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## Original Paper

# Interval Cancers and Cancers in Non-attenders in the Östergötland Mammographic Screening Programme. Duration Between Screening and Diagnosis, S-phase Fraction and Distant Recurrence

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**The study was based on a population mammographic screening programme for women aged 40–74 years. Metastatic potential was analysed in 843 invasive breast cancers with regard to mode of detection and a number of prognostic factors. There was a higher metastatic capacity in clinically detected cases, but multivariate analyses showed that neither the mode of detection (hazard rate ratio of distant recurrence RR = 1.39, 95% CI 0.78–2.46 interval cancers and RR = 1.6, 95% CI 0.76–3.36 non-attenders) nor the duration between screening and diagnosis for true interval cancers (RR = 0.47, 95% CI 0.16–1.35 in tumours detected later than one year after screening) were independent prognostic factors. A correlation was found between metastatic potential and the SPF (RR = 2.94, 95% CI 1.57–5.50 in tumours with a high SPF), the oestrogen receptor status and the tumour stage. In conclusion, interval cancers intrinsically are not different from other breast cancers with equivalent characteristics; the duration between screening and diagnosis in interval cancers was not clearly correlated to the prognosis, but the S-phase fraction was a powerful predictor of prognosis.** © **1997 Elsevier Science Ltd.**

**Key words: screening, interval breast cancer, S-phase fraction, distant recurrence, metastatic potential**

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## INTRODUCTION

FOUR SUBGROUPS of breast cancers can be identified by mode of detection in a female population offered mammographic screening: (a) *prevalent cancers*, detected at the first screening round; (b) *incident cancers*, detected at the subsequent rounds; (c) *non-attender cancers*, presenting in invited women who failed to attend for screening; and (d) *interval cancers*, i.e. those diagnosed in women between two consecutive screening rounds following a negative screen. In the latter subgroup we recognise *true interval cancers* where even retrospectively there are no abnormal mammographic features on the preceding screening mammograms; *observer errors* with signs of malignancy overlooked at the preceding screen; *misinterpreted cases* with detectable but non-specific signs on the preceding mammograms; and *mammographically occult tumours* where no abnormal mammographic findings were present at the time of diagnosis despite the clinical signs of breast cancer.

Biologically breast cancers are a non-homogeneous group of tumours that vary in growth rate, metastatic potential and prognosis. Previous studies have shown a higher pro-

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portion of slow-growing tumours with a lower metastatic potential and a more favourable prognosis in screen detected cancers [1–6], particularly in tumours detected in the prevalent screening round [6, 7].

It has been suggested that interval cancers constitute a group of more aggressive tumours with a faster growth rate, shorter relapse-free period after treatment and poorer prognosis [6–10]. In the Malmö mammographic screening trial, interval cancers were found to be more aggressive and associated with a lower survival rate than was the case for the total cancers in the non-screened control population [2, 10]. In other studies, however, no statistically significant difference in prognosis was found between the two groups [11–15]. The association of poor prognosis with a short duration between diagnosis of the interval cancer and the previous negative screen has been suggested by some authors, [8–10, 16], but this relationship could either not be confirmed or was contradicted by others [11, 12, 17].

A higher mortality from breast cancer in clinically presenting cases, probably explained by a more advanced stage at diagnosis, has been confirmed in several studies [1, 2, 4, 15, 18]. However, the results from screening trials may not be directly applicable to service screening.

The aim of this study was to investigate prognostic differences among the four subgroups of invasive breast cancers detected in a dynamic population of women aged 40–74 years offered regular mammographic screening. Furthermore, we focused on metastatic potential and its possible correlation with cell proliferation rate (S-phase fraction, SPF) in all subgroups and for interval cancers we explored the significance of the duration between diagnosis and the previous screen. The first report of distant recurrence was chosen as the endpoint of interest for the present study.

## PATIENTS AND METHODS

In Östergötland county, mammographic screening was carried out between 1978 and 1986 as part of a randomised controlled trial, the Swedish Two-County Study [1]. Since 1987 a population mammographic screening programme has been available for women aged 40–74 years. The mean eligible female population in the county was 81 000 during the period of this study, 1987–1992.

The screening programme includes both prevalent screening examinations (those attending at their first screening invitation) and subsequent incident screening examinations (those attending as a result of a second or later routine screening invitation whether they accepted their previous invitations or not). Some 40 000 women were invited each year, the rescreening interval being approximately 18 months for women aged 40–54 years and 3 years for older women (Table 1).

Two-view (oblique and cranio-caudal) mammography was carried out at the first screening visit with a single oblique view being used for subsequent screens except for women with radiologically dense breast tissue as determined by the radiologist interpreting the preceding screen who could request the addition of the cranio-caudal view at the subsequent screen. The mammographic appearance of breast tissue was clarified according to Wolfe [21].

Women whose mammograms showed a possible suspicious abnormality were recalled and re-examined with three-view (cranio-caudal, oblique and latero-medial) mammography and if necessary with other complementary projections or coned compression views with or without microfocus magnification. If the suspicion of malignancy could still not be ruled out, the diagnostic work-up was continued on the same day in the mammography department, with clinical examination and fine-needle aspiration biopsy, the diagnosis being discussed with the patient. The assessment of self-referred clinical cases was carried out at one of four hospitals in the county in a similar way.

All cases with a previous history of ipsi- or contralateral breast cancer or other breast malignancies were excluded as were all *in situ* carcinomas ($n = 67$). A further five cases were excluded since data on size or lymph node status were not available.

The study comprised 128 cancers detected at the prevalent screen; 368 detected at an incident screen; 85 cancers detected in non-attenders and 262 interval cancers.

Among the cases detected at an incident screen ($n = 368$), 10 women (2.7%) were identified who did not accept any of their previous invitations. These tumours were *de facto* prevalent screen detected. However, these cases were not excluded as the number was very small and they did not disturb the comparison of clinically detected with screen detected tumours. A further 22 women (6.0%) in this subgroup of incident screen detected tumours had attended for their first and later routine screening rounds but did not accept the invitation preceding their current screening round, thus extending the last rescreening interval.

Interval cancers were defined as those diagnosed in previously healthy women between two consecutive screening rounds, when the earlier examination failed to reveal an

*Table* 1. *Age distribution and attendance rate in the prevalent and the incident screenings and mean age-specific breast cancer incidence in the Östergötland county during* 1987–1992

| | Prevalent screening | | Incident screening | | All women |
|---|---|---|---|---|---|
| Age group (years) | No. of invitations | Attendance rate (%) | No. of invitations | Attendance rate (%) | Breast cancer incidence per 100 000 women per year |
| 40–44 | 23 014 | 86.0 | 34410 | 84.4 | 114 |
| 45–49 | 6360 | 86.2 | 42635 | 84.9 | 172 |
| 50–54 | 3222 | 85.5 | 32725 | 84.2 | 198 |
| 55–59 | 3501 | 84.6 | 17505 | 83.9 | 197 |
| 60–64 | 4278 | 83.5 | 19629 | 82.5 | 250 |
| 65–69 | 4386 | 81.3 | 21688 | 78.5 | 292 |
| 70–74 | 3864 | 75.5 | 19192 | 71.0 | 306 |
| Total | 48 625 | 84.4 | 187 784 | 82.2 | |

abnormality. There was no time limit for the interval between the last screen and diagnosis except for women older than 74 years when interval cancer was considered to be a cancer diagnosed within two years from the previous screen. All relevant mammograms of the interval cancer cases were rescrutinised and cancers categorised as true interval cancers, overlooked, misinterpreted, or mammographically occult lesions.

For non-attenders, cancers in women older than 74 years were included if the tumour was detected within two years from the last invitation.

Tumour size was measured as the widest diameter on histological sections of the specimen. TNM classification as defined by the International Union against Cancer was used. During the study period, no regular grading of ductal carcinoma was carried out.

Oestrogen receptor (ER) status, DNA ploidy and SPF were routinely assessed except for very small tumours since for each of these analyses a sample of tumour some 3 mm wide is required. In practice, full analysis was routinely performed only on tumours 7–9 mm or larger. ER status alone was usually obtained for tumours of 6–8 mm. Somewhat different procedures in handling the samples and accidental technical problems occasionally caused loss of data even in larger tumours.

ER concentrations below 0.3 fmol/mg DNA were considered as negative (ER–), values of 0.3 fmol/mg DNA or higher as positive (ER+). Data on ER status were not available in 69 screen-detected (14%), 31 interval (12%) and 13 non-attender cancers (15%).

DNA flow cytometry was performed for estimation of SPF and assessment of abnormalities in cellular DNA content (DNA ploidy). An SPF below 5.0% was considered as low, values 5.0–9.9% as medium and 10.0% or more as high. Data on SPF were not available for 156 screen-detected (31%), 77 interval (29%) and 26 non-attender cancers (31%). Data on DNA ploidy were not available in 106 screen-detected (21%), 52 interval (20%) and 19 non-attender cancers (22%).

All cases were offered surgical and adjuvant therapy in accordance with the Treatment Programme of the Oncological Centre in Linköping. In general, women with tumours around 30 mm or smaller had breast-conserving surgery with postoperative radiotherapy. Patients aged 40–49 years with stage II and III cancers were given the opportunity to participate in a trial comparing tamoxifen medication with a combination of tamoxifen and Gosereline (Zoladex®) for two years postoperatively. Patients with an increased risk of recurrence (lymph node metastasis and ER–) were offered CMFchemotherapy (a combination of Cyclofosfamide, Methotrexate and Flourouracil). Patients aged 50–75 years with stage II and III cancers were offered adjuvant therapy within a trial comparing postoperative tamoxifen medication for 2 or 5 years. The treatment protocol was not changed for any of the groups over the period of the study.

The diagnostic and follow-up data were obtained from the records at the Mammography Screening Clinic and the Oncological Centre, University Hospital Linköping and the Cytology and Pathology Departments in the county. Data were obtained from the treating hospital for the single patient treated in another county.

The endpoint of interest for this study was the first report of distant recurrence, directing attention to the metastatic potential of the tumour rather than the overall survival of the patient since the follow-up time was rather short.

Chi-squared tests for contingency were performed to test the comparability of categorical variables and when applicable ordered variables were used. The prediction of SPF by detection mode and other variables was analysed using multiple regression.

The Cox proportional hazards method was used in order to investigate the effects of mode of detection and other prognostic variables on the malignant potential. The incident screen detected tumours were used for reference. The product-limit method was used for estimation of cumulative probabilities of recurrence-free interval for the different modes of detection of breast cancer and for the subgroups of interval cancers. Women with breast cancer who died of other causes were censored [22].

## RESULTS

The ratio of age-specific interval cancer incidence to age-specific breast cancer incidence in the county (Table 1) was 0.28 in women aged 40–49 years, 0.29 in women aged 50–59 years, 0.23 in women aged 60–69 years and 0.20 in the oldest group. The ratio of age-specific incidence of interval cancers detected within 12 months after the preceding screen to age-specific breast cancer incidence in the county was 0.26 in women aged 40–49 years, 0.16 in women aged 50–59 years, 0.10 in women aged 60–69 years and 0.07 in the oldest group.

Histopathological classification showed that screen detected cases consisted of 83% ductal carcinoma, 14% lobular carcinoma and 3% other types. Among interval cancers there was 82% ductal carcinoma, 12% lobular carcinoma and 6% other types and for cancers in non-attenders there was 88% ductal carcinoma, 7% lobular carcinoma and 5% other types.

Among screen-detected cancers there was a higher proportion of DNA diploid tumours in the prevalent compared to the incident lesions ($P = 0.054$). The non-attender cancers when compared with screen detected tumours were larger, with a higher proportion having lymph node metastases and more advanced stage at the time of diagnosis (all $P < 0.0001$). There were more ER negative and DNA aneuploid tumours ($P = 0.028$ res. 0.030), but no significant differences in age distribution or SPF (Table 2).

Compared to the screen-detected tumours, interval cancers occurred more frequently in younger women (both 40–49 years and 50–59 years), were larger tumours with a higher proportion having lymph node metastases and were more advanced tumours often being stage II or more (all $P < 0.0001$). Interval cancers also had a higher proportion of ER negative and DNA aneuploid tumours ($P = 0.002$ res. 0.013) and a higher proportion of tumours with high SPF ($P = 0.0007$) (Table 2).

If adjusted for size and lymph node status, the age ($P = 0.007$) and SPF ($P = 0.008$) were independently associated with the detection mode. A higher SPF was found in large tumours and interval cancers. The SPF was correlated independently with tumour size ($P < 0.001$) and detection mode ($P = 0.001$, Table 3).

In the group of women with tumours detected within one year after the last screen ($n = 152$), the mammographic

*Table 2. Characteristics of 843 invasive breast cancers by mode of detection*

| | Prevalent screen | | Incident screen | | Interval cancers | | Cancers in non-attenders | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | (%) | *n* | (%) | *n* | (%) | *n* | (%) | *n* | (%) |
| All: | 128 | (15) | 368 | (44) | 262 | (31) | 85 | (10) | 843 | (100) |
| Age (years) | | | | | | | | | | |
| 40–49 | 22 | (17) | 63 | (17) | 69 | (26) | 13 | (15) | 167 | (20) |
| 50–59 | 20 | (16) | 87 | (24) | 80 | (31) | 18 | (21) | 205 | (24) |
| 60–69 | 55 | (43) | 133 | (36) | 74 | (28) | 31 | (36) | 293 | (35) |
| ⩾70 | 31 | (24) | 85 | (23) | 39 | (15) | 23 | (27) | 178 | (21) |
| Tumour size (mm) | | | | | | | | | | |
| 1–10 | 46 | (36) | 127 | (35) | 40 | (15) | 8 | (9) | 221 | (26) |
| 11–15 | 35 | (27) | 101 | (27) | 71 | (27) | 12 | (14) | 219 | (26) |
| 16–20 | 19 | (15) | 75 | (20) | 54 | (21) | 17 | (20) | 165 | (20) |
| 21–30 | 21 | (16) | 48 | (13) | 66 | (25) | 24 | (28) | 159 | (19) |
| >30 | 7 | (5) | 17 | (5) | 31 | (12) | 24 | (28) | 79 | (9) |
| Mean tumour size (mm) | 15.8 | | 15.6 | | 21.1 | | 29.4 | | | |
| Nodal status | | | | | | | | | | |
| Negative | 94 | (73) | 273 | (74) | 146 | (56) | 42 | (49) | 555 | (66) |
| Positive 1–3 | 24 | (19) | 73 | (20) | 69 | (26) | 24 | (28) | 190 | (23) |
| Positive >3 | 10 | (8) | 22 | (6) | 47 | (18) | 19 | (22) | 98 | (12) |
| pTNM stage | | | | | | | | | | |
| I | 81 | (63) | 239 | (65) | 109 | (42) | 26 | (31) | 455 | (54) |
| II | 46 | (36) | 118 | (32) | 139 | (53) | 41 | (48) | 344 | (41) |
| III | 1 | (1) | 8 | (2) | 13 | (5) | 16 | (19) | 38 | (5) |
| IV | 0 | (0) | 3 | (1) | 1 | (0) | 2 | (2) | 6 | (1) |
| Oestrogen receptor status | | | | | | | | | | |
| Positive | 92 | (80) | 233 | (75) | 150 | (65) | 46 | (64) | 521 | (71) |
| Negative | 23 | (20) | 79 | (25) | 81 | (35) | 26 | (36) | 209 | (29) |
| Not available | 13 | | 56 | | 31 | | 13 | | 113 | |
| DNA ploidy | | | | | | | | | | |
| Diploid | 58 | (56) | 128 | (45) | 78 | (37) | 22 | (33) | 286 | (43) |
| Aneuploid | 46 | (44) | 158 | (55) | 132 | (63) | 44 | (67) | 380 | (57) |
| Not available | 24 | | 82 | | 52 | | 19 | | 177 | |
| S-phase fraction | | | | | | | | | | |
| Low | 39 | (42) | 119 | (48) | 61 | (33) | 21 | (36) | 240 | (41) |
| Medium | 26 | (28) | 68 | (27) | 53 | (29) | 22 | (37) | 169 | (29) |
| High | 27 | (29) | 61 | (25) | 71 | (38) | 16 | (27) | 175 | (30) |
| Not available | 36 | | 120 | | 77 | | 26 | | 259 | |
| Mean SPF (%) | 7.0 | | 6.7 | | 9.1 | | 7.4 | | | |

appearance of breast tissue was classified in 73% as N1 or P1. However, the proportion of women with radiologically dense breast tissue (P2 and DY) was 38% in women aged 40–49 years ($n = 65$) and 18% in women aged 50 years or more.

The subgroup of true interval cancers had more DNA aneuploid tumours ($P = 0.003$) with higher SPF ($P = 0.023$) in comparison with missed cancers. There was also a trend towards more ER-negative tumours ($P = 0.29$). The highest proportion of young women and the highest mean SPFs were found in the true interval cancers detected within one year after the last screen. The highest percentage of ER– tumours was found in the group of missed lesions detected within one year after the last screen (Table 4).

The probability of distant recurrence was significantly increased for interval cancer patients and non-attenders ($P < 0.001$, Table 5, Figure 1), with true interval cancer cases detected within one year after the last screen having a higher recurrence rate than those detected later ($P = 0.04$, Figure 2).

We found a significantly increased relative risk of distant recurrence in patients with tumours larger than 20 mm; with lymph node metastasis at the time of diagnosis; with oestrogen receptor negative lesions and in patients with medium or high SPF (Table 5). These relationships were confirmed for nodal status, the ER-negative status and the SPF even by analysis of the interval cancer cases only

*Table 3. SPF in invasive breast cancers by tumour size and detection mode*

| | No. of cases | | S-phase fraction (%) | |
|---|---|---|---|---|
| | *n* | (%) | Mean | S.E. |
| Tumour size (mm) | | | | |
| 1–10 | 121 | (21) | 5.86 | 0.46 |
| 11–15 | 157 | (27) | 6.79 | 0.40 |
| 16–20 | 124 | (21) | 7.38 | 0.43 |
| 21–30 | 122 | (21) | 9.34 | 0.56 |
| >30 | 60 | (10) | 10.14 | 0.95 |
| Detection mode* | | | | |
| Screen-detected cancers | 340 | (65) | 6.79 | 0.27 |
| Interval cancers | 185 | (35) | 9.14 | 0.49 |

*Non-attender cancers not included.

*Table 4. Characteristics of 139 true interval cancers and 80 overlooked or misinterpreted interval cancers by duration between the last screen and diagnosis*

| | True interval cancers | | | Missed interval cancers | | |
|---|---|---|---|---|---|---|
| Duration | <1 year | 1–2 years | >2 years | <1 year | 1–2 years | >2 years |
| No. of cases | 34 | 53 | 52 | 26 | 35 | 19 |
| Age (*n* (%)) | | | | | | |
| 40–49 years | 21 (62) | 13 (25) | 2 (4) | 8 (31) | 7 (20) | 2 (11) |
| 50–59 years | 6 (18) | 17 (32) | 19 (37) | 13 (50) | 9 (26) | 6 (32) |
| 60–69 years | 3 (9) | 15 (28) | 18 (35) | 1 (4) | 16 (46) | 7 (37) |
| ⩾70 years | 4 (12) | 8 (15) | 13 (25) | 4 (15) | 3 (9) | 4 (21) |
| Mean tumour size (mm) | 22 | 21 | 21 | 23 | 18 | 20 |
| ER negative* (*n* (%)) | 16 (50) | 15 (31) | 17 (37) | 12 (55) | 8 (25) | 1 (7) |
| DNA aneuploid (*n* (%)) | 21 (68) | 27 (66) | 30 (77) | 11 (50) | 14 (48) | 6 (43) |
| Mean SPF (%) | 10.6 | 7.8 | 9.7 | 6.9 | 6.7 | 6.4 |

*$P = 0.016$.

(Table 6). The detection mode, age distribution and duration between the last screen and diagnosis in the interval cancers showed only statistically non-significant trends.

## DISCUSSION

This study was carried out during population service screening of a dynamic population within a specific age range in contrast to the cohort studies of the screening trials which followed an age band of increasing age during the study and follow-up period [1–3, 5]. The number of screening examinations was higher in women younger than 55 years due to a shorter rescreening interval in those age categories.

In order to investigate the association of malignant potential with different prognostic factors TNM stage was assessed in all included cases and ER status, DNA ploidy and SPF in all except for the very small tumours. Somewhat different procedures in handling the surgical specimens and technical problems in the analyses were considered to be the major cause of missing data that randomly affected all cancer size groups. For that reason the proportions of missing data were equal in all subgroups and were not strictly size dependent.

*Table 5. Cox proportional hazards analysis of the effects of detection mode and other prognostic factors on relative risk ratio (RR) of distant recurrence in invasive breast cancer cases*

| | Univariate analysis | | Multivariate analysis ($n = 577$) | | |
|---|---|---|---|---|---|
| | RR | *P* value | RR | 95% CI | *P* value |
| Detection mode | | | | | |
| Incident screen | 1.00 | – | 1.00 | – | |
| Prevalent screen | 1.07 | 0.85 | 0.87 | (0.38–1.97) | 0.46 |
| Interval cancers | 3.01 | <0.0001 | 1.39 | (0.78–2.46) | 0.28 |
| Non-attenders | 3.94 | <0.0001 | 1.60 | (0.76–3.36) | 0.14 |
| Age (years) | | | | | |
| 40–49 | 1.00 | – | 1.00 | – | |
| 50–59 | 1.10 | | 1.12 | (0.62–2.03) | |
| 60–69 | 0.45 | 0.0043* | 0.72 | (0.37–1.41) | 0.30* |
| ⩾70 | 0.60 | | 0.85 | (0.40–1.83) | |
| Tumour size (mm) | | | | | |
| 1–10 | 1.00 | – | 1.00 | – | |
| 11–15 | 3.33 | | 1.70 | (0.61–4.79) | |
| 16–20 | 5.10 | <0.0001* | 1.47 | (0.51–4.22) | |
| 21–30 | 4.36 | | 1.08 | (0.37–3.18) | 0.0038* |
| >30 | 18.2 | | 4.35 | (1.52–12.4) | |
| Nodal status | | | | | |
| Negative | 1.00 | – | 1.00 | – | |
| Positive 1–3 | 5.42 | <0.0001* | 3.16 | (1.75–5.69) | <0.0001* |
| Positive >3 | 10.1 | | 6.41 | (3.50–11.8) | |
| ER receptor status | | | | | |
| Positive | 1.00 | – | 1.00 | – | |
| Negative | 2.70 | <0.0001 | 2.38 | (1.49–3.81) | 0.0001 |
| SPF | | | | | |
| Low | 1.00 | – | 1.00 | – | |
| Medium | 2.21 | <0.0001* | 1.83 | (0.93–3.61) | 0.0004* |
| High | 4.7 | | 2.94 | (1.57–5.50) | |

*Test for trend.

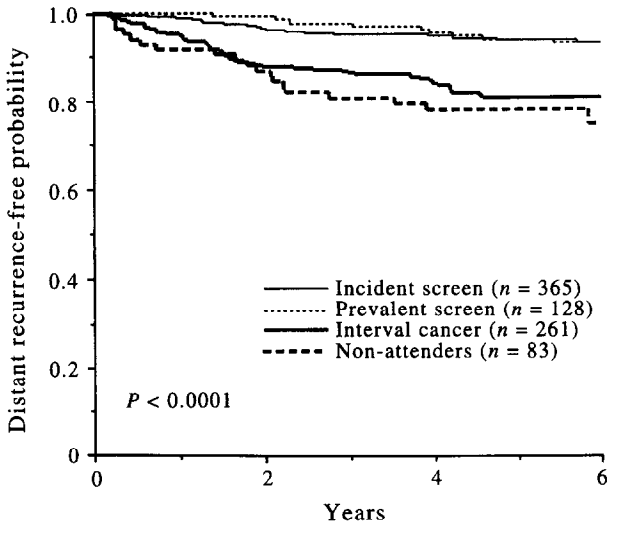


**Figure 1. Kaplan–Meier recurrence-free probability of invasive breast cancer by mode of detection. Women still at risk at 6 years in incident cases: 126 (35%); prevalent cases: 104 (81%), interval cancers: 77 (30%) and non-attenders: 20 (24%).**

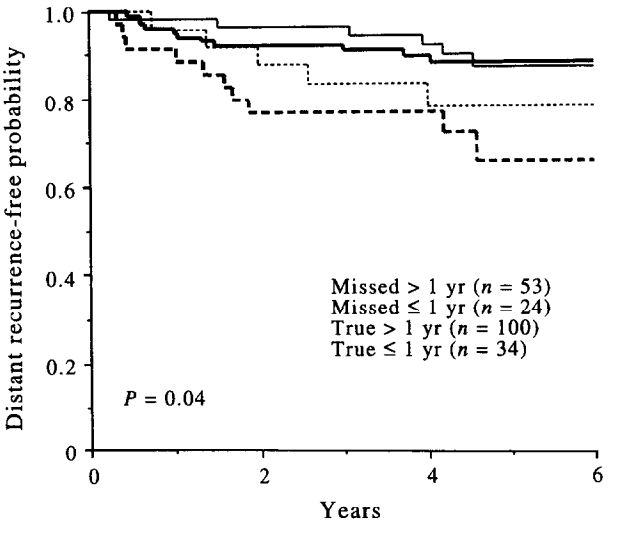


**Figure 2. Kaplin–Meier recurrence-free probability of invasive interval breast cancer. Women still at risk at 6 years in missed tumours diagnosed within one year after the last screen: 6 (25%); missed tumours diagnosed later in the rescreening interval: 20 (38%); true interval cancers detected within one year after the last screen: 5 (15%) and true interval cancers detected later in the rescreening interval: 35 (35%).**

No significant difference in metastatic potential was demonstrated between tumours detected in the prevalent and incident screens even though the majority of prevalent screening examinations during the period of study (74%) were carried out on younger women aged 40–59 years (Tables 1 and 5, Figure 1). However, the major part of prevalent screen-detected cancers (67%) was found in women older than 60 years and there was no real difference in distribution of cancers by size, nodal and receptor status, stage or SPF within those two groups (Table 2). The relatively long rescreening interval in women aged 55–74 years was one conceivable explanation of the equivalent metastic potential of prevalent and incident-screen detected tumours.

The incidence of interval cancers was similar in women aged 40–49 and 50–59 years possibly the consequence of the short rescreening interval in younger women (<55 years). However, the relative incidence rate of interval cancer detected within one year after the last screen was much higher in women aged 40–49 years. In this subgroup of interval cancers, the proportion of women with dense breast tissue was 38% in women aged 40-49 years and 18% in

*Table 6. Cox proportional hazards analysis of the effects of duration between the last screen and diagnosis and other prognostic factors on relative risk ratio (RR) of distant recurrence in invasive interval breast cancer cases*

| | | Univariate analysis | | Multivariate analysis ($n$ = 149) | | |
|---|---|---|---|---|---|---|
| | $n$ | RR | $P$ value | RR | 95% CI | $P$ value |
| Duration (months) | | | | | | |
| True interval cancers | | | | | | |
| 1–12 | 34 | 1.00 | | 1.00 | | |
| >12 | 100 | 0.33 | 0.015 | 0.47 | (0.16–1.35) | 0.10 |
| Missed-interval cancers | | | | | | |
| 1–12 | 24 | 0.63 | 0.39 | 0.28 | (0.05–1.57) | 0.06 |
| >12 | 53 | 0.37 | 0.042 | 0.56 | (0.15–2.11) | 0.25 |
| Tumour size (mm) | | | | | | |
| 1–20 | 136 | 1.00 | | 1.00 | | |
| 21–30 | 52 | 0.86 | 0.037* | 0.58 | (0.18–1.90) | 0.16* |
| >30 | 23 | 3.29 | | 2.83 | (1.03–7.81) | |
| Nodal status | | | | | | |
| Negative | 118 | 1.00 | | 1.00 | | |
| Positive 1–3 | 58 | 2.73 | <0.0001* | 2.42 | (0.77–7.64) | <0.0001* |
| Positive >3 | 35 | 11.4 | | 11.1 | | |
| ER receptor status | | | | | | |
| Positive | 119 | 1.00 | | 1.00 | | |
| Negative | 70 | 3.33 | 0.0009 | 2.38 | (0.92–6.20) | 0.026 |
| SPF | | | | | | |
| Low and medium | 98 | 1.00 | | 1.00 | | |
| High | 52 | 3.61 | 0.0012 | 2.70 | (1.02–7.16) | 0.056 |

*Test for trend.

women 50 years or older. The proportions certainly reflect the difficulties in interpreting mammograms in cases with dense breast tissue.

The study confirmed the less favourable prognosis for interval cancer cases and those in non-attenders compared with screen-detected cases, but the multivariate analysis indicated that the mode of detection was not a genuine and independent prognostic factor (Table 5, Figure 1).

A high proportion of younger women was found in the group of true interval cancers detected within one year after the preceding screen and these tumours presented the highest mean SPF (Table 4). Multivariate analysis did not show any significant difference in the relative risk of distant recurrence between the true interval cancers detected within one year after the last screen and the true interval cancers detected later in the rescreening interval (Table 6). These findings are in accordance with other studies [11, 12, 17], but the number of these patients is still too small to secure statistically significant trends.

The study confirmed that the metastatic potential and the SPF increased with increasing tumour size (Tables 3, 5 and 6). The size effect, however, is most powerful in the comparison between clinically detected tumours (mostly 20 mm or more) and screen-detected tumours (mainly smaller than 20 mm) [13, 19]. Consequently, the effect of tumour size was much less apparent in the size comparison of interval cancers alone because all these tumours were relatively large (mean size 21.1 mm, Tables 2 and 6).

Among clinically detected cases, the SPF was increased in interval cancers while there was no actual increase in non-attender cancers. Multiple regression showed significantly increased SPF values in interval cancers independently of tumour size, intimating that even other factors control the proliferation rate (Tables 2 and 3).

The inter-relationship between the growth rate and malignant capacity of the primary tumour has been stated by other authors and the use of growth rate as a prognostic factor has been strongly questioned or contradicted [11–14, 17]. Our multivariate analyses of the whole dataset and of the interval cancers alone showed a significantly increased risk of distant recurrence in cases with a high or medium SPF (Tables 5 and 6).

Heterogeneity for DNA ploidy, hormone receptor status and thymidine labelling index indicating the presence of different cell populations in one and the same tumour has been stated [13, 20]. These observations make variations of the growth rate and change in malignant capacity during the evolution of the tumour possible. The study leaves the question concerning phenotypic drift open due to the absence of data for a proportion of tumours. It is imaginable that the tumour growth rate is a complex and dynamic variable and the SPF at the time of diagnosis is thus a questionable indicator of the tumour growth rate. In this study, however, an increased SPF appeared to be a powerful predictor of a greater malignant potential.

Biologically, breast cancers comprise a broad spectrum of cases that vary in stage, ER status, SPF and age at the time of diagnosis as well as growth rate and malignant potential. The implementation of mammographic screening divides the breast cancers into screen detected cancers, more or less fast growing interval cancers and non-attender cancers that comprise both slow and fast growing cancers. The choice of radiological technique, recall criteria, rescreening interval, possible addition of clinical examination and the quality of assessment in suspicious cases will all influence the characteristics of interval cancers as will the duration and nature of symptoms triggering investigation during the rescreening interval. In other words, the selection of interval cancers is highly dependent on the design and quality of the screening programme. Consequently, the interval cancers constitute, even prognostically, a non-homogenous group, inappropriate for direct comparisons. The mode of detection was not an independent prognostic factor in our study.

The study focused principally on comparison of the tumours detected at screening compared with clinically-detected cancers. The screening procedure brings the time of diagnosis forward and enables us to detect the lesion at a preclinical stage. For that reason alone, clinically-detected tumours are usually more advanced at the time of diagnosis when compared with the screen-detected tumours. The prognostic difference between the subgroups of breast cancer was therefore principally interpreted as a consequence of either an early or late arrest of the disease. An earlier diagnosis and better prognosis could possibly be achieved by a more intensive education in symptomatology and breast self-examination for all women in order to raise their awareness of breast cancer.

The main conclusions were that the mode of detection was not an independent predictor of the metastatic potential of breast cancer; the higher metastatic capacity in interval cancers and non-attenders could be explained by differences in characteristics at the time of diagnosis. There was no clear association of metastatic capacity with the duration between the last screen and diagnosis in the true interval cancers, but there was a strong correlation between an increased SPF and greater metastatic potential of the tumours.


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