% palpated) and those who had a true positive finding (58%, $P = 0.66$), nor was there any difference in the frequency of ultrasound examinations performed (48% of those with a false negative finding had an ultrasound examination versus 55% of the remaining patients, $P = 0.38$).

Women with a true positive mammogram had a median delay of 2 weeks (95% confidence interval from 2 to 3 weeks; range, from 0 to 18 weeks) to surgery as calculated from the date of mammography, whereas the median time interval from mammography to surgery was 5.5 weeks (2–10 weeks; range, from 0 to 22 weeks) in women who had an indecisive finding, and 8 weeks (5–13 weeks; range, from 0 to 240 weeks) in those with a false negative mammogram ($P < 0.0001$). A delay longer than 2 months from the date of mammography to the date of surgery took place in only 5 (2%) of the 224 true positive cases, whereas 6 (38%) of the women with an indecisive mammogram for cancer and 30 (45%) of those whose mammogram was false negative had a longer delay ($P < 0.0001$, Table 2). None of the women with a true positive mammogram had a delay longer than 6 months as compared with 19 (29%) women with a false negative mammogram ($P < 0.0001$).

Women with a false negative mammogram and longer delay than 2 months to surgery had a larger primary tumour size as compared with those with a shorter delay (pT2–4, 60% versus 26%, $P = 0.005$, Table 3). They also more often had positive axillary nodes for cancer (pN+, 60 versus 32%, $P = 0.03$) and higher postsurgical stage (stage II–IV 80 versus 50%, $P = 0.01$).

DISCUSSION

As many as 22% of all mammograms were false negative in women with histologically confirmed breast cancer, and the sensitivity of mammography to diagnose invasive breast cancer was 77% (Table 1). Although sensitivity of mammography has been found to exceed 90% in some centres [5], a fairly low sensitivity has been reported in many other studies. Edeiken [6] found 22% of women with palpable breast cancer had a false negative mammogram. In his review of six studies, the sensitivity of mammography for diagnosing breast cancer ranged from 42 to 87%, with a mean sensitivity of 77% among the total of 1403 women, which is similar to results we found.

Mammography was less sensitive among women younger than 50 compared with those over 50 at the time of the diagnosis. There is some evidence from screening trials for breast cancer that screening may be more efficient among women older than

Table 2. Time interval from the date of mammography to surgery

Mammography result	Time interval from mammography to surgery (months) 0–2 n (%)	3–4 n (%)	5–6 n (%)	7–12 n (%)	> 12 n (%)
Malignant (class IV/V)	219 (98)	4 (2)	1 (0)	0 (0)	0 (0)
Indecisive (class III)	10 (63)	4 (25)	2 (13)	0 (0)	0 (0)
Benign (class I/II)	36 (55)	8 (12)	3 (5)	9 (14)	10 (15)

Table 3. Size of breast cancer in 65 women with breast cancer and a false negative mammogram at the time of the diagnosis*

Variable	Time interval from mammography to surgery† ≤ 2 months *n* (%)	> 2 months *n* (%)	*P*
Primary tumour size			
pT1	26 (74)	12 (40)	
pT2–4	9 (26)	18 (60)	0.0005
Axillary nodal status‡			
pN0	23 (68)	12 (40)	
pN +	11 (32)	18 (60)	0.03
Postsurgical stage			
Stage I	17 (50)	6 (20)	
Stage II–IV	17 (50)	24 (80)	0.01

*1 patient with primary breast sarcoma was deleted from the analysis. †When a 3-, 4- or 6-month interval was tested instead of the 2-month interval, a P value < 0.05 was obtained for the primary tumour size with all cut-offs, and for axillary nodal status with the 3 month cut-off. ‡Postsurgical axillary nodal status was not available for 1 patient.

50 than among those younger than 50 [7, 8]. Edeiken found the false negative rate to be 44% among women of 50 or younger, and 13% among those more than 50 years of age [6]. The greater density of breast tissue causing more difficult interpretation of mammograms in premenopausal women is likely to explain the lower sensitivity of mammography in premenopausal women, at least partially.

The 2-month time interval from the date of mammography to surgery was chosen as a cut-off value to identify patients with delayed treatment. Although such an interval has no biological meaning, a 2-month interval has been recommended in the literature to distinguish women who have been left untreated after mammography from those treated for their breast tumour [2]. A 2-month interval appears to be appropriate in the present series as well, because only 2% of women with a true positive mammogram had surgery later than 2 months after mammography. This figure contrasts with the frequency of 45% found among women with a false negative mammogram (Table 2). Women with a delayed biopsy had often a large primary tumour size and positive axillary lymph nodes, which are both well established adverse prognostic factors in breast cancer [9]. Long-term survival has been found to be greater in patients with a shorter delay between the appearance of symptoms and diagnosis in breast cancer [10], but results at variance with this do exist [11].

There are little data in the literature on the effect of false negative mammography result on treatment delay. In a retrospective study from a single centre, Mann and colleagues [2] investigated the case histories of 36 women with breast cancer and with a mammogram interpreted as benign, and found that 19 (53%) of these patients had a tissue biopsy delayed for longer than 2 months. In accordance with the present study, they found that women with a longer than 2-month interval to tissue biopsy more often had axillary nodal metastases than those with a shorter delay (58 versus 18%).

Fine-needle aspiration biopsy has been recommended as the first-line examination in women with a breast mass, because it requires no special equipment, is quicker and less invasive than a core-needle biopsy, and extensive sampling is possible [1]. The overall accuracy of fine-needle biopsy in diagnosing breast cancer has been found to be generally greater than 95% [12], but such results may be affected by a publication bias, and may require an experienced cytopathologist. Fine-needle biopsy may be associated with a false negative rate of up to 35% and false positive rate up to 11% [12]. Mammography also needs to be carried out before surgery to diagnose occult multicentric cancer in the ipsilateral or the contralateral breast, and to provide more information on the nature of the tumour. Malignant or suspicious malignant finding in mammography may shorten the delay to surgery in some women with breast cancer. Preoperative mammography has also been recommended in order to determine the size of the cancer, but in a recent study, clinical measurement of breast cancer size was as accurate as that performed with mammography or ultrasonography [13].

We conclude that although mammography is able to detect the great majority of invasive cancers in women aged more than 50, approximately every third cancer may be missed in women who are younger than 50 at the time of the diagnosis. Too much reliance on the sensitivity of mammography to detect breast cancer may lead to a delay in the diagnosis of breast cancer, which in turn may lead to a larger primary tumour size and metastatic disease. We suggest that women with a palpable mass should be investigated with a needle or open biopsy.

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Plasminogen Activators and Plasminogen Activator Inhibitors in Blood and Tumour Fluids of Patients with Ovarian Cancer

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We quantitated urokinase and tissue plasminogen activator (u-PA, t-PA), plasminogen activator inhibitor 1 and 2 (PAI-1, PAI-2), and fibrinolytic activity in peripheral blood (PB), tumour blood (TB), peritoneal/ascitic fluid (PAF) and cystic fluid (CF) from 104 patients with benign and 36 patients with malignant ovarian tumours, and in peripheral blood from 62 healthy controls. PB levels of u-PA were higher in patients with benign and malignant tumours than in controls. High concentrations of u-PA were found in CF, but not in TB, suggesting that u-PA is released by the tumour tissue, but not by the tumour vasculature. PB levels of t-PA were higher in both tumour groups than in controls. Increased levels of t-PA were found in TB, but not in CF, indicating that t-PA is released by the tumour vasculature, but not by the tumour tissue. PB levels of PAI-1 were higher in patients with both benign and malignant tumours than in controls. High levels of PAI-1 were present in both TB and CF from malignant tumours, suggesting that PAI-1 is released from the tumour vasculature as well as the tumour tissue. Elevated concentrations of PAI-2 were found in CF, but not in TB, indicating release from the tumour tissue, but not from the vasculature. High levels of t-PA, PAI-1 and PAI-2 were found in PAF of malignant tumours, and resorption from this compartment may explain elevated PB levels in patients with ascites. None of the PAs/PAIs proved useful as a PB marker for detection of early stage ovarian cancer. However, an index based on PAF levels of t-PA and PAI-1 discriminated between malignant and benign ovarian cysts in the absence of ascites. In addition, our study stresses the importance of including patients with benign tumours as well as healthy controls when markers for malignant tumours are evaluated.

Key words: ovarian cancer, ovarian cyst, ascites, plaminogen activator, plasminogen activator inhibitor, tumour marker

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INTRODUCTION

TUMOUR GROWTH and spread involves proteolytic degradation of surrounding intercellular matrix by tumour cells. Several enzymes, e.g. collageneses, elastase, cathepsins and plasmin, are involved in this process [1]. Plasmin has a central function, since it acts both directly on certain matrix proteins i.e. fibronectin, laminin, entactin and fibrin, and indirectly as an activator of latent collagenases [2, 3]. Plasmin is formed after activation of the zymogen plasminogen, which is abundant throughout the extracellular space. Activation is catalysed by two specific serine proteases, tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA). t-PA is synthesised in a number of cell types, like vascular endothelial cells, macrophages and some tumour cells [4]. It binds with high affinity to fibrin, and is mainly involved in fibrinolysis and thrombolysis. u-PA, in contrast, is synthesised by many cell types, such as tumour cells and macrophages, during proliferation and migration [4]. It binds to specific receptors on the cell membrane, and activation