

# Age specific sensitivity and sojourn time in a breast cancer screening programme (DOM) in The Netherlands: a comparison of different methods

Cecile T M Brekelmans, Paul Westers, Joop A J Faber, Petra H M Peeters, Hubertine J A Collette

## Abstract

**Study objective** - To estimate age dependent sensitivity and sojourn time in a breast cancer screening programme by different methods.

**Population and methods** - The study population comprised women participating in the DOM project - the Utrecht screening programme for the early detection of breast cancer. Breast cancer screening prevalence data and incidence rates after a negative screen were used to estimate age specific sensitivity and mean sojourn time by different methods.

**Main results** - Maximum likelihood estimates of the mean sojourn time varied from one year for women aged 40-49 years to three years for women over the age of 54. Sensitivity was calculated by two different methods. Both pointed to a high sensitivity (around 100%) in the age groups 40-49 and over 55 years. For women aged 50-54, the sensitivity varied from 63% to 100%, depending on the method used and the value of the baseline incidence rate.

**Conclusions** - Different methods of estimating sensitivity pointed at an acceptable level in women over and under 50 years of age. Sojourn time, and thus the tumour growth rate, seemed to be age dependent. This could mean that the until now disappointing screening results in women under 50 years of age are not so much a result of low sensitivity as of a relatively high tumour growth rate in younger women.

(*J Epidemiol Community Health* 1996;50:68-71)

Department of  
Epidemiology,  
University of Utrecht,  
Postbus 80035,  
3508 TA Utrecht,  
The Netherlands.  
C T M Brekelmans  
P H M Peeters  
H J A Collette

Centre for  
Biostatistics,  
University of Utrecht,  
The Netherlands  
P Westers  
J A J Faber

Correspondence to:  
Dr C T M Brekelmans.  
Accepted for publication  
July 1994

Mammographic screening for breast cancer has been accepted as beneficial in women over 50 years of age.<sup>1</sup> Until now, however, screening results in women under 50 years have been generally disappointing.<sup>2-4</sup> Only the Health Insurance Plan study showed a delayed effect on mortality after eight years of follow up.<sup>5</sup> The recently published overview of the five Swedish trials also showed a (non-significant) mortality reduction, again only after eight years of follow up.<sup>6</sup> Reasons for the delay or even absence of benefit in these young women has been sought in either a low sensitivity of mammography or

a high tumour growth rate in young women, which implicates a short sojourn time.<sup>7-11</sup>

There are several ways of estimating sensitivity. In a previous publication we used the so called classic method - the proportion of all cancers detected within a certain time after screening in relation to those detected at screening. This estimate was used in women under and over the age of 50 for various time intervals after screening. In this way we found indications that the reason for the disappointing screening results in women under 50 years of age was not so much a low sensitivity as a relatively high tumour growth rate in this age group.<sup>12</sup> The validity of this method is uncertain as it is not possible to distinguish truly false negative cases from cases with a short pre-clinical phase that had not begun at the time of screening. Furthermore, this estimate is affected by the inclusion of cases with indefinitely long lead times. Alternative methods of estimating sensitivity have been derived that deal with these issues.

In the current study two of these methods are used to estimate age specific sensitivity and mean sojourn time.<sup>13,14</sup>

## Methods

In 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. Up to 1987, four successive birth cohorts of women had been invited for screening by mammography and physical examination. For scientific reasons, each of the four projects had a different study design. In contrast to women aged 50 to 64, who had up to five screening rounds, the youngest birth cohorts (1932-41 and 1942-45), aged 40 to 49 at entry, were screened only once. We therefore limited the material for this study to first round data only.

The cancer registry, set up to evaluate the screening procedure, was used to obtain information on age specific numbers of prevalent and incident cancers. The local authorities and the Central Bureau of Statistics provided follow up data for all women participating in the DOM project, so that person-years at risk for each year after screening could be calculated. A woman contributed person-time from the date of the first negative screen to the date of diagnosis of breast cancer, the date of the next

Table 1 The DOM project for the early detection of breast cancer: first round results, 1974-87

	Age at entry		
	40-49y	50-54y	55-64y
No of women screened	6564	9606	9762
No of prevalent cases	14	51	71
Prevalence rate (‰)	2.13	5.31	7.27
Expected incidence rate (‰) <sup>15</sup>	1.48	1.77	2.30

screening examination, death, or the end of the study period. For this study, data up to four years after the first screening were used.

Incidence rates for each year after screening were calculated by dividing the number of interval cancers by the total number of person-years at risk in that year. The 95% confidence intervals were calculated assuming a Poisson distribution.

The number of cases expected in the absence of screening was estimated from age and calendar period specific regional cancer registry data.<sup>15</sup> For each year after screening, the number of observed cases was divided by the number of expected cases in the absence of screening to obtain the proportion of expected cases.

The length of time by which diagnosis is advanced in a screening programme depends both on the length of time the disease is in the preclinical detectable phase (the sojourn time) and the probability that the disease is detected by the screening test (sensitivity). Both parameters (mean sojourn time and sensitivity) were estimated simultaneously by a statistical method described by Day and Walter.<sup>13,16</sup> In their method, the incidence after a negative screen and the prevalence at each screening are expressed in terms of the sensitivity, probability distribution of the sojourn time (assumed to be negative exponential), and the baseline incidence rate in the absence of screening. From data on the number of cases found at each screen and the number of cases diagnosed between screens, the false negative rate (1 minus the sensitivity) and mean sojourn time are estimated by maximisation of the log likelihood. A joint confidence interval can be constructed for both parameters.

Although the baseline incidence can also be estimated by the model, Day and Walter suggest that this parameter is fixed, for instance by cancer registry data. In our analyses, both approaches were used. A disadvantage of the above mentioned model is the use of prevalence data. As Walter and Day pointed out, these include cases that might take years to surface,

or never surface at all.<sup>16</sup> The model proposed by Day in 1985 requires incidence data only and the probability distribution of the sojourn time.<sup>14</sup> Using his model and the estimate of the mean sojourn time from the previous model, sensitivity has been adjusted as follows:

$$S = \frac{1 - I_T/I}{T - \int_0^T F(t) dt}$$

in which S is the sensitivity,  $I_T$  is the incidence in time T after the first screen, I is the baseline incidence in the absence of screening. The integral in the denominator is the proportion of cases with a sojourn time of duration less than time T. In this formula, F(t) is taken as the exponential distribution of the sojourn time with mean ( $\lambda$ ) estimated from the model of Day and Walter:  $[1 - \exp(-\lambda t)]$ .<sup>13</sup>

Both methods were applied to three different age groups - 40-49, 50-54, and >54 years.

## Results

Table 1 shows the age specific numbers of women screened, prevalence rates, and the expected incidence rate in the absence of screening. As expected, the prevalence rate increased with age as did the ratio of the prevalence rate to the expected incidence rate.

Table 2 gives the age specific incidence rates per year after screening. In the last column these rates were divided by the expected incidence rates (see table 1) to obtain the proportion of expected cases in the absence of screening. This shows that in the age group 40-49 the incidence rate is back on the pre-screening level within two years, while this takes three years in women over the age of 50.

Table 3 presents maximum likelihood estimates and 95% confidence intervals for the sensitivity and mean sojourn time. In the first model, baseline incidence data were fixed. The mean sojourn time was 1.05 years for the age group 40-49, 4.44 years for the age group 50-54, and 2.89 years for the age group 55-64. Sensitivity varied from 100% in the youngest age group to 63% in women aged 50-54 and 100% in women aged 55-64 at entry. Results with regard to sensitivity in both younger age groups must be interpreted with caution as confidence intervals were wide in these age groups.

Table 2 Age specific incidence data after the first screening test for the 1st four years after screening

Time interval since screening (mth)	Age group at entry				Age group at entry				Age group at entry			
	40-49y				50-54y				55-64y			
	No of interval cases	Women-years at risk	Incidence rate (‰)	Proportion of expected cases (%) <sup>*</sup>	No of interval cases	Women-years at risk	Incidence rate (‰)	Proportion of expected cases (%) <sup>*</sup>	No of interval cases	Women-years at risk	Incidence rate (‰)	Proportion of expected cases (%) <sup>*</sup>
0-6	0	3282	0	0	2	4803	0.42	23	1	4881	0.20	9
7-12	3	3280	0.91	61	3	4776	0.62	34	0	4826	0	0
13-24	11	6362	1.88	100	7	5048	1.37	77	1	2053	0.48	21
25-36	14	5883	2.38		5	1707	2.93	100	4	1725	2.31	100
37-48	8	5147	1.55		1	1466	0.68		5	1698	2.94	

\* Incidence expressed as percentage of expected incidence in the absence of screening.<sup>15</sup>

Table 3 Maximum likelihood estimates (95% confidence intervals) of sensitivity and mean sojourn time in relation to age group

	Baseline incidence fixed			Baseline incidence estimated from model		
	Age group 40-49y	50-54y	55-64y	Age group 40-49y	50-54y	55-64y
Baseline incidence* (%)	1.77 (—)	1.83 (—)	2.49 (—)	2.13 (1.80, 2.53)	2.50 (2.20, 2.93)	2.30 (2.10, 2.70)
Mean sojourn time (y)	1.05 (0.72, 1.49)	4.44 (3.48, 5.64)	2.89 (2.35, 3.51)	1.03 (0.68, 1.49)	2.08 (1.65, 2.56)	3.09 (2.53, 3.73)
Sensitivity (%)	100 (44, 100)	63 (40, 100)	100 (83, 100)	100 (47, 100)	100 (63, 100)	100 (81, 100)
Goodness of fit $\chi^2$ value	3.64 (3 df)	6.64 (3 df)	4.87 (3 df)	2.12 (2 df)	2.77 (2 df)	5.55 (2 df)

\* Values differ from table 1 as the aging of the population was taken into account.

In the second model, baseline incidence as well as sensitivity and mean sojourn time were estimated. For the two youngest age groups (40-49 and 50-54), the baseline incidence rate estimated from the model was higher than the rates based on cancer registry data. Consequently, the estimates for the mean sojourn time were lower than in the previous model. Maximum likelihood estimates for sensitivity in both age groups are 100%, but again the confidence intervals for both variables are wide, especially in the age group 40-49. As can be derived from the goodness of fit  $\chi^2$  value in the last row, the second model fits the data better than the first.

In table 4, age specific estimates of the mean sojourn time from table 3 were used to adjust the sensitivity according to the formula proposed by Day.<sup>14</sup> Results pointed in the same direction: a sensitivity around 100% in the age groups 40-49 and 55-64 and a somewhat lower sensitivity in the 50-54 age group (six month sensitivity 80%; one year sensitivity 79%).

Again, especially in this last age group, sensitivity increased when using expected incidence data estimated from the maximum likelihood model instead of cancer registry data. After six months and one year respectively, sensitivities of 88% and 99% were seen.

### Discussion

Breast cancer screening by mammography is thought to advance the date of diagnosis of breast cancer. The duration of this so called "lead time" is influenced by the growth rate of the breast tumour and the sensitivity of screening. There are indications that the tumour growth rate depends on the age of the patient and that tumours generally grow more

quickly in younger women.<sup>7,8,11</sup> This was confirmed in our study: the mean sojourn time – the length of time the disease is in the preclinical detectable phase – varied from 1 year for women aged 40-49 years to more than 3 years for women aged 55-65 years. A sojourn time of around 1 year for women under the age of 50 has been reported by other groups. Mean sojourn times of 1.63 (0.97-5.04) years and 1.25 (0.87-2.15) years were found for women aged 40 to 49 participating in the Florence district programme and the Swedish two county study respectively.<sup>17,18</sup>

In contrast to our expectations, no negative association between sensitivity and age was seen. We found a high sensitivity both in women under the age of 50 and over the age of 55, and an indication of a lower sensitivity in women aged 50-54.

The estimate of 100% sensitivity in the age group 40-49 years should be interpreted with caution as numbers were small and confidence intervals were therefore wide, especially in this age group. However, both methods used to calculate sensitivity in this study point in the same direction. Furthermore, these results are in line with those of our previous study. Here, age specific sensitivity was estimated by the "classic" method using time intervals varying from 6 months to 2 years.<sup>12</sup> Our results are not in agreement with other studies which found a low sensitivity in women under the age of 50. Sometimes sensitivity is calculated in the classic way using a 1 or even 2 year interval, which seems improbable in the light of a mean sojourn time of 1 year.<sup>19,20</sup> Results from the Nijmegen screening programme, calculating age specific estimates of sensitivity using different methods, also show an acceptable sensitivity in women under 50 years of age.<sup>10</sup>

Table 4 Adjusted sensitivity using 6 month and 1 year intervals (Day 1985)<sup>14</sup>

Baseline incidence	Age group (y)	6 month interval			1 year interval		
		Observed no of interval cancers $I_T$	Expected no in the absence of screening $I^*$	Adjusted sensitivity	Observed no of interval cancers $I_T$	Expected no in the absence of screening $I_1$	Adjusted sensitivity
Fixed	40-49	0	4.92	$\frac{1 - I_T/I}{1 - I_T/I} = 1.00$	3	9.84	$\frac{1 - I_T/I}{0.6440} = 1.00$
	50-54	2	8.95	$\frac{1 - I_T/I}{0.9724} = 0.80$	5	17.29	$\frac{1 - I_T/I}{0.8945} = 0.79$
	55-65	1	11.16	$\frac{1 - I_T/I}{0.9591} = 0.95$	1	22.33	$\frac{1 - I_T/I}{0.8453} = 1.00$
Estimated	40-49	0	6.89	$\frac{1 - I_T/I}{0.8958} = 1.00$	3	13.78	$\frac{1 - I_T/I}{0.6395} = 1.00$
	50-54	2	11.97	$\frac{1 - I_T/I}{0.9438} = 0.88$	5	23.95	$\frac{1 - I_T/I}{0.7929} = 0.99$
	55-65	1	11.16	$\frac{1 - I_T/I}{0.9608} = 0.95$	1	22.33	$\frac{1 - I_T/I}{0.8631} = 1.00$

\* The expected incidence in the absence of screening was obtained from cancer registry data (fixed) or estimated from the model of Day and Walter (estimated).

The sensitivity of around 100% in the oldest age group (55–64) was in accordance with earlier findings. Data of the first birth cohort of the DOM project (aged 50–64 at entry) were analysed previously and showed the same finding of a (nearly) 100% sensitivity.<sup>13,21</sup>

Most estimates of sensitivity indicated a lower sensitivity in women aged 50–54. As most women of this age group will be perimenopausal or early postmenopausal, a possible explanation for this finding could be more difficulty in reading mammograms of women around the menopause. This possibility has been described previously.<sup>22</sup>

Estimates of sojourn time and sensitivity differed when using fixed or estimated incidence rates. This difference was most marked in the age group 50–54. In this group, baseline incidence was 2.5 per thousand as estimated by the model whereas an incidence of 1.8 per thousand was expected from cancer registry data. Similar differences were found in the youngest age group, but did not lead to important differences in the estimates of mean sojourn time and sensitivity. Only in the oldest age group was the estimate from the model equal to the fixed value.

An explanation for the difference in baseline incidence could be that breast cancer incidence in both groups of younger screenees is higher than expected, which is contrary to what is usually found in screening projects. If this were true, the incidence in the non-participants should be lower than expected. For the age group 50–64, it was shown in a previous publication that there were no indications that this was the case.<sup>23</sup> This was investigated in the current study for the age group 40–49 by calculating incidence rates in non-participants until 3 years after the screening invitation. A mean incidence rate of 1.5 per thousand women-years at risk was calculated, which was equal to the expected rate. Together with the rate before the start of screening of this birth cohort, which was also 1.5 per thousand, a higher than expected incidence in screenees seemed an unlikely explanation for our findings. Another possibility could be a more complete registration of interval cancers than of the population at risk. Again, we did not have indications that this was the case. If this had a role, it is unlikely that registration of the interval cancers would be more incomplete in both younger age groups than in the oldest age group.

Finally, the underlying assumptions of the model, such as a negative exponential distribution of the sojourn time, could hold better for older than for younger women.

In essence, the general conclusions of this study remained the same, whether using externally fixed or estimated baseline incidence rates. Tumour growth rate is age dependent and varied from 1 year in women under 50 years of age to 3 years in women over 55. Age

specific sensitivity as estimated by two different methods pointed at an acceptable sensitivity both in women over and under the age of 50. This suggests that the most important cause of the current disappointing screening results in women under the age of 50 might be a higher tumour growth rate at a young age.

This study was funded by the "Praeventiefonds" and the ministry of Health. We thank J Fracheboud and B Slotboom for providing the data and PMG Peer for valuable comments.

- Fletcher SW, Black W, Harris R, Rimer BK, Shapiro S. Report of the international workshop on screening for breast cancer. *J Natl Cancer Inst* 1993;85:1644–6.
- Miller AB, Baines CJ, To T, et al. Canadian national breast screening study: 1. Breast cancer detection and death rates among women aged 40 to 49 years. *Can Med Assoc J* 1992;147:1459–76.
- Miller AB. Mammographic screening guidelines for women 40 to 49 and over 65 years old. *Ann Epidemiol* 1994;4:96–101.
- Peer PMG, Holland R, Hendricks JHCL, Mravunac M, Verbeek ALM. Age-specific effectiveness of the Nijmegen population-based breast cancer screening program: assessment of early indicators of screening effectiveness. *J Natl Cancer Inst* 1994;86:436–41.
- Shapiro S, Venet W, Strax P, Venet L. Current results of the breast cancer screening randomized trial: the Health Insurance Plan of greater New York. In: Day NE, Miller AB, eds. *Screening for breast cancer*. Toronto: Hans Huber publishers, 1988;3–15.
- Nyström L, Rutqvist LE, Wall S, et al. Breast cancer screening with mammography: overview of Swedish randomised trials. *Lancet* 1993;341:973–8.
- Moskowitz M. Breast cancer: age-specific growth rates and screening strategies. *Radiology* 1986;161:37–41.
- Spratt JS, Greenberg RA, Heuser LS. Geometry, growth rates and duration of cancer and carcinoma in situ of the breast before detection by screening. *Cancer Res* 1986;46:970–4.
- Tabár L, Fagerberg G, Day NE, Holberg L. What is the optimum interval between mammographic screening examinations? An analysis based on the latest results of the Swedish two-county breast cancer. *Br J Cancer* 1987;55:547–51.
- Verbeek ALM, Straatman H, Hendricks JHCL. Sensitivity of mammography in Nijmegen women under the age of 50: some trials with the Eddy model. In: Day NE, Miller AB, eds. *Screening for breast cancer*. Toronto, Hans Huber publishers, 1988:29–32.
- Peer PGM, Dijk JAAM van, Hendricks JHCL, Holland R, Verbeek ALM. Age-dependent growth rate of primary breast cancer. *Cancer* 1993;71:3547–51.
- Brekelmans CTM, Collette C, Fracheboud J, Waard F de. Breast cancer after a negative screen: follow-up of women participating in the DOM screening programme. *Eur J Cancer* 1992;28A:893–5.
- Day NE, Walter SD. Simplified models of screening for chronic disease: estimation procedures from mass screening programmes. *Biometrics* 1984;40:1–14.
- Day NE. Estimating the sensitivity of a screening test. *J Epidemiol Community Health* 1985;39:364–6.
- Cancer incidence and survival, 1975–1987*. Eindhoven: Comprehensive Cancer Centre South/Eindhoven Cancer Registry, 1991;24–25.
- Walter SD, Day NE. Estimation of the duration of a pre-clinical disease state using screening data. *Am J Epidemiol* 1983;118:865–86.
- Paci E, Duffy SW. Modelling the analysis of breast cancer screening programmes: sensitivity, lead time and predictive value in the Florence district programme (1975–1986). *Int J Epidemiol* 1991;20:852–8.
- Tabár L, Fagerberg G, Duffy SW, Day NE, Gad A, Grönroft O. Update of the Swedish two-county program of mammographic screening for breast cancer. *Radiologic Clin North Am* 1992;30:187–210.
- Moss SM, Coleman DA, Ellman R, et al. Interval cancers and sensitivity in the screening centres of the UK trial of early detection of breast cancer. *Eur J Cancer* 1993;29A:255–8.
- Harris R. Breast cancer among women in their forties: toward a reasonable research agenda. *J Natl Cancer Inst* 1994;86:410–2.
- Day NE, Walter SD, Tabár L, Fagerberg CJG, Collette HJA. The sensitivity of the results of different studies. In: Day NE, Miller AB, eds. *Screening for breast cancer*. Toronto, Hans Huber publishers, 1988:105–9.
- Whitehead J, Cooper J. Risk factors for breast cancer by mode of diagnosis: some results of a breast cancer screening study. *J Epidemiol Community Health* 1989;43:115–20.
- Collette HJA, Day NE, Rombach JJ, de Waard F. Evaluation of screening for breast cancer in a non-randomised study (the DOM project) by means of a case control study. *Lancet* 1984;i:1224–6.