Eur J Cancer Clin Oncol, Vol. 23, No. 7, pp. 959–962, 1987.
Printed in Great Britain

0277–5379/87$3.00+0.00
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Detection Method, Tumour Size and Node Metastases in Breast Cancers Diagnosed During a Trial of Breast Cancer Screening

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Abstract—*The relationship between tumour size and lymph node metastases was examined in screening-detected and clinically detected breast cancers. The data used were from a randomized trial of breast cancer screening wih mammography. 964 cancers were reviewed, in both arms of the trial, in women aged 40–74. Lymph node status was significantly related to detection method* ($P < 0.001$), *metastases being less common in screening-detected cancers. Node status was also significantly related to tumour size* ($P < 0.001$), *metastases being commoner in larger tumours. Similarly, tumour size was significantly associated with detection method* ($P < 0.001$), *smaller tumours being detected by screening. No significant interaction was observed among all three factors, indicating that the relationship between node status and tumour size did not change with detection method. When detection method was replaced with randomly allocated study (invited to screening) and control (not invited to screening) groups, the same results were observed. It is concluded that if screening detects tumours with a different natural hisory to that of those which surface clinically, this is not reflected in the relationship between tumour size and lymph node metastases.*

INTRODUCTION

IT HAS BEEN suggested that screening for breast cancer may detect tumours with a natural history and a lethal potential distinct from those which surface clinically [1]. Indeed, there is a suspicion that screening can lead to overtreatment by detecting tumours which will never be dangerous [2]. If screening does tend to diagnose less dangerous tumours, a spurious benefit of screening may be observed. In assessing the effects of screening programmes, this problem can be avoided by randomization, analysing mortality from breast cancer as the outcome variable, and comparing the two randomized groups on an "intention to treat" basis [3]. Nevertheless, suspicion about the presence of the phenomenon persists, even though its misleading effects can be avoided.

One potential manifestation of the phenomenon might be that two tumours of the same physical size might take differing periods of time to invade the regional lymph nodes. The data recorded in the randomized controlled trial of screening for breast cancer in Kopparberg county, Sweden, yield an opportunity to test this hypothesis.

MATERIALS AND METHODS

The two-county Swedish trial is a population-based, randomized trial of breast cancer screening by mammography in the counties of Kopparberg and Östergötland in Sweden. The design and methodology of the trial have already been described [4]. In Kopparberg county, 1252 cancers were diagnosed between July 1977 and February 1986. Including only unilateral tumours among women aged 40–74, there were 964 cases. 674 of these were in the group invited to screening and 290 in the control group. Of the former, 461 were actually detected by screening, 13 were diagnosed between randomization and commencement of screening, 135 were diagnosed between screening visits and 52 occurred among women refusing to take part. The remaining 13 cases were in elderly women

Accepted 2 January 1987.
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whose cancer was diagnosed after they had reached the age of 70, when they were no longer invited for screening.

Statistical analysis was by logistic regression of presence or absence of lymph node metastases on tumour size and detection method [5]. This approach provides:

1. Odds–ratio estimates of risk of metastases for screening-detected relative to clinically detected tumours, adjusted for tumour size, and vice versa, i.e. relative risk estimates for different tumour size categories adjusted for detection method;
2. separate odds–ratio estimates of risk of metastases by screening status, in each tumour size category, and
3. log-likelihood ratio chi-squared tests for significance of the above effects.

A significant deficit risk of metastases in screening-detected tumours after adjustment for tumour size might suggest a fundamental difference in the natural history of some screening-detected tumours, but this could also be attributed to the effect of early detection. A significant *interaction*, however, between tumour size and detection method would be strong evidence that the relationship between tumour size and lymph node metastases is different in screening-detected tumours, to that in tumours detected clinically. In risk terms, this would be manifested by a significant difference among tumour size categories, in relative risks of metastases for screening-detected relative to clinically surfacing tumours.

For purposes of formal statistical analysis, the *in situ* tumours were included in the 1–9 mm size group.

RESULTS

Node status and tumour size by detection method (by screening or clinically, i.e. in the control group or in the screened group but detected before screening commenced, between screening visits or among women who refused to participate) are shown in Table 1(a) and (b). Both are significantly associated with detection status, the clinical group being more prone to larger tumours and lymph node metastases. As can be seen from Table 1(c), tumour size and node status are significantly related to each other, metastases tending to occur in the larger tumours. The odds–ratio estimate of risk of metastases for screening-detected relative to clinically detected cancers, adjusted for tumour size, was 0.76. This was not significantly different from unity. The effect of tumour size was significant when adjusted for detection method. Relative to a tumour size of less than 10 mm (including *in situ* tumours) the detection method-adjusted risks of metastases for tumour size categories 10–14, 15–19 and 20 mm or more, were 23.7, 52.1 and 128.4. Note that when those with node status and/or tumour size unknown were excluded, this left 833 cases. The unrecorded quantity was in most cases lymph node status, usually for one of the following reasons: inadequate axillary exacresis, an inoperable tumour or the patient's poor condition (particularly in conjunction with a minimal finding).

Table 1. Pairwise tabulation of 964 breast cancer cases by detection group, lymph node status and tumour size

(a) *Detection group by tumour size*

Detection group	Tumour size (mm) 0/I.S.	1–9	10–14	15–19	20+	Total	N.K.
Screening	42	96	120	92	106	456	5
(%)	(9)	(21)	(26)	(20)	(23)	(100)	
Clinical	26	32	71	84	274	487	16
(%)	(5)	(7)	(15)	(17)	(56)	(100)	
Total	68	128	191	176	380	943	21
(%)	(7)	(14)	(20)	(19)	(40)	(100)	

Chi-squared = 122.1 on 4 degrees of freedom, $P < 0.001$.

(b) *Detection group by lymph node metastases*

Detection group	Lymph node metastases? No	Yes	Total	N.K.
Screening(%)	327 (80)	83 (20)	410 (100)	51
Clinical(%)	267 (61)	168 (39)	435 (100)	68
Total(%)	594 (70)	251 (30)	845 (100)	119

Chi-squared = 34.1 on one degree of freedom, $P < 0.001$.

(c) *Tumour size by lymph node metastases*

Lymph node status	Tumour size (mm) 0/I.S.	1–9	10–14	15–19	20+	Total	N.K.
No metastases	36	112	153	121	170	592	2
(%)	(6)	(19)	(26)	(20)	(29)	(100)	
Metastases	0	1	25	45	170	241	10
(%)	(0)	(0)	(10)	(19)	(71)	(100)	
Total	36	113	178	166	340	833	12
(%)	(4)	(14)	(21)	(20)	(41)	(100)	
N.K.	32	15	13	10	40	110	9

Chi-squared = 150.7 on four degrees of freedom, $P < 0.001$.
N.K. = not known.

The data are tabulated by the three factors, tumour size, detection method and lymph node metastases in Table 2. There was no significant interaction between the three factors, indicating that the relative risks of metastases by detection method did not differ significantly between tumour size categories (this also means that relative risk of metastases for a given tumour size, relative to the baseline of 0–9 mm was not significantly affected

Table 2. Three-way tabulation of 833 tumours by lymph node status, tumour size and detection group, with results of logistic regression analysis

Tumour size	Lymph node status		Detection method: Screening		Clinical		Total	Relative risk* (95% CI)
0/*in situ*	No metastases	(%)	22	(100)	14	(100)	36	0.12†
	Metastases	(%)	0	(0)	0	(0)	0	(0.004,3.12)
	Total		22		14		36	
1–9 mm	No metastases	(%)	86	(100)	26	(96)	112	
	Metastases	(%)	0	(0)	1	(4)	1	
	Total		86		27		113	
10–14 mm	No metastases	(%)	100	(88)	53	(83)	153	0.67
	Metastases	(%)	14	(12)	11	(17)	25	(0.28,1.56)
	Total		114		64		178	
15–19 mm	No metastases	(%)	64	(74)	57	(71)	121	0.85
	Metastases	(%)	22	(26)	23	(29)	45	(0.43,1.69)
	Total		86		80		166	
20+ mm	No metastases	(%)	54	(55)	116	(48)	170	0.77
	Metastases	(%)	45	(45)	125	(52)	170	(0.48,1.23)
	Total		99		241		340	

Log-likelihood ratio chi-squared on three degrees of freedom for a three-way interaction is 2·4.
*Odds-ratio estimate of risk of metastases for screening detected relative to clinically detected tumours, and 95% confidence interval on the relative risk.
†For purposes of formal inference, the first two tumour size categories were merged.

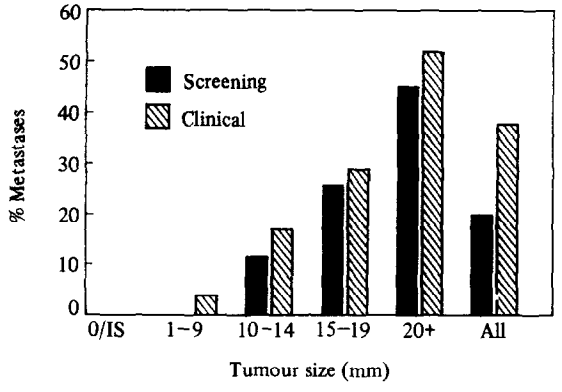

Fig. 1. Percentage of lymph node metastases in categories of tumour size for the screening-detected and clinically detected cancers.

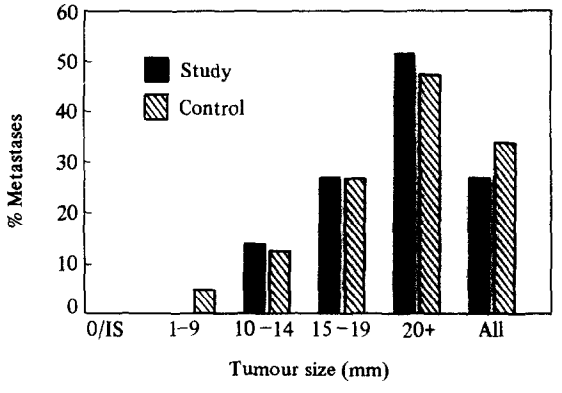

Fig. 2. Percentage of lymph node metastases in categories of tumour size for cancers in the study (invited to screening) and control (not invited to screening) groups.

by detection method). Data are displayed as percentages with metastases in Fig. 1. Here, the similarity between the tumour size/node status associations is more evident. Although the rate of metastases appears to differ proportionally between detection groups for tumour size 1–9, this is based on one case of metastases in the clinically detected group and none in the screening-detected, and is not statistically significant (Fisher's exact test, $P = 0.3$).

As a further check, the above analysis was repeated with detection method replaced by randomized group (invited to screening or not). The results were substantially similar and the three-way interaction was not significant (see Table 3). Percentages with metastases for each category of tumour size and each group are displayed in Fig. 2.

DISCUSSION

Probably the most important results above are the negative ones. The relationships between detection method and node status and detection method and tumour size are as we would expect. That lymph node metastases occur more frequently in larger tumours is already known, as is the relationship of both to distant metastases [6]. The lack of a difference between the relationships of tumour size and lymph node status is notable, although it is not entirely unprecedented. Gibbs [7] found that the percentages with metastases in those with tumour

Table 3. Three-way tabulation of 833 tumours by lymph node status, tumour size and study groups/control group memberships, with results of logistic regression analysis

Tumour size	Lymph node status		Randomized group: Study		Control		Total	Relative risk* (95% CI)
0/*in situ*	No metastases	(%)	29	(100)	7	(100)	36	0.07†
	Metastases	(%)	0	(0)	0	(0)	0	(0.002,1.77)
	Total		29		7		36	
1–9 mm	No metastases	(%)	94	(100)	18	(95)	112	
	Metastases	(%)	0	(0)	1	(5)	1	
	Total		94		19		113	
10–14 mm	No metastases	(%)	120	(86)	33	(87)	153	1.03
	Metastases	(%)	20	(14)	5	(13)	25	(0.37,2.85)
	Total		140		38		178	
15–19 mm	No metastases	(%)	89	(73)	32	(73)	121	0.97
	Metastases	(%)	33	(27)	12	(27)	45	(0.45,2.09)
	Total		122		44		166	
20+ mm	No metastases	(%)	96	(48)	75	(52)	170	1.18
	Metastases	(%)	103	(52)	67	(48)	170	(0.76,1.82)
	Total		199		141		340	

Log-likelihood ratio chi-squared on three degrees of freedom for a three-way interaction is 3.9.
*Odds–ratio estimate of risk of metastases for study group tumours relative to control group, and 95% confidence interval on the relative risk.
†For purposes of formal inference, the first two tumour size categories were merged.

size 1–2 cm and > 2 cm are broadly comparable between screened and control groups. The present results indicate that the similarity occurs when tumour size is classified more minutely, and between methods of detection. The above findings also hold if the grouping factor is "invited to screening", regardless of detection method, or "not invited to screening". However, it is important to consider the differences, or absences thereof, between detection groups, since if an "over-diagnosis" phenomenon is active, it will be manifest in those cases detected by screening rather than those randomly selected for invitation. The results presented here, as can particularly be seen from Figs 1 and 2, indicate that if such a phenomenon is present, it is not manifested in the association between tumour size and lymph node metastases.

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