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Original Paper

Mammographic Screening for Breast Cancer. What Cancers Do We Find?

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The aim of this study was to compare lymph node involvement of breast cancer cases detected at mammography screening with clinically-detected cases. During a 3-year period, 273 primary breast cancers were detected in a population-based screening programme, and 149 primary breast cancers were diagnosed clinically. Lymph node involvement was evaluated in univariate and multivariate logistic regression models correcting for tumour size, histological grade, steroid receptor status and DNA-ploidy. Patients with screen-detected cancers had a low relative risk of having lymph node metastases (univariate, OR = 0.31; 95% confidence interval = 0.19–0.52). In the multivariate logistic regression model, the relative risk was halved (OR = 0.47; 0.28–0.78). The reduced risk was more pronounced for women younger than 50 years of age compared to older women. The risk for screen-detected cases of having lymph node metastases at diagnosis was statistically significantly lower than for clinically-detected cases. The marked reduction, even when correcting for tumour size, makes it less likely that factors such as detection of clinically innocent tumours, length bias sampling or clinical symptoms related to axillary metastases can explain the whole difference. The results indicate at least part of the effect may be explained by tumour progression in the late preclinical detectable phase.

Key words: breast neoplasms, mammography, mass screening

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INTRODUCTION

IT HAS been implied that the reduction in breast cancer mortality among women with screen-detected cancers results not only from the smaller tumour mass, but also from finding the tumours in an earlier, less aggressive state [1]. More *in situ* cancers and tubular cancers are detected by mammography screening compared to clinical detection [2]. Screening-detected cases less frequently have lymph node metastases and are less often poorly differentiated cancers than clinically-detected cases [3]. There are some cancers detected by screening that probably would never have been diagnosed clinically [4]. Their detection would cause an apparent shift in the prognostic factors towards a more favourable distribution among the cases detected by screening.

A reduction in breast cancer mortality in women 50–69 years of age because of mammography screening has repeatedly been shown [5–12], while the results of women 40–49 years of age are still inconclusive [13]. There are many tentative explanations for the differences in effect by age group; these range from study design and characteristics of the test, to considerations of tumour biology. One point is that premenopausal breast cancer progressives to an aggressive behaviour more rapidly and thus stays in a preclinical detectable and biologically favourable phase only for a very short time. Studies comparing histopathological character-

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istics, steroid receptor status, DNA-ploidy and other tumour characteristics of screen-detected cancers and clinically-detected cases show equivocal results. There are no clear indications of differences depending on age groups in this respect [14–17].

Presence of axillary lymph node metastases at the time of primary surgery is known to be the principal prognostic factor in breast cancer [18]. Thus, lymph node involvement can be seen as an indicator of metastatic capacity when the tumour diameter is controlled for, and used as a measure of tumour aggressiveness at detection. The aim of this study was to compare lymph node involvement between screen-detected and clinically-detected breast cancers, taking into account the tumour diameter, steroid receptor content, DNA ploidy and histopathological grading. Stratification by age group was used to examine possible differences in tumour biology between younger and older women.

PATIENTS AND METHODS

Women born between 1914 and 1948 who underwent surgery for a primary invasive breast cancer or cancer *in situ* during 1988–1990 were included in the study. The study cohort is a population-based series of consecutive cases. All were recruited from the primary catchment area of the three surgical departments that provide all in-patient surgical care in Uppsala County. This catchment area and the birth cohort correspond to the recruitment domain of the mammography screening programme of Uppsala County, Sweden [19]. The cohort was identified through the computerised database at the department of pathology and the computerised database at the mammography screening centre.

In 1988, a population-based mammography screening programme was started in Uppsala County, Sweden [19]. Women aged 40–74 years were invited to screening with an intended 18-month screening interval for women aged 40–54 years and a 24-month interval for women older than 55 years. During the first 8 months, the invitations to screening were limited to women older than 54 years and living in Uppsala City.

All screening films were processed and evaluated at the assessment centre at Uppsala University Hospital. If there was no suspicion of malignancy, the women were notified by mail. Otherwise, they were recalled to the assessment centre for further examination by the radiologist with complete mammography, cone-down projections, magnification, ultrasound, palpation and fine-needle aspiration biopsy, whenever indicated. The decision to refer a case for surgery was based on the mammographic diagnosis without awaiting the cytology diagnosis. Surgical treatment was performed at the University Hospital or in one of the two community hospitals in the county.

Women with clinically-detected lesions were referred for clinical mammography and fine-needle aspiration biopsy by their general practitioner, gynaecologist or surgeon. Patients for whom a malignant lesion could not be ruled out were referred for surgical treatment to one of the three departments of surgery in the county.

Sector resection and axillary dissection at levels I and II were routinely performed for invasive cancers. If multifocal tumours were suspected, or when tumours could not be radically resected with a satisfactory cosmetic result with breast conserving surgery, a mastectomy with axillary dissection at levels I and II was recommended. During 1988–1990, the median number of nodes investigated was seven. The axilla was not explored in women with cancer *in situ* or in women with a deteriorated general condition. Non-palpable lesions were pre-operatively localised with a hook-wire and the excised specimens were radiographed before histological examination.

All tumour specimens were examined at the Department of Pathology at the University Hospital. The tumour diameter was measured on the fresh specimen. Information about tumour diameter, axillary lymph node involvement, histopathological classification, oestrogen and progesterone receptor status and DNA ploidy were prospectively stored in a computerised database. All specimens were retrospectively and blindly evaluated for histological grade by a pathologist.

Oestrogen receptor (ER) and progesterone receptor (PR) analyses were made by an immuno-assay according to the manufacturer's description (ER-EIA, PgR-EIA, Abbot Laboratories, North Chicago, Illinois, U.S.A.). Tumour specimens were stored at −70 C for no more than 2 weeks before analysis. The amount of receptor was related to the DNA content of the specimen analysed and, when dichotomised into positive and negative, a cut-off level of 0.10 fmol/μg DNA was used. The DNA contents of tumour cells were analysed by flow cytometry. Tumour cell populations with an S1 peak more than 10% over the normal euploid value (i.e. >1.10) were considered aneuploid.

Uni- and multivariate logistic regression models were constructed using the SAS package. In some analyses—as specified below—the diameter in mm and age in years were used as continuous variables, but otherwise the variables were categorised. Variables with more than two categories were represented in the models by dummy variables. The esti-

Table 1. Breast cancer detection mode by age group

	Clinically-detected				Screen-detected			
Age group	Before invitation	Non-attenders	Interval cancers	Total clinical	First round	Second round	Total screening	All cancers
40–49	21	2	12	35	28	10	38	73
50–59	24	6	11	41	62	16	78	119
60–69	25	2	11	38	74	9	83	121
70–76	21	4	10	35	70	4	74	109
Total	91	14	44	149	234	39	273	422

Table 2. Comparison of some tumour characteristics between screen-detected and clinically-detected cancers

Detection	Tumour diameter mean (S.D.) mm	Tumour diameter >20 mm	Axillary nodes involved	ER-negative*	PR-negative*	Aneuploid	*In situ*	Grade III
Screening	16.5 (11.0)	25.8%	19.6%	33.0%	26.7%	62.6%	10.6%	30.4%
Clinically	22.3 (18.3)	58.8%	39.2%	32.2%	24.8%	70.5%	8.7%	49.0%

*Oestrogen receptor and progesterone receptor less than 0.10 fmol/μg DNA.

mates from the models are shown as odds ratios (OR) with 95% confidence intervals.

RESULTS

A total of 422 cases of breast cancers were diagnosed, of which 273 were screen-detected and 149 clinically-detected (Table 1). For women younger than 50 years of age, there was a similar number of cases detected by screening as detected clinically: 38 versus 35 cases. For women over 50 years of age, approximately twice as many were detected by screening as detected clinically: 235 versus 114 cases.

The proportion of tumours larger than 20 mm and tumours with lymph node metastasis was greater in the clinically-detected group than in the screening-detected group (Table 2). Oestrogen and progesterone receptor negativity was similar in the two groups. Slightly more aneuploid cancers were found in the clinically-detected group. Proportionally more grade III cancers were found among the clinically-detected cases.

A total of 42 cases were diagnosed with cancer *in situ*, 29 were detected through screening, and 13 were detected clinically. The cases with cancer *in situ* were excluded from further analysis.

Lymph node involvement

All cases. A total of 380 cases of primary invasive cancers were diagnosed, of which 244 were detected by screening and 136 detected clinically. Information concerning lymph node status was missing for 29 cases. Axillary lymph node metastases were present in 96 (27%) of 351 cases with known lymph node status. The proportion of lymph node metastases was twice as high among the clinically-detected cases: 51 (40%) of 127 clinically-detected cases compared to 45 (20%) of 224 screen-detected cases.

Screen-detected cancers ran a significantly lower relative risk of having lymph node metastases with an OR of 0.31 in the univariate analysis (Table 3). Each increment by 1 mm in tumour size was associated with a 6% increase in risk. In a multivariate logistic regression model corrected for tumour size, the relative risk was still significantly lower for the screen-detected cases with an OR of 0.45 (Model I). Further models were made, corrected for ploidy, receptor negativity and histological grading. Even in this complex model, the screen-detected cancers ran a significantly reduced relative risk of lymph node metastases (OR = 0.47).

Younger women. A total of 62 cases of primary invasive cancers were diagnosed among women aged 40–49 years; 30 were detected by screening, and 32 were detected clinically. Axillary lymph node metastases were present in 17 (29%) of 58 cases with known lymph node status. Lymph node involvement was a much more common finding among the clinically-detected cases: 15 (52%) of 29 clinically-detected cases compared to 2 (7%) of 29 screen-detected cases. There was no difference in lymph node involvement between clinically-detected cases diagnosed before invitation and those diagnosed in the interscreening interval: 8 of 16 cases and 5 of 11 cases, respectively. All 8 cases diagnosed in the second screening round were node-negative, while 2 of 21 cases diagnosed in the first round had lymph node metastases.

The risk of having lymph node metastases was assessed in logistic regression models. In a multivariate model corrected for tumour size, screen-detected cases in the age group 40–49 years had a significantly reduced relative risk of having lymph node metastases with an OR of 0.08 (0.02–0.43) (Table 4). Models corrected for grade and receptor status (ER and PR) gave virtually the same results (numbers not shown).

Table 3. Lymph node involvement related to tumour characteristics (all invasive cancers)

	Univariate estimates	Model I multivariate	Model II multivariate	Model III multivariate	Model IV multivariate
Screen-detected	0.31 (0.19–0.52)	0.45 (0.27–0.75)	0.45 (0.27–0.75)	0.45 (0.27–0.74)	0.47 (0.28–0.78)
Clinically-detected	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Diameter, cont. (mm)	1.06 (1.03–1.08)	1.05 (1.02–1.07)	1.05 (1.02–1.07)	1.05 (1.02–1.07)	1.04 (1.01–1.06)
Aneuploidy			1.21 (0.69–2.10)	1.21 (0.70–2.10)	0.99 (0.55–1.77)
Receptor-negative*				0.83 (0.42–1.63)	0.78 (0.39–1.56)
Grade I					1.00 (ref.)
Grade II					3.33 (1.22–9.11)
Grade III					4.41 (1.57–12.33)

*Oestrogen receptor and progesterone receptor less than 0.10 fmol/μg DNA.

Logistic regression models. Odds ratios (OR) and 95% confidence interval (CI) of having lymph node metastases at primary surgery. Only women with invasive cancers and informtion on axillary status were included. Univariate risk estimates for screen-detected compared to clinically-detected and relative to diameter. Multivariate models are stepwise corrected for diameter, DNA-ploidy, receptor negativity (ER and PR) and histological grading.

Table 4. Lymph node involvement related to tumour characteristics, stratified by age group

	Age group 40–49 years	Age group 50–76 years
Clinically-detected	1.00 (ref.)	1.00 (ref.)
Screen-detected	0.08 (0.02–0.43)	0.58 (0.33–1.01)
Diameter, cont. (mm)	1.06 (1.00–1.13)	1.05 (1.01–1.07)

Age groups 40–49 years and 50–76 years analysed separately. Only women with invasive cancers and information on axillary status were included. Logistic regression models. Odds ratios (OR) and 95% confidence interval (CI) of having lymph node metastases at primary surgery. Multivariate model corrected for tumour size.

Older women. A total of 318 cases of primary invasive cancers were diagnosed among women over 50 years of age; 214 were detected by screening, and 104 were detected clinically. Axillary lymph node metastases were present in 79 (27%) of 293 cases with known lymph node status. As expected, axillary lymph node metastases were more common among the clinically-detected cases: 36 (37%) of 98 clinically-detected cases compared to 43 (22%) of 195 screen-detected cases.

In the multivariate model corrected for tumour size, screen-detected cases in women aged 50 years or older had a non-significant reduced relative risk of having lymph node metastases with an OR of 0.58 (0.33–1.01) (Table 4). Models correcting for grade and receptor status (ER and PR) gave similar results (numbers not shown).

The age factor was further tested. The beta-estimate for interaction for age under 50 years and screen-detection was statistically significant ($P = 0.02$).

DISCUSSION

The risk of patients with screen-detected invasive breast cancers having lymph node metastases was less than half that of patients with clinically-detected cancers. The lower risk was evident even after correction for tumour size, DNA-ploidy, receptor negativity (ER and PR) and histological grading. The lower risk was more pronounced for women younger than 50 years of age compared to older women.

Correction for tumour size can be considered as an over-correction since the aim with screening is to detect breast cancer earlier, and thus with a smaller size. However, if anything, correction for tumour size leads to an underestimate of the differences between screen-detected cancers and clinically-detected cancers. This is reflected by the rise in OR when the multivariate models are compared to the univariate model in Table 3. Nevertheless, correcting for tumour size helps us to determine whether the metastatic potential is different in screen-detected cases compared to clinically-detected cases. If the metastatic capacity, defined as the risk of having axillary metastases given a certain tumour size, was the same in the two tumour groups, one would expect the OR in Model II in Table 3 to come close to 1.0. The other factors corrected for in Models III and IV do not seem to explain the difference between screen-detected and clinically-detected cases, either. Thus our analysis does not refute the idea that tumour progression occurs.

Another possible explanation is that screening mammography systematically detects cancers with inherently less metastatic potential and misses other more aggressive tumours. However, this is less likely to be the only determinant of our outcome, since randomised breast cancer screening trials have repeatedly shown a reduction in breast cancer mortality rate [5, 20, 21]. Thus, many screen-detected cancers are potentially capable of disseminating, but are diagnosed before they have developed the capacity or have had the time to give rise to clinically important micro-metastases. One important aim of mammography screening is to detect breast cancers before they disseminate. The results indicate that this was accomplished in many cases in the Uppsala screening programme.

Screening tends to sample more slow-growing cases—i.e. length bias sampling [22]. In our study, length bias sampling might be exaggerated compared to a randomised trial, for two reasons. The study period was dominated by the first screening round in which length bias sampling is more noticeable than in subsequent screening rounds. Furthermore, because of the study design, the clinical group was probably deprived of some slow-growing cancers that would have been diagnosed clinically within the study period had they not been detected by screening. However, length bias sampling is not likely to be the only explanation to our results. Furthermore, observations on interval cancers suggest that there is no direct parallel relationship between growth rate and metastatic capacity [23].

A fourth more speculative explanation could be that there might be some subtle symptoms associated with lymph node involvement. Thus, some breast cancers with lymph node metastases might be diagnosed clinically at a smaller size than an otherwise comparable case without lymph node involvement.

There are two explanations for the high clinical to screen-detected ratio for women aged 40–49 years. Women aged 40–54 years were generally invited later to screening than older women during the study period. Therefore, the younger women were at risk for longer before being diagnosed with breast cancer before invitation to screening. Another explanation is the fact that the ratio of interval cancers to screen-detected cancers was higher for younger women than for older women [24].

We cannot explain the difference in lymph node involvement by age group. A chance finding in a subgroup analysis must be considered. The confidence interval for the risk of women younger than 50 years of age having lymph node metastases was wide (0.02–0.43), and the reduced risk for older women was close to significant (0.33–1.01). However, the statistically significant interaction term is not readily explained by chance.

In spite of a significantly lower reduced risk of having lymph node metastases for screen-detected invasive cancers for women aged 40–49 years, the proportion of all invasive breast cancers with lymph node metastases was the same for women younger and older than 50 years of age. Thus, it should be possible to reduce the proportion of invasive breast cancers with lymph node metastases for women under 50 years old by shortening the screening intervals, thereby detecting more cases with screening.

In conclusion, it is likely that the difference in risk of having lymph node metastases between screen-detected cases and clinically-detected cases is, at least, partly due to biological differences—i.e. that tumour progression occurs late in the preclinical detectable phase. However, the non-experimental study design does not allow for an unbiased quanti-

tative estimate of that phenomenon. The difference by age group may be explained by the study design, but since it was so striking, it may also reflect a biological reality which may be further explored to understand why the results from mammography screening differ when broken down by age group.

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