Pergamon

European Journal of Cancer Vol. 31A, No. 11, pp. 1830–1835, 1995

0959-8049/95 $9.50+0.00

0959-8049(95)00324-X

Original Paper

Survival in Interval Breast Cancer in the DOM Screening Programme

C.T. Brekelmans, P.H. Peeters, J.J. Deurenberg and H.J. Collette

The study describes breast cancer survival of 75 interval cancer cases (cancer occurring within 2 years of a negative screen) detected in women who participated in the DOM screening programme. After mammographic revision, this group was divided into 17 so-called 'missed' cases and 58 'true' interval cases. Ten year survival of these 58 'true' interval cases was 58%, which was not significantly different from that of 219 cancers detected in a non-screened, control group of women, diagnosed with breast cancer before the start of screening (63%; log rank χ^2 test, $P = 0.98$). Results remained essentially the same after correction for age at diagnosis, tumour size, axillary status and year of diagnosis. Ten year survival of 'true' interval cancers (58%) was slightly worse than that of 'missed' cases (67%; log rank χ^2 test: $P = 0.38$). This difference could largely be explained by differences in tumour size and axillary status. We conclude that there was no important difference in survival between 'true' interval cancers and non-screened historical controls. This could mean that either this subgroup of interval cancers does not constitute an excess of rapidly growing tumours, or if it does, that a fast growth rate is not associated with an exceptionally poor prognosis.

Key words: survival, interval cancer, breast cancer, screening
Eur J Cancer, Vol. 31A, No. 11, pp. 1830–1835, 1995

INTRODUCTION

INTERVAL CANCERS are defined as cancers that occur in negative screened patients, before the next screening examination would have taken place. This group consists of cancers that were existent at the time of screening but 'missed' for some reason, as well as newly developed (incident) cancers. There are indications that this is a group of cancers with a fast tumour growth rate, high malignancy potential and an unfavourable prognosis [1–4]. However, other studies report a survival that is equal to or even better than non-screened control breast cancer patients [5–10].

Results from these studies are difficult to compare, as criteria used to define interval cancers and the selection of control cases differ between projects. Differences in design of the various screening trials caused a variation in length of the maximum time interval between two consecutive screens from 12 months (BCDDP (Breast Cancer Detection and Demonstration Project), HIP (Health Insurance Plan)) to 4 years (DOM project). Some, but not all studies, separate interval cancers after mammographic revision into cancers with and without visible tumour signs at the last screening mammogram. Further, survival of interval cancers is compared with different control groups of other breast cancer cases. A worse survival of interval cancers as compared to screen-detected cases is to be expected, as there are indications that the group of screen-detected cases contains an excess of slow-growing tumours with a favourable prognosis [11]. Studies that compare survival of interval cases and cancers detected in an unscreened population generally found no significant differences or even a better survival of the interval cases [5–7, 9, 10]. Previous results from the Utrecht DOM project showed that the survival of a combined group of interval cancers (maximum interval between screens varying from 12 months to 4 years) and cases detected in women who withdrew from the programme after being screened at least once (so-called non-compliance group) was equal to that of a historical control group [8].

In this study, we were interested in the group of interval cancers occurring within 2 years of a negative screen, since this group is considered to consist of an excess of fast-growing tumours. Survival of this group, divided into 'missed' and 'true' interval cases, is described and compared with other groups of breast cancer cases, detected in the DOM screening programme, and a control group of non-screened cases.

PATIENTS AND METHODS

In December 1974, the DOM project, a population-based non-randomised screening programme for the early detection of breast cancer, was started in the city of Utrecht, The Netherlands and its suburbs. By 1987, four successive birth cohorts (age at

Correspondence to C.T.M. Brekelmans.
C.T. Brekelmans, P.H. Peeters and H.J. Collette are at the Department of Epidemiology, University of Utrecht, Postbus 80035, 3508 TA Utrecht; and J.J. Deurenberg is at Stichting Preventicon, Stationsplein 91, 3511 ED Utrecht, The Netherlands.
Revised 27 Jan. 1995; accepted 26 May 1995.

entry 40–65 years) with a total number of 25 932 women living in the city of Utrecht, The Netherlands were screened by (xero-)mammography and physical examination.

From 1973 onwards, a breast cancer registry has been collecting data on the occurrence of breast cancer in screened and non-screened women. In this study, cancer cases detected between 1973 and 1989 in the city of Utrecht, The Netherlands were used. Included were all histologically confirmed primary breast cancers (invasive and ductal *in situ*).

219 breast cancer cases diagnosed before the start of the programme or before receiving a screening invitation were considered as a historical control group of non-screened women. This group also included women moving into the city of Utrecht, The Netherlands after the start of the screening programme. These women received no screening invitation. Diagnosis was made between 1973 and 1985, age at diagnosis varied between 47 and 71 years. The total group of 219 cases is called hereafter the 'historical control group'.

Three hundred and two breast cancers occurred in women who participated in the DOM screening programme. One hundred and thirty-two cancers were detected at first screening and 95 detected at following screens. As there were practically no differences between survival curves and frequency of histopathological tumour characteristics, these two groups were amalgamated for most analyses to form one group of 'screen-detected cases' (n = 227).

Seventy-five interval cancers occurred within 2 years of one or more negative screen(s): 22 within 1 year and 53 between 1 and 2 years after screening. The screening mammograms preceding the diagnosis of all 75 interval cancers were reviewed by one author. In 17 cases (8 detected within 1 year, 9 between 1 and 2 years), hereafter called 'missed cases', direct or indirect signs of tumour were seen on the preceding mammogram. In 58 cases, no visible tumour signs could be seen. It was hypothesised that this last subgroup of 58 cases could be regarded as 'true' interval cancers, consisting of an excess of fast-growing tumours with a possibly poor prognosis.

Histopathology

Data on histological type, tumour size and axillary status were extracted from pathological files.

Assessment of oestrogen receptor status

As the oestrogen receptor (ER) status was not routinely assessed in the years before screening and in the early days of the programme, the ER status of only 262 cases (50%) were available.

The ER content was expressed as femtomoles of receptors per mg of cytosolic protein (fmol/mg). Values up to 3 fmol/mg were considered as ER-negative, values higher than 10 fmol/mg as positive. Values of 3–10 fmol/mg (5 cases) were considered as unknown receptor state.

Follow-up

Follow-up data on progression and cause of death were collected in hospitals and, when necessary, from general practitioners. For this study, data up to the end of 1991 were used. Follow-up times varied from 1 month to 19 years, with a mean of 9 years. By 31 December 1991, 143 women had died of breast cancer, 51 of other causes, while six women were lost to follow-up.

For this study, death of breast cancer was taken as the endpoint of interest. This was done because of the interest in the malignancy potential of the tumour rather than the overall survival of the patient.

Statistical methods

The distribution of tumour characteristics and age at diagnosis were described separately for 'true' and 'missed' interval cancers, screen-detected cases and the historical control group. χ^2 tests to test comparability between the four subgroups were performed for the categorical variables histology, axillary status, tumour stage and ER status, and analysis of variance (ANOVA) for age at diagnosis and tumour diameter.

Kaplan–Meier survival probabilities were computed for mode of detection and other possible prognostic factors. Equality of survival curves was tested by the log rank χ^2 test. Survival time of screen-detected cases was corrected for lead time; 2.5 years when detected at first screen and half the length of the preceding interval when detected at a following screen [8]. This correction can lead to a negative follow-up time. This happened in one case, which was excluded from the analyses.

The simultaneous effect of several prognostic variables on survival time was investigated by the Cox proportional hazards method. Mode of detection was entered as a categorical variable with four levels, representing the four subgroups of breast cancer cases, with 'true' interval cases as the reference category. Factors that proved to be important confounders and fulfilled the proportional hazards assumption were included in the model. Axillary status was coded as 0 (node-negative) or 1 (node-positive), tumour size was entered as a continuous variable. 'Year of diagnosis' (entered as continuous variable) was included to correct for possible changes in survival (as a result of changes in therapy) over time during the follow-up period. The adequacy of the proportional hazards assumption was tested graphically by examining log min log plots. As the variable 'age at diagnosis' did not fulfil this assumption, models stratified on age (in 5 year age categories) were fitted to obtain weighed summaries of the hazard ratios for the other variables [12].

The presence of interaction was tested by comparing models with and without product terms of detection mode and the other prognostic variables. No significant interaction was found. All statistical analyses were performed using SPSS-PC and EGRET software.

RESULTS

Table 1 compares the distribution of some important prognostic variables of true interval cancers and the three other subgroups of breast cancer cases. Mean age at diagnosis did not differ greatly between subgroups.

Of true interval cancers, 52.6% were node-positive, which was more than in any other group, including the historical control group. Only for the screen-detected patients was the difference between node-positive and node-negative patients significant. The distribution of histological tumour type, stage and mean tumour size of interval cases was between screen-detected cases and the historical group. The difference in tumour size and stage between interval cases and the historical group was statistically significant.

Of true interval cancers, 35.3% were oestrogen receptor-negative, which was more, but non-significantly so, than the screen-detected and historical group.

In Table 2 and Figure 1, Kaplan–Meier survival probabilities are shown for mode of detection. Long-term survival of true interval cases did not differ significantly from the historical control group (log rank χ^2 test: P = 0.98), and was slightly worse, although not significantly, than the group of 'missed' cases (P = 0.38). As expected, the difference in survival

Table 1. *Selected characteristics of* 520 *breast tumours by mode of detection*

Variable (*n*)	True interval (*n* = 58)	Missed cases (*n* = 17)	Screen detected (*n* = 226)	Historical controls (*n* = 219)
Mean age at diagnosis (520)	56.1	57.9	58.1	55.8
Histological tumour type				
DCIS (33)	5.2	0.0	11.8	1.8
Invasive (487)	94.8	100.0	88.2	98.2
Axillary status				
Negative (291)	47.4	62.5	73.2*	51.0
Positive (187)	52.6	37.5	26.8	49.0
Tumour stage†				
A (218)	41.1	50.0	66.0*	30.5*
B (50)	7.1	12.4	6.8	18.3
C (110)	30.4	18.8	23.9	25.0
D (65)	21.4	18.8	3.3	26.2
Mean tumour size (mm) (475)	19.8	17.1	12.7*	24.6*
Oestrogen receptor status				
Positive (192)	64.7	55.0	74.4	79.8
Negative (65)	35.3	45.0	25.6	20.2

With the exception of age at diagnosis and tumour size, all figures represent percentages. *Denotes groups significantly different from 'true' interval cancers at the 0.05 level; †Tumour stage A: tumour size ≤ 20 mm, node-negative. B: tumour size >20 mm, node-negative. C: tumour size ≤ 20 mm, node-positive. D: tumour size >20 mm, node-positive. DCIS, ductal carcinoma *in situ*.

between interval and screen-detected cases was highly significant ($P < 0.001$).

Five and 10 year survival probabilities are also presented in Table 2 for a number of possible prognostic factors. The importance of tumour size and axillary status were confirmed (log rank χ^2 test: $P < 0.001$). For ER status, no clear difference in 5 year survival was seen. Ten year survival of ER-negative tumours was higher than that of ER-positive tumours but non-significant.

No significant difference in survival for different age categories was seen. Only the youngest age group, women under the age of 50 years, appeared to have a slightly better survival compared to women over 50 years.

In Table 3, crude and adjusted hazard ratios are presented for detection mode and other prognostic factors. With true interval cases as the reference group, all other groups had hazard ratios below 1, which indicated a better survival than the interval cases. The difference with the group of screen-detected cases was significant and remained so after adjustment for tumour size, axillary status and year of diagnosis.

The crude hazard ratio of 0.90 (95% C.I. 0.54–1.50) for the historical control group as compared to the reference group of 'true' interval cancers changed after adjustment for the above-mentioned factors to 0.76 (95% C.I. 0.39–1.47). Year of diagnosis made the most important contribution to this change.

No clear effect of length of interval was found: survival of 53 cancers detected between 1 and 2 years after screening was non-significantly worse as compared to 22 cancers detected within 1 year after screening (log rank χ^2 test: $P = 0.18$).

Survival curves of four subgroups of interval cases according to the results of mammographic revision and length of interval are shown in Figure 2. Of 17 'missed' cases, 8 were detected within 1 year after screening, 9 between 1 and 2 years after screening. Of 58 'true' interval cases, 14 were detected within 1 year and 44 between 1 and 2 years after screening. This last subgroup appeared to have a worse survival than the other groups: a 5 year survival of 69% (95% C.I. 52–81%) and a 10 year survival of 44% (95% C.I. 22–65%).

DISCUSSION

Ten year breast cancer survival of 'true' interval cancer cases (defined as cancers occurring within 2 years after a negative screen, without visible tumour signs on the last screening mammogram) occurring in the DOM screening programme was not significantly different from that of a control group of non-screened patients, diagnosed before the start of the screening programme or before receiving an invitation. Results remained essentially the same when using death from all causes as an endpoint instead of death from breast cancer.

As the DOM project was set up as a non-randomised trial, the selection of a control group that is comparable to cases diagnosed in women participating in a screening programme is a difficult problem. We chose a control group of women from the city of Utrecht, The Netherlands, who were diagnosed with breast cancer before the start of the programme or before receiving an invitation, the so-called 'historical controls'. A well-known disadvantage of such a group is that changes over time in (for instance) treatment could confound the results on survival differences between groups of screened and non-screened cases. As breast cancer survival indeed improved over the study period (Table 3), we expected to see this reflected in the multivariate hazard ratio. While the univariate hazard ratio for historical controls as compared to interval cancers was 0.90, the adding of 'year of diagnosis' caused the hazard ratio to decrease to 0.81, indicating that survival of the historical controls may be slightly better than that of interval cases. As the power of our study was

Table 2. Kaplan–Meier 5 and 10 year breast cancer survival probabilities

Variable (*n*)	5 year survival (95% C.I.)	10 year survival (95% C.I.)	*P*-value*
Detection mode			
True interval (58)	0.73 (0.59–0.83)	0.58 (0.40–0.72)	—
Missed (17)	1.00 (1.00–1.00)	0.67 (0.37–0.85)	0.38†
Screen-detected (226)	0.94 (0.90–0.97)	0.90 (0.85–0.94)	<0.001†
Historical control (219)	0.75 (0.69–0.81)	0.63 (0.37–0.85)	0.98†
Age at diagnosis			0.74
<50 (52)	0.92 (0.81–0.97)	0.82 (0.66–0.92)	
50–54 (161)	0.82 (0.75–0.87)	0.71 (0.63–0.78)	
55–59 (110)	0.82 (0.73–0.88)	0.71 (0.62–0.79)	
60–64 (145)	0.84 (0.77–0.89)	0.75 (0.67–0.82)	
>65 (52)	0.87 (0.71–0.95)	0.70 (0.46–0.85)	
Tumour size (mm)			<0.001
<6 (48)	0.98 (0.86–0.99)	0.98 (0.88–0.99)	
6–10 (125)	0.92 (0.85–0.96)	0.86 (0.78–0.92)	
11–20 (181)	0.86 (0.80–0.91)	0.73 (0.65–0.80)	
21–50 (107)	0.75 (0.65–0.82)	0.58 (0.48–0.68)	
>50 (14)	0.46 (0.19–0.70)	0.39 (0.14–0.63)	
Axillary status			<0.001
Negative (291)	0.95 (0.92–0.97)	0.87 (0.81–0.91)	
Positive (187)	0.67 (0.59–0.73)	0.52 (0.45–0.60)	
Tumour stage‡			<0.001
A (218)	0.96 (0.93–0.98)	0.89 (0.83–0.93)	
B (50)	0.91 (0.79–0.97)	0.76 (0.59–0.86)	
C (110)	0.76 (0.67–0.83)	0.64 (0.53–0.72)	
D (65)	0.57 (0.44–0.69)	0.41 (0.28–0.53)	
Oestrogen receptor status			0.13
Negative (65)	0.89 (0.78–0.95)	0.85 (0.73–0.92)	
Positive (192)	0.85 (0.78–0.89)	0.72 (0.63–0.77)	

*Log rank χ^2 test; †Compared with survival curve of 'true' interval cancers; ‡Tumour stage A: tumour size ≤ 20 mm, node-negative; B: tumour size >20 mm, node-negative; C: tumour size ≤ 20 mm, node-positive; D: tumour size >20 mm, node-positive.

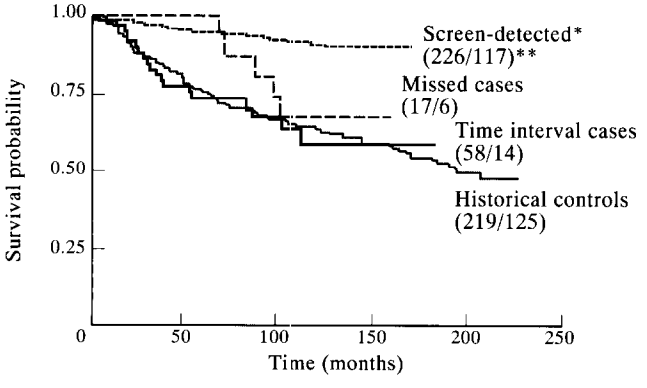

Figure 1. Kaplan–Meier survival of breast cancer by mode of detection. *Corrected for lead time. **Number of breast cancer cases at start after 10 year follow-up.

not sufficient to detect a difference of such small magnitude, we cannot exclude this possibility.

We would have been able to detect a difference in the hazard ratio of 0.50 or more, and taken together with the results from the log rank test, the graphical appearance of the survival curves and the results from most randomised trials, we feel able to conclude that there is no important difference in survival between interval cancers and non-screened historical controls.

Randomised trials have generally found no notable differences in survival between interval cancers and non-screened control cases [5, 6]. Recent results from the Stockholm, Sweden, randomised screening trial even described a significantly better survival of interval cancers as compared to cancers detected in the unscreened control group [9]. Only the Malmö trial shows a significantly worse survival of interval cases as compared to the non-screened control group [4].

Within the group of cancers detected in women participating in the screening programme, true interval cancers had the worst prognosis: a 10 year survival of 58% as compared to 90% in screen-detected cases and 67% in 'missed' cases.

Differences in axillary status and tumour size could not fully account for the difference in survival between 'true' interval cancers and both groups of screen-detected cases. After correction for these factors, survival for screen-detected cases remained significantly better than for true interval cases. Information on additional prognostic factors, such as histological grade, could very likely explain more of the difference in survival, at least between interval cancers and cancers detected at following screens. One study has shown that, for cancers detected at the prevalence screen, adjustment for the three aforementioned prognostic factors cannot account fully for the favourable prognosis of these cancers [13].

The somewhat worse prognosis of true interval cancers as compared to missed cases could be largely explained by differ-

Table 3. Results of Cox proportional hazards analysis of detection mode and other prognostic variables on survival of breast cancer (invasive tumours only)

Variable	Crude hazard ratio	95% C.I.	Adjusted hazard ratio	95% C.I.
Detection mode				
True interval	1.00	—	1.00	—
Missed	0.59	0.22–1.58	0.83	0.30–2.28
Historical control	0.90	0.54–1.50	0.76	0.39–1.47
Screen detected	0.21	0.11–0.40	0.33	0.17–0.66
Tumour size in mm†	1.03	1.02–1.04	1.02	1.01–1.03
Axillary status				
Negative	1.00	—	1.00	—
Positive	4.48	2.95–6.81	3.58	2.33–5.49
Year of diagnosis‡	0.94	0.88–0.99	0.97	0.89–1.05

*Stratified on age at diagnosis (5 year age categories) and adjusted for all other factors in table; †One unit increase represents 1 mm (tumour size); ‡One unit increase represents 1 year (year of diagnosis).

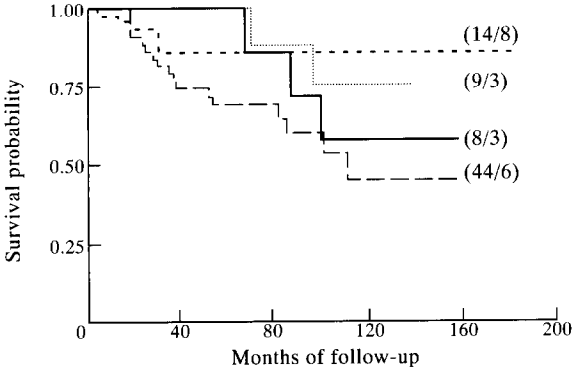

Figure 2. Kaplan–Meier survival of breast cancer for 'true' interval cancers and 'missed' cancers, separated for cancers detected within 1 year and between 1 and 2 years after screening. (–·–)'True' interval cancer detected within 1 year after screening. (——)'Missed' cancer detected within 1 year after screening. (– –)'True' interval cancer detected between 1 and 2 years after screening. (····)'Missed' cancer detected between 1 and 2 years after screening. *Number of breast cancer cases at start/after 10 year follow up.

ences in tumour size and axillary status; after correction for these factors, no clear difference in survival remained (adjusted hazard ratio 0.83, 95% C.I. 0.30–2.28). This is in agreement with recent results from the Stockholm, Sweden trial [9]. It could be that mammographic revision is not sufficient to separate a group of fast-growing tumours. Cases without visible tumour signs at the last screening mammogram are regarded as cancers at a stage not yet detectable for mammography, implying a fast tumour growth rate. However, there are indications from other studies that at least part of this group consists of radiographically occult tumours that probably were large enough to be detected at screening but were somehow 'masked' from detection [7, 14].

We found no clear relationship between interval length and breast cancer survival, which is in accordance with other studies [6, 9]. Perhaps the combination of length of interval and mammographic revision can better differentiate between subgroups. Ten year survival of 44 'true' interval cancers detected between 1 and 2 years after screening appeared worse than other subgroups. As numbers within the three other subgroups were small, we could not investigate the importance of this difference further.

In conclusion, 10 year breast cancer survival of 'true' interval cancer cases did not differ significantly from cancers occurring in a non-screened population. This could mean that either this subgroup of interval cancers does not constitute an excess of rapidly growing tumours, as has been previously hypothesised, or that a fast growth rate is not associated with a poor prognosis. This latter possibility is supported by several observations that growth rate and metastatic capacity need not be parallel phenomena [15]. Future studies at our department will attempt to clarify this matter further.

1. DeGroote R, Rush BF, Milazzo J, Warden MJ, Rocko JM. Interval breast cancer: a more aggressive subset of breast neoplasias. *Surgery* 1983, **94**, 543–547.
2. Heuser LS, Spratt JS, Kuhns JG, Chang AF-C, Polk HO Jr, Buchanan JB. The association of pathologic and mammographic characteristics of primary human breast cancers with "slow" and "fast" growth rates and with axillary lymph node metastases. *Cancer* 1984, **53**, 96–98.
3. Rosen von A, Erhardt K, Hellström L, Somell A, Auer G. Assessment of malignancy potential in so-called interval mammary carcinomas. *Breast Cancer Res Treat* 1985, **6**, 221–227.
4. Andersson I, Aspegen K, Janzon L, *et al.* Mammographic screening and mortality from breast cancer: the Malmö mammographic screening trial. *Br Med J* 1988, **297**, 943–948.
5. Shapiro S, Venet W, Strax Ph, Venet L, Roeser R. Ten-to-fourteen year effect of screening on breast cancer mortality. *J Natl Cancer Inst* 1982, **69**, 349–355.
6. Holmberg LH, Adami HO, Tabar L, Bergström R. Survival in breast cancer diagnosed between mammographic screening examinations. *Lancet* 1986, **ii**, 27–30.
7. Peeters PHM, Verbeek ALM, Hendriks JHCL, Holland R, Mravunac M, Vooijs GP. The occurrence of interval cancers in the Nijmegen screening programme. *Br J Cancer* 1989, **59**, 929–932.
8. Collette C, Collette HJA, Fracheboud J, Slotboom BJ, de Waard F. Evaluation of a breast cancer screening programme—The DOM project. *Eur J Cancer* 1992, **28A**, 1985–1988.
9. Frisell J, von Rosen A, Wiege M, Nilsson B, Goldman S. Interval cancer and survival in a randomized breast cancer screening trial in Stockholm. *Breast Cancer Res Treat* 1992, **24**, 11–16.
10. Moss SM, Ellman R, Coleman D, Chamberlain J. Survival of patients with breast cancer diagnosed in the United Kingdom trial of early detection of breast cancer. *J Med Screen* 1994, **1**, 193–198.
11. Kalloniemi O-P, Kärkkäinen A, Auvinen O, Mattila J, Koivula T, Hakama M. DNA flowcytometric analysis indicates that many

breast cancers detected in the first round of mammographic screening have a low malignant potential. *Int J Cancer* 1988, **42**, 697–702.
12. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. New York, John Wiley, 1980.
13. Duffy SW, Tabar L, Fagerberg G, *et al*. Breast screening, prognostic factors and survival—results from the Swedish two county study. *Br J Cancer* 1991, **64**, 1133–1138.
14. Holland R, Mravunac M, Hendriks JHCL, Bekker BV. So-called interval cancers of the breast. Pathologic and radiologic analysis of sixty-four cases. *Cancer* 1982, **49**, 2527–2533.
15. Holmberg L, Pontén J, Adami H-O. The biology and natural history of breast cancer from the screening perspective. *World J Surg* 1989, 25–30.

Acknowledgements—The authors acknowledge Dr J.A.J. Faber (Centre for Biostatistics, University of Utrecht, The Netherlands) for statistical advice and Drs J. Fracheboud and G.A.J. Miltenburg (Department of Epidemiology, University of Utrecht, The Netherlands) for collecting the data.