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Breast Cancer After a Negative Screen: Follow-up of Women Participating in the DOM Screening Programme

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First-round screening results for women participating in the DOM project (a screening programme for early detection of breast cancer) are described for the age groups 40–49 and 50–64 at entry. In the younger age group, a low pick-up rate (1.96 per 1000) in proportion to the expected incidence rate in the absence of screening (1.46 per 1000) was found. For the older age group, these rates were 4.25 and 2.03, respectively, per 1000. Interval cancers occurred (relatively) more frequently in younger women. After 2 years the ratio between interval-cancers and screen-detected tumours was about 1:1 in the younger age group and 1:2.5 in the older age group. These different results can be caused by too low a sensitivity of mammography and/or a higher tumour growth rate at a young age. The sensitivity of the screen at various periods of follow-up, was compared: a rapidly decreasing sensitivity of mammography was seen for women under the age of 50, in contrast to a slower decrease for women over this age. This rapid decrease may be caused by a relatively high tumour growth rate in younger women.
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INTRODUCTION

In 1974, a population-based non-randomised screening programme for the early detection of breast cancer was started in the city of Utrecht (The Netherlands), the DOM project. In the beginning it was limited to the 1911–1925 birth cohort (women aged 50–64 at entry). The study design and results for this birth cohort have been described previously [1, 2]. From 1981 on other birth cohorts, including women aged 40–49, were also invited [3].

This gave us the opportunity to study the effect of screening in various age groups. It is known from other projects that screening results for women under the age of 50 are not promising [4–8]. One of the parameters to evaluate the (early) effect of screening is the number of cancers occurring after a negative screen, the so-called interval cancers.

High numbers of interval cancers within 2 years after a negative screen in women under the age of 50 are described [9, 10]. This can be explained by too low a sensitivity of mammography or a high tumour growth rate in young women. In order to differentiate between these two possibilities, information on age-specific tumour growth rate and distribution of the preclinical detectable phase is needed.

The purpose of this paper is to add some material to the discussion on whether or not to screen women under the age of 50.

PATIENTS AND METHODS

In 1974–1987, four successive birth cohorts of women living in the city of Utrecht and its suburbs, were invited for screening, with different study designs.

In this study we were interested in the 2-year follow-up of women after the first negative screen. For this reason the 1911–1925 birth cohort, that was offered a second screen after 1 year, was excluded.

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The first cohort described in this study consists of women aged 50–64 at entry (1926–1931 birth cohort, or 1917–1931 in suburbs participating for the first time). This group was first screened in 1981; a second round was offered after a 2-year interval.

The second cohort, 40–49 at entry (1932–1941 birth cohort), was screened from 1982 on and offered only one screen. The third cohort consists of women aged 40–44 at entry (1942–1945 birth cohort); this cohort was offered one screen, from 1985 onwards. For the analysis these three cohorts were combined and the resulting group was divided into women under and over the age of 50 at first screen.

The cancer registry, set up to evaluate the screening procedure, was used to obtain information about cancers occurring after a negative screen.

In this study, data on the occurrence of cancer were used from a selected region with a reliable follow up. The length of the interval was computed by comparing the date of diagnosis of the cancer with the date of the previous screen. This was done for the first 2 years after screening.

For each age group, the ratio between the number of interval cases and screen-detected cancers at the first round was calculated, together with the sensitivity of the screening test.

As we have no reasons to assume that in the 2-year follow-up period the size of the population-at-risk changed differently in the two age groups, absolute numbers are used.

Sensitivity of the screening test

The sensitivity of a screening test is defined as the proportion of truly diseased persons in the screened population who are identified as diseased by the screening test [11].

Sensitivity is important as a general 'quality control' of the procedure. Moreover, sensitivity may be estimated by subgroup to identify those individuals for whom screening is of the greatest potential benefit [12].

It is customary to described the performance of a screening test in terms of the following 2 × 2 table [13]:

		True disease state	
		+	−
Screening test	+	a	b
	−	c	d

With a = number of true positives
b = number of false positives
c = number of false negatives
d = number of true negatives.

The 'classical' approach to estimate sensitivity is to divide the number of true positives (a) by the sum of this number and the number of cancers occurring within a certain interval after a negative screen (c): sensitivity = a/(a+c).

A 1-year interval is usually chosen. However, this decision is rather arbitrary. In this study we estimate sensitivity, according to this method, by using intervals with different length of time (0.5, 1, 1.5, and 2 years), both for women under the age of 50 and in those over this age.

RESULTS

Table 1 shows the number of women examined in the first round per age group, the number of cancers detected at first screening, the pick-up rate and the expected incidence rate in the absence of screening. For the age group 40–49, a pick-up rate of 1.96 per 1000 was found, whereas the expected incidence rate in the absence of screening was 1.46 per 1000. These rates were 4.25 and 2.03, respectively (per 1000) in the age group 50–64.

Table 1. The DOM project for the early detection of breast cancer: first round results (1981–1987)

Age at entry (years)	No. of women investigated	No. of cases detected in 1st round	Pick-up rate with 95% C. I. (per 1000)	Expected* Inc. rate (per 1000)
40–49	12 731	25	1.96 (1.19–2.73)	1.46
50–64	15 767	67	4.25 (3.23–5.27)	2.03

* Expected incidence rates in the absence of screening based on first hospital admissions for breast cancer, total Dutch population (1985) [14].
C.I. = confidence interval.

In Table 2 the age specific numbers of interval cancers are presented as well as the sensitivity of the test, using different periods of follow-up.

Interval cancers occurred (relatively) more frequently in younger than in older women. After 1.5 years, the number of interval cancers (n = 24) in the former group already equalled the number of screen-detected tumours (n = 25); a ratio of 1:1. After 2 years, this ratio was 1:0.75 (33:25), versus a ratio of about 1:2.5 (26:67) in the older age group.

The sensitivity of mammography was estimated using follow-up periods from 6 months up to 2 years.

After 6 months, the sensitivity for the younger group was 89% vs. 94% in the older age group; the 95% confidence interval in the younger age group contained that of the older age group.

After 1 year, a sensitivity of 76% was observed for the younger age group versus 88% in the older age group, while the 95% confidence intervals still overlapped one another.

In contrast to the slower decrease in sensitivity for the older age group, the sensitivity for the younger age group decreased rapidly after this period (Fig. 1).

DISCUSSION

There is general agreement about the benefit of screening for breast cancer in women over the age of 50.

On the contrary, screening of women under the age of 50 remains controversial. Studies including women under the age

Table 2. Estimates of age-specific sensitivity, using various periods of follow-up

Duration of follow-up (years)	40–49 years at entry			50–64 years at entry		
	c	S	95% C.I.	c	S	95% C.I.
0.5	3	0.89	0.77–1.01	4	0.94	0.88–1.00
1	8	0.76	0.61–0.91	9	0.88	0.81–0.95
1.5	24	0.51	0.37–0.65	16	0.81	0.73–0.89
2	33	0.43	0.30–0.56	26	0.72	0.63–0.81

c = (cumulative) number of interval cancers; S = sensitivity with 95% confidence interval (C.I.). Sensitivity estimated by S = $a/(a+c)$, with a = number of screen-detected cases in the 1st round.

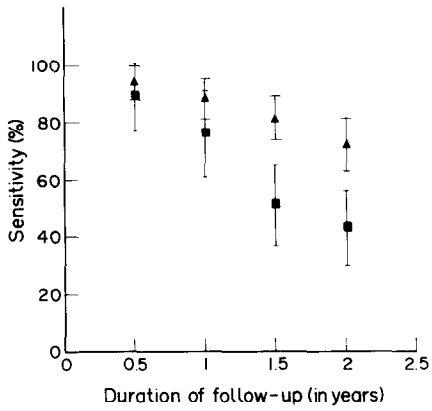

Fig. 1. Age-specific sensitivity using various periods of follow-up. ■ = Sensitivity with 95% C.I., age group 40–49. ▲ = Sensitivity with 95% C.I., age group 50–64.

of 50 all show a smaller or delayed effect of screening on breast cancer mortality or no effect at all in this age group [4–8].

In this study, a low pick-up rate (1.96 per 1000) in proportion to the expected incidence rate in the absence of screening (1.46 per 1000) was found in the younger age group.

For the older age group, these rates were 4.25 and 2.03, respectively (per 1000).

Comparison of the occurrence of cancers after a negative screen in women under 50 and in those over the age of 50 showed that interval cancers occurred relatively more frequently in the younger age group. After 2 years, the ratio between interval cancers and screen-detected cancers was more than 1:1 in the younger age group, while it was 1:2.5 in the older age group. This is in accordance with other findings [10].

Possible explanations for these different screening results are too low a sensitivity of the screening test and/or a higher growth rate at a younger age.

There are several ways to estimate sensitivity. We used the 'classical' method. As Day pointed out this method may be biased, amongst other things because of the inclusion of cases which surface after screening but were not in the pre-clinical detectable phase (PCDP) at the time of the test. He proposed some alternative ways of estimating sensitivity based only on incidence rates and knowledge about the distribution of the pre-clinical detectable phase [15]. Still, the 'classical' approach, an easy and quick method to estimate sensitivity, is widely used.

We think that by using this method in a different way, by means of comparing various periods of follow-up for women under and over the age of 50, some preliminary inferences can be made on possible causes of the different screening results in these two age groups. To exclude (as much as possible) cases that were not yet in the PCDP at the time of screening, a 6-month interval was used. This gives a more pure estimate of sensitivity for the first interval, as the cancers occurring in this interval are almost certainly missed cases.

In this study it appeared that the test's sensitivity after 6 months was quite acceptable in the younger age group (89%, versus 94% in the older age group). The increasing difference in sensitivity with each longer period could be caused by the occurence of rapidly growing cancers in the younger age group, due to the relatively higher growth rate of tumours at this age [16, 17]. In other words, it might be not so much a low sensitivity, as a (relatively) higher growth rate of tumours in young women, that caused the difference in the occurrence of cancers (over a longer period) found after a negative screen in women under 50 and in those over this age.

This would point to the need of a high screening frequency in this age group (once a year), in case a screening programme for women under the age of 50 would be started. However, more data on the effect of screening on mortality in this age group and a cost-effectiveness analysis are needed to decide whether or not to screen women under the age of 50.

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