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THE INFLUENCE OF PARTICIPATION AND REGULARITY OF PARTICIPATION IN THE BREAST CANCER SCREENING PROGRAM ON TUMOUR CHARACTERISTICS

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Contents

Abstract

Background: Breast cancer is the most common form of cancer in women in the Netherlands. To improve the prognosis for women diagnosed with breast cancer, a national screening program started in 1989. Until 1999, only women aged between 50 and 70 years old were invited to participate in the screening program. From then on, women were invited until the age of 75. However, the effectiveness of screening is unclear. Hardly no information can be found about the influence of participation and regularity of participation in the screening program. This is especially the case for the elderly women that are invited to participate in screening.

Objective: To determine whether participation and regularity of participation in the screening program influences the tumour characteristics in women aged between 70 and 75 years and women aged 75 years and older, diagnosed with breast cancer between 1999 and 2012 in the northern region of the Netherlands.

Method: Data from the Netherlands Cancer Registry and Bevolkingsonderzoek Noord were matched. Using Pearson's Chi-square tests, tumour characteristics were compared between women who have participated in the screening program and who have never participated, and between women who have participated on a regular and irregular basis. For both analyses a distinction was made between women aged between 70 and 75 years and women aged older than 75 years. The analyses are performed in Stata version 13.

Results: Participation in screening shows lower tumour stage, less lymph node involvement, less metastasis and more positive receptor statuses compared to no participation in women aged between 70 and 75 years. No differences were found between women who participated regularly or irregularly. When comparing women over 75 years old that participated in screening or never participated, only a difference can be found in tumour stage and oestrogen receptor status. No differences were found in tumour characteristics between women who participated regularly or irregularly.

Conclusion: Participation in breast cancer screening by elderly women appears to influence tumour characteristics in a positive way compared to no participation. However, it does not seem to have any influence whether these women participate regularly or irregularly.

Background

Breast cancer is the most common form of cancer in women in the Netherlands (1). In 2011, 16,031 per 100,000 women were diagnosed with breast cancer (2). Mortality due to breast cancer in that year was 3,621 per 100,000 women (3).

To increase the possibility of successful treatment and to reduce mortality, a national screening program started in 1989 (4). This screening program is organised by the 'Bevolkingsonderzoek Borstkanker'. All women aged between 50 and 70 years were invited to participate once every 24 months (5). Since 1999 women between 70 and 75 years old are also invited (5). Participation in the screening program is voluntary (5). In 2012, 1,266,559 women in the Netherlands received an invitation, and 986,084 of those women participated in screening (5).

Relatively most breast cancer deaths are found in elderly women, aged 70 years and older (figure 1) (6). By early detection, the number of deaths in this age group can be decreased, because there is a bigger chance of detection of smaller tumours and successful treatment (7). This high mortality can be decreased by screening of these women.

However, the effectiveness of screening for this age group is being questioned. It is unclear whether screening influences mortality of the disease, due to lack of clear evidence (4, 8). Also the quality of breast cancer treatment has improved and women have become more aware of the disease and therefore, for example, perform more breast self-examination which influences mortality (4, 5).

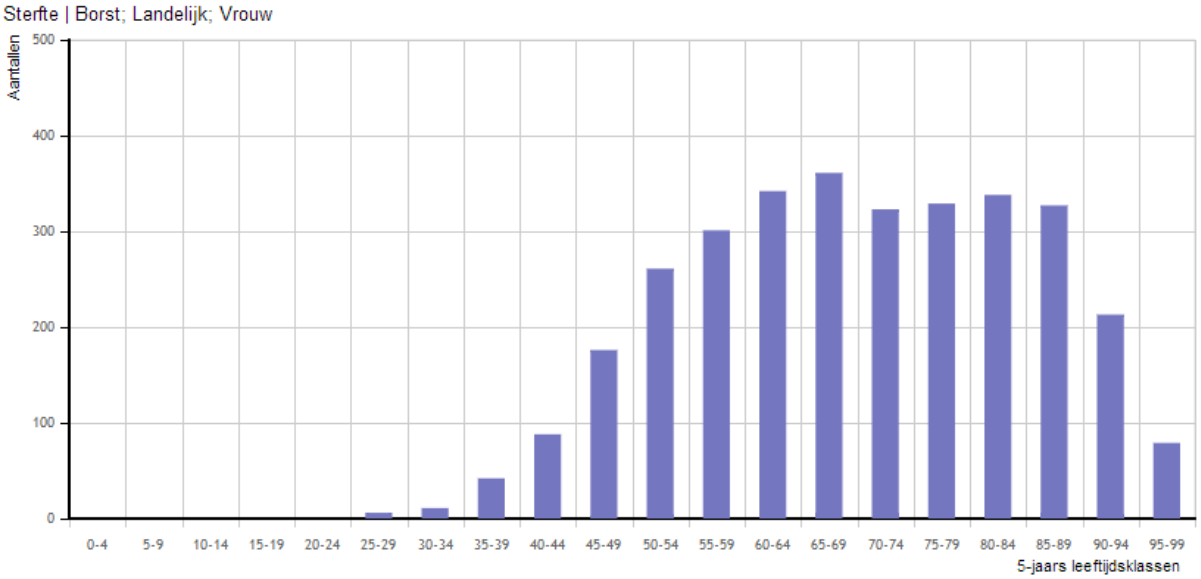


Figure 1: Mortality of breast cancer in women in 2012, per five-year age categories (6).

In addition to the unclear effectiveness, screening of elderly women can also lead to over-diagnosis (4, 5, 7, 9-11) and additional physical and psychological burden (4, 7). By participating in screening, it can be expected that more smaller tumours and more ductal carcinoma in situ (DCIS) will be detected, and as a consequence will be further researched and possibly be treated. However, if an older woman would not have participated in screening, this abnormality might have never been detected and the woman might not have perceived any harm of it during the rest of her life (5, 7, 10, 11).

This is a reason to question the value of breast cancer screening in elderly women. There is also not much evidence that supports continuing screening in elderly women (4, 8). Most studies performed on the subject include younger women. The studies that are available about screening elderly women show different results. For example, it is stated that screening can do more harm than good in elderly women (10, 11), while other studies show positive results on mortality, tumour characteristics and life expectancy (8, 12). Nowadays people grow older in a relatively good health state (4). Therefore it can be advantageous for these relatively healthy women to participate in the screening program (4).

Since 1999, women aged between 70 and 75 years are invited to participate in screening. However, this increase and the effectiveness of screening for this group of women was based on limited scientific evidence: outcomes of only two studies were available (13). These studies showed no significant results in screening elderly women, but gave some indications that screening elderly women might have a positive influence on breast cancer mortality in this group (13). Also there were no arguments against participation of these women (13). Therefore, despite limited evidence, the Health Council of the Netherlands concluded that women aged between 70 and 75 years should also be invited to participate in the screening program.

The influence of regularity of participation in the screening program on tumour characteristics is unclear, especially in elderly women with breast cancer. Hardly no information can be found about this subject. It can be expected that a high regularity of participation has a positive influence on tumour characteristics, for example lower tumour stages and less metastasis at diagnosis. It can also be expected that participation in screening has a protective effect: after the age of 75, when women are no longer invited for participation, less tumours will be diagnosed, because these tumours should have been detected during screening.

The lack of evidence on effectiveness of screening in elderly women makes it difficult to indicate whether it is useful to screen women aged 70 years and older to lower mortality. It is also unclear what influence participation of these women in the screening program has on tumour characteristics. Therefore, the aim of this study is to determine the influence of participation and regularity of participation in the screening program on tumour characteristics in women aged 70 years and older with breast cancer.

Method

Sources

The women included in this study were selected from the Netherlands Cancer Registry (CR) and the 'Bevolkingsonderzoek'. The Netherlands Cancer Registry records all information about malignancies detected in patients in the Netherlands, like the type of malignancy, TNM-stage and treatment. The BOB is divided in five regions that each perform their own screening program and have their own resources. These organisations also collect information about invitations sent for participation, attendance of each of the screening rounds and the results of the screening mammogram. For this study, data from the 'Bevolkingsonderzoek Noord' (BOB) are used. This region covers the three northern provinces Drenthe, Friesland and Groningen. The matching data from the CR were obtained on region level using zip-codes of these regions. Permission for using both data sources was obtained by the Committee of Privacy of the CR and the BOB. Permission of the women included in this study was not explicit, however at the moment of participation in the screening program, every woman fills in a form on which she can indicate whether or not she wants her information to be shared with and/or used by other persons and organisations, like the Comprehensive Cancer Centre the Netherlands (IKNL). If she explicitly states that she does not want her information to be shared and/or used, it will not be included in the data.

Study population

Patients included in the study were diagnosed with breast cancer between 1999 and 2012. 1999 is the first year in which women between 70 and 75 years were screened since the increased age limit of the screening program. Only women who have developed breast cancer and/or were screened after the age of 70 were included in the study, since the goal of this research was to determine the effect of participation and regularity of participation in the screening program on tumour characteristics in elderly women. Men were excluded from the data, since they do not participate in the BOB and breast cancer rarely occurs in men.

In the study, only women who are screened in the three northern provinces that are covered by the BOB were included. Including the data of all women in the Netherlands would cost a lot of time due to getting permission to use the data. There was not sufficient time available to get this permission. The attendance rate of screening for the northern region is comparable to the national attendance rate (5, 14). Using only the information of the region covered by the BOB will give enough data to give results which could be generalizable for the whole of the Netherlands.

To do the analyses, two cohorts were used. The first cohort is based on the CR and existed of women who are 70 years or older and were diagnosed with breast cancer between 1999 and 2012. This cohort was matched with a cohort of the BOB that contained information about women who were 70 years or older in the same period and participated in screening. Women with a match are women who were diagnosed with breast cancer and have participated in screening and women without a match, are women who were diagnosed with breast cancer, but have never participated in screening. All the women who participated less than four times were left out of the cohort, except for the women who have never participated in screening. Women who participated less than four times, will have only one or two intervals between the screening rounds they participated in and probably this time interval will be shorter than 108 months. Therefore it is likely that these women will always be regularly participating in screening while this might not always be true. This could bias the results. Leaving these

women out of the cohort, creates a more equal and comparable cohort. That means that the cohort existed of women older than 70 years with breast cancer that have participated in screening at least four times, and women older than 70 years with breast cancer that have never participated in screening. This cohort was used to determine the influence of participation in the screening program on tumour characteristics in elderly women. A more elaborate description of the analysis will be given in below in 'Statistical analysis'.

The second cohort is based on the BOB and consisted of all women who were 70 years or older between 1999 and 2012 and have participated in screening in the northern region of the Netherlands at least four times. To this cohort, information of the CR was matched. Women with a match, are women that participated in screening and were diagnosed with breast cancer. Women without a match are women who have participated in screening, but were not diagnosed with breast cancer. If a woman participated less than four times in screening, she was left out of the cohort for the same reason as in the CR cohort. Therefore this cohort exists of all women aged 70 years or older who have participated in screening at least four times, of which some have breast cancer and others do not. For all of these women, information about all screening rounds they participated in since they were 50 years old were available, for example the dates of the rounds she participated in and the results of the screening mammogram (BI-RADS for the left and right breast). This cohort was used to determine the influence of regularity of participation in the screening program (regular or irregular participation) on tumour characteristics in elderly women. A more elaborate description of the analysis will be given below.

Statistical analysis

The analyses were performed using Stata version 13. For the analysis of the data, the two cohorts were used. In the analyses, a distinction was made between women aged between 70 and 75 years and women aged older than 75 years. The first cohort, the CR cohort, was used to determine the relation of the tumours to the screening program for women aged between 70 and 75 years and women older than 75 years, and the way of detection and incidence of tumours per age for the whole cohort. It was also used to determine the differences in tumour characteristics between women who have participated in screening and women who have never participated, for both women aged between 70 and 75 years and women older than 75 years. This cohort was also used to determine whether there was a difference in the number of DCIS between women who participated regularly or irregularly and women who never participated. The regularity of participation could also be determined in this cohort, because for the women in this cohort who participated in screening also the last four screening rounds and the time interval between them was available because the CR cohort and data of the BOB were matched.

The second cohort, the BOB cohort, was used to analyse the influence of regularity of participation (regular vs. irregular participation) in the screening program on tumour characteristics for women between 70 and 75 years and women older than 75 years. It was also used to determine whether or not there is a difference in the incidence of breast cancer between women who participated regularly and irregularly in the total cohort. This last analysis is the only analysis in which data was used of women who participated in screening, but were not diagnosed with breast cancer. In the other analyses using this cohort, these women were left out of the analysis.

For determining the relation of tumours to the screening program, and the way of detection and incidence of tumours per age, counts were made and visually represented in charts. To determine

differences in tumour characteristics between women who participated in screening and women who did not, a Pearson's Chi-square test was used, with α=0.05. When the analysis included small subgroups (smaller than six), a Fisher's exact test was used, also with α=0.05. This analysis is done for comparing participation and non-participation in women aged 70 to 75 years, and for comparing participation and non-participation in women older than 75 years. The same is done for determining differences in tumour characteristics in women that participated regularly or irregularly, for both women aged between 70 and 75 years and women older than 75 years. It will be indicated per analysis what test was used.

For determining the difference in the number of tumours detected between women who participated in screening regularly or irregularly for the whole BOB cohort, a Pearson's Chi-square test was used, with α=0.05. A Pearson's Chi-square test (α=0.05) was also used for determining the difference in the number of DCIS detected between women aged between 70 and 75 years who participated regularly or irregularly.

Unknown data were not included in the analysis. This means that for both cohorts, the number of unknown data were left out of the analysis. The number of unknown data is shown in the table below, with what percentage the unknown data are from the total number of women per tumour characteristic, per age group. A distinction is made between the two cohorts, the tumour characteristics and the two age groups.

CR cohort*	Tumour characteristic	Number of unknown data (%)
	Tumour stage	
	70-75 years	50 (1.9)
	>75 years	160 (4.2)
	Lymph node involvement	
	70-75 years	258 (9.9)
	>75 years	455 (11.9)
	Metastasis	
	70-75 years	101 (3.9)
	>75 years	972 (25.5)
	Progesterone receptor status	
	70-75 years	860 (33.0)
	>75 years	1,191 (31.2)
	Oestrogen receptor status	
	70-75 years	709 (27.2)
	>75 years	949 (24.9)
	Her2 receptor status	
	70-75 years	991 (38.0)
	>75 years	1,649 (43.2)

BOB cohort**	Tumour characteristic	Number of unknown data (%)
	Tumour stage	
	70-75 years	25 (1.3)
	>75 years	10 (1.8)
	Lymph node involvement	
	70-75 years	161 (8.3)
	>75 years	19 (3.4)
	Metastasis	
	70-75 years	38 (2.0)
	>75 years	25 (4.5)
	Progesterone receptor status	
	70-75 years	553 (28.6)
	>75 years	71 (12.7)
	Oestrogen receptor status	
	70-75 years	453 (23.4)
	>75 years	36 (6.5)
	Her2 receptor status	
	70-75 years	659 (34.0)
	>75 years	77 (13.8)

* The CR cohort exists of women diagnosed with breast cancer, who were screened or who were never screened (N=6,421).
** The BOB cohort exists of women screened by the BOB, diagnosed with breast cancer or not diagnosed (N=98,119). These missing data only involve the women who participated in screening and were diagnosed with breast cancer (N=2,493).

Outcome measures

In this study, the influence of participation to the screening program on tumour characteristics in elderly breast cancer patients was determined. These tumour characteristics are tumour stage, lymph node involvement, metastasis, morphology, oestrogen receptor status, progesterone receptor status

and Her2 receptor status. Tumour stage is divided in T0 (no evidence of primary tumour), T1 (<2cm), T2 (between 2 and 5cm), T3/4 (>5cm and extension to other tissues) and Ductal Carcinoma in Situ (DCIS). Usually, T3 and T4 are separate categories, however in this research they are combined because both groups are relatively small and both are considered as a higher stage tumour. Lymph node involvement is classified as positive or negative, just as metastasis. Morphology is classified as ductal, lobular, mixed ductal and lobular or other. Oestrogen, progesterone and Her2 receptor status are divided in positive and negative.

A distinction is made in the different ways a tumour is detected. A tumour can be screen detected, which means that a tumour is found at a screening mammogram and is diagnosed within 12 months after participation in screening that lead to a referral to a physician. An interval tumour is a tumour that is detected between two consecutive screening rounds: the tumour is not found at the screening mammogram, but is diagnosed within 24 months after the last screening round a woman participated in. It can also be a tumour that is detected at screening for which a woman got referred to a physician, but was only diagnosed between 12 and 24 months after screening. A 'no relation tumour' is a tumour that is detected more than 24 months after the last participation in the screening program, but was not visible on a screening mammogram. It can also be a tumour that was visible on a screening mammogram, but is diagnosed as breast cancer more than 24 months after screening. This means that women with a no relation tumour have participated in the screening program at least four times, but the tumour has no relation to the screening program in a sense that it was not diagnosed directly after screening. Women with a non-screen tumour have never participated in the screening program since they were first invited.

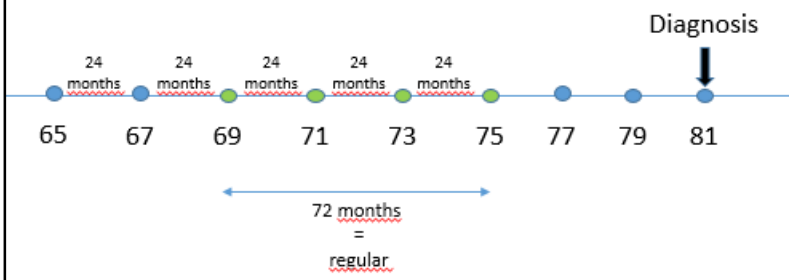
Participation and regularity of participation

In the Netherlands, women aged between 50 and 75 years are invited to participate in the screening program once every two years. In this study, participation to the screening program is defined as participating at least four times in screening, regardless the time interval between these screening rounds. This means that non-participation is defined as having never participated in any of the screening rounds a woman got invited to. This definition is the same for women aged between 70 and 75 and for women older than 75 years. Since women older than 75 years are no longer invited for participation in the screening program, participation is based on former (non-)participation in the screening program.

Regularity of participation in the screening program is determined by taking length in months of the three time intervals between the last four screening rounds a woman has participated in before she was diagnosed with breast cancer. Some examples are shown in figure 2. In this study it is assumed that participation in the last screening rounds mostly influence tumour characteristics. Since women get invited for participation in the screening program once every two years, women can participate only three times between the ages of 70 and 75. This means that also screening rounds before the age of 70 are taken into account.

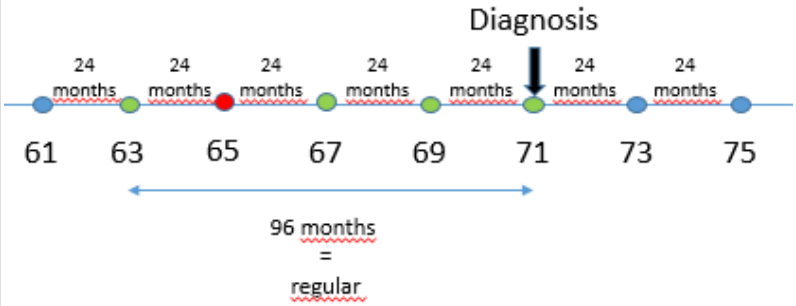
To determine the regularity of participation, so whether a woman participated regularly or irregularly in screening, a limit of 36 months per interval was used. This means that over the complete time period, a limit of 108 months was used to determine whether a women participated regularly or irregularly (see figure 2). Using a limit of 36 months per interval takes into account the possibility of a woman moving within the region, which can cause her to miss a screening round in the community she comes from, and, if any, participation in the new community she lives in. It also takes into account

possible delay and breakdown of equipment of the BOB, which can cause the screening to take place at a later time. This can increase the interval to more than 24 months after the previous screening. After taking this into account, it can be said that if a woman does not participate in screening four times within 108 months, her participation in the screening program is irregular.



2.A. A woman diagnosed at the age of 81, who participated in the last four screening rounds she was invited to. This tumour is classified as a no relation tumour, because she is diagnosed more than 24 months after her last participation.

2.B. A woman diagnosed with breast cancer at the age of 72. She did not participate four times within 108 months before she was diagnosed. This tumour is classified as an interval tumour, because it is not detected during screening, but within 12 to 24 months after participating in screening.



2.C. A woman who was diagnosed with breast cancer at the age of 71 during screening (screen detected tumour). She missed one screening round for example due to moving within the region, but is still regular because she still participated four times within 108 months.

Figure 2: examples of regular and irregular participation, and the way of detection of the tumour. The green dots indicate screening rounds a woman has participated in, the red dots indicate screening rounds a woman missed.

Results

Patient characteristics

The characteristics of the study population based on the CR cohort can be found in Table 1. In the CR cohort, 6,421 women were included, with an average age of 78.7 years (SD=6.6). Of those women, 2,607 women (41%) were diagnosed at the age of 70 to 75 years (M=72.3, SD=1.7), and 3,814 women (59%) at an age older than 75 years (M=83.1, SD=4.8). In the group of 70 to 75 years, 1,369 women (53%) have a screen detected tumour, 431 women (17%) have an interval detected tumour, 807 women (31%) have a no relation tumour, and 671 women (26%) have a non-screen tumour. In the group of women aged older than 75 years, 1 woman (0.03%) has a screen detected tumour, 53 women (1%) have an interval detected tumour, 503 women (13%) have a no relation tumour and 3,257 women (85%) have non-screen tumour.

In table 1, also a distinction in participation and non-participation is made. The participation group exists of screen detected, interval and no relation tumours, the non-participation group exists of the non-screen tumours. The total number of women in this group is also 6,421, of which 2,493 women (38.8%) participated in screening at least four times, and 3,928 women (61.2%) never participated in screening. 2,607 women were diagnosed with breast cancer between the ages of 70 and 75, of which 1,936 (74.3%) participated in screening at least four times and 671 (25.7%) never participated. Of the women aged over 75 years (N=3,814), 557 women (14.6%) participated in screening and 3,257 women (85.4%) never participated.

Table 2 shows the patient characteristics of the BOB cohort, used to determine the influence of regularity of participation in the screening program in women aged between 70 and 75 years and women older than 75 years. A total of 98,119 women were included. 95,912 women (97.8%) participated regularly in screening and 2,207 women (2.2%) were irregularly participating. Looking at the number of women diagnosed with breast cancer, a total of 2,493 women were diagnosed, of which 2,432 women (97.6%) participated regularly and 61 women (2.4%) irregularly. Of the women diagnosed with breast cancer, 1,936 (77.7%) were aged between 70 and 75 years, and 557 women (22.3%) were aged older than 75 years. Of the women diagnosed with breast cancer, aged between 70 and 75 years, 1,886 women (97.4%) participated regularly in screening, and 50 (2.6%) participated irregularly. 98.0% (N=546) of the women older than 75 years who were diagnosed with breast cancer participated in screening on a regular basis, while 2.0 % (N=11) participated on an irregular basis.

Table 1: Patient characteristics of the CR cohort. Women aged 70 years and older, diagnosed with breast cancer between 1999 and 2012 in the northern region of the Netherlands, matched with the BOB cohort.

		Participation				Non-participation	Total	
		Screen detected tumours (%)	Interval tumours (%)	No relation tumours (%)	Total number of participation tumours (%*)	Non-screen tumours (%)	Total (100%)	P-value between participation and non-participation **
Nr. of women		1,370 (21.4)	484 (7.5)	639 (10.0)	2,493 (38.8)	3,928 (61.1)	6,421	
Age at diagnosis	70-75 years	1,369 (52.5)	431 (16.5)	136 (5.2)	1,936 (74.3)	671 (25.8)	2,607	
	>75 years	1 (0.03)	53 (1.3)	503 (13.2)	557 (14.6)	3,257 (85.4)	3,814	
Tumour characteristics in women aged between 70 and 75 years								
Tumour stage	T0	0	7 (100,0)	0	7 (100)	0	7	0.00
	T1	978 (62.0)	196 (12.4)	72 (4.6)	332 (21.0)	332 (21.0)	1,578	
	T2	192 (33.4)	159 (27.7)	40 (7.0)	184 (32.0)	184 (32.0)	575	
	T3	15 (27.8)	14 (25.9)	3 (5.6)	22 (40.7)	22 (40.7)	54	
	T4	5 (7.6)	8 (12.1)	8 (12.1)	45 (68.2)	45 (68.2)	66	
	DCIS	170 (61.4)	35 (12.6)	9 (3.2)	63 (22.7)	63 (22.7)	277	
	Unknown	9 (18.0)	12 (24.0)	4 (8.0)	25 (50.0)	25 (50.0)	50	
Lymph node involvement	Yes	279 (42.8)	132 (20.2)	39 (6.0)	450 (69.0)	450 (69.0)	652	0.00
	No	963 (56.7)	270 (15.9)	92 (5.4)	1,325 (78.1)	372 (21.9)	1,697	
	Unknown	127 (49.2)	29 (11.2)	5 (1.9)	161 (62.4)	97 (37.6)	258	
Metastasis	Yes	6 (13.6)	13 (30.0)	5 (11.4)	24 (54.5)	24 (54.5)	44	0.00
	No	1,354 (55.0)	398 (16.2)	122 (5.0)	1,874 (76.1)	588 (23.9)	2,462	
	Unknown	9 (8.9)	20 (19.8)	9 (8.9)	38 (37.6)	63 (62.4)	101	
Morphology	Ductal	1,130 (53.7)	325 (15.4)	112 (5.3)	1,567 (74.5)	1,567 (74.5)	2,104	0.43
	Lobular	145 (45.2)	77 (24.0)	12 (3.7)	234 (72.9)	87 (27.1)	321	
	Mixed ductal lobular	26 (61.9)	5 (11.9)	4 (9.5)	35 (83.3)	7 (16.7)	42	
	Other	68 (48.6)	24 (17.1)	8 (5.7)	100 (71.4)	40 (28.6)	140	
Progesterone receptor status	Positive	703 (57.6)	202 (16.5)	73 (6.0)	978 (80.1)	978 (80.1)	1,221	0.14
	Negative	234 (44.5)	131 (24.9)	40 (7.6)	405 (77.0)	121 (23.0)	526	
	Unknown/not determined	432 (50.2)	98 (11.4)	23 (2.7)	553 (64.3)	307 (35.7)	860	
Oestrogen receptor status	Positive	905 (55.6)	286 (17.6)	98 (6.0)	1,289 (79.2)	1,289 (79.2)	1,627	0.005
	Negative	102 (37.6)	66 (24.4)	26 (9.6)	194 (71.4)	77 (28.4)	271	
	Unknown/not determined	362 (51.1)	79 (11.1)	12 (1.7)	453 (63.9)	256 (36.1)	709	

Her2 receptor status	Positive	48 (35.0)	39 (28.5)	12 (8.8)	99 (72.3)	99 (72.3)	137	0.04
	Negative	803 (54.3)	275 (18.6)	100 (6.8)	1,178 (79.6)	301 (20.4)	1,479	
	Unknown/not determined	518 (52.3)	117 (11.8)	24 (2.4)	659 (66.5)	332 (33.5)	991	
Tumour characteristics in women aged >75 years								
Tumour stage	T0	0	0	2 (33.3)	2 (33.3)	2 (33.3)	6	0.00
	T1	1 (0.1)	26 (2.1)	202 (16.6)	229 (18.8)	988 (81.2)	1,217	
	T2	0	20 (1.2)	221 (13.0)	241 (14.2)	1,456 (85.8)	1,697	
	T3	0	2 (1.0)	22 (10.9)	24 (11.9)	177 (88.1)	201	
	T4	0	1 (0.3)	23 (6.2)	24 (6.5)	345 (93.5)	369	
	DCIS	0	3 (1.8)	24 (14.6)	27 (16.5)	137 (83.5)	164	
	Unknown	0	1 (0.6)	9 (5.6)	10 (6.3)	150 (93.8)	160	
Lymph node involvement	Yes	0	19 (1.5)	180 (14.4)	199 (15.9)	199 (15.9)	1,248	0.93
	No	1 (0.05)	33 (1.6)	305 (14.4)	339 (16.1)	1,772 (83.9)	2,111	
	Unknown	0	1 (0.2)	18 (4.0)	19 (4.2)	436 (95.8)	455	
Metastasis	Yes	0	3 (2.8)	20 (18.9)	23 (21.7)	23 (21.7)	106	0.42
	No	1 (0.04)	49 (1.8)	461 (16.8)	509 (18.6)	2,227 (81.4)	2,736	
	Unknown	0	3 (0.3)	22 (2.3)	25 (2.6)	947 (97.4)	972	
Morphology	Ductal	1 (0.03)	41 (1.4)	390 (13.2)	432 (14.7)	432 (14.7)	2,944	0.33
	Lobular	0	7 (1.3)	69 (13.1)	76 (14.4)	452 (85.6)	528	
	Mixed ductal lobular	0	1 (1.7)	12 (20.3)	13 (22.0)	46 (78.0)	59	
	Other	0	4 (1.4)	32 (11.3)	36 (12.7)	247 (87.3)	283	
Progesterone receptor status	Positive	1 (0.05)	29 (1.6)	305 (16.5)	335 (18.1)	335 (18.1)	1,846	0.44
	Negative	0	15 (1.9)	136 (17.5)	151 (19.4)	626 (80.6)	777	
	Unknown/not determined	0	9 (0.8)	62 (5.2)	71 (6.0)	1,120 (94.0)	1,191	
Oestrogen receptor status	Positive	1 (0.04)	37 (1.5)	392 (16.0)	430 (17.5)	430 (17.5)	2,456	0.00
	Negative	0	12 (2.9)	79 (19.3)	91 (22.2)	318 (77.8)	409	
	Unknown/not determined	0	4 (0.4)	32 (3.4)	36 (3.8)	913 (96.2)	949	
Her2 receptor status	Positive	0	2 (1.1)	35 (18.6)	37 (19.7)	37 (19.7)	188	0.40
	Negative	1 (0.05)	44 (2.2)	397 (20.1)	442 (22.4)	1,535 (77.6)	1,977	
	Unknown/not determined	0	7 (0.4)	71 (4.3)	78 (4.7)	1,571 (95.3)	1,649	

* Percentage is determined using the total of all the tumours in the participation group as a percentage of the total number of tumours detected.

** P-values marked with an asterisk are determined using a Fisher's exact test instead of a Pearson's Chi-square test. P-values are based on the total number of participation tumours and the non-participation tumours.

Table 2: Patient characteristics of the BOB cohort. Women, aged 70 years and older, screened between 1999 and 2012 in the northern region of the Netherlands, merged with the CR cohort.

			Regular participation (%)	Irregular participation (%)	Total (100%)	P-value *
Total nr. of women			95,912 (97.8)	2,207 (2.2)	98,119	
	Nr. of women diagnosed **		2,432 (97.6)	61 (2.4)	2,493	0.22
	Nr. of women not diagnosed		93,480 (97.8)	2,146 (2.2)	95,626	
Age at diagnosis	70-75 years		1,886 (97.4)	50 (2.6)	1,936	
	>75 years		546 (98.0)	11 (2.0)	557	
Tumour characteristics in women aged between 70 and 75 years						
	Tumour stage	T0	7 (100)	0	7	0.45*
		T1	1,214 (97.4)	32 (2.6)	1,246	
		T2	383 (98.0)	8 (2.0)	391	
		T3	31 (97.0)	1 (3.0)	32	
		T4	19 (90.5)	2 (9.5)	21	
		DCIS	207 (97.0)	7 (3.0)	214	
		Unknown	25 (100)	0	25	
	Lymph node involvement	Yes	441 (98.0)	9 (2.0)	450	0.40
		No	1,289 (97.3)	36 (6.7)	1,325	
		Unknown	156 (97.0)	5 (3.0)	161	
	Metastasis	Yes	24 (100)	0	24	1.00*
		No	1,824 (97.3)	50 (2.7)	1,874	
		Unknown	38 (100)	0	38	
	Morphology	Ductal	1,527 (97.4)	40 (2.6)	1,567	0.59*
		Lobular	226 (96.6)	8 (3.4)	234	
		Mixed ductal lobular	34 (97.1)	1 (2.9)	35	
		Other	99 (99.0)	1 (1.0)	100	
	Progesterone receptor status	Positive	950 (97.1)	28 (2.9)	978	0.88
		Negative	394 (97.3)	11 (2.7)	405	
		Unknown/not determined	542 (98.0)	11 (2.0)	553	
	Oestrogen receptor status	Positive	1,254 (97.3)	35 (2.7)	1,289	0.77
		Negative	188 (96.9)	6 (3.1)	194	
		Unknown/not determined	444 (98.0)	9 (2.0)	453	
	Her2 receptor status	Positive	96 (97.0)	3 (3.0)	99	0.76*
		Negative	1,145 (97.2)	33 (2.8)	1,178	
		Unknown/not determined	645 (97.9)	14 (2.1)	659	
Tumour characteristics in women aged >75 years						
	Tumour stage	T0	2 (100)	0	2	0.68*
		T1	224 (97.8)	5 (2.2)	229	
		T2	236 (97.9)	5 (2.1)	241	
		T3	24 (100)	0	24	
		T4	24 (100)	0	24	
		DCIS	26 (96.3)	1 (3.7)	27	
		Unknown	10 (100)	0	10	
	Lymph node involvement	Yes	196 (98.5)	3 (1.5)	199	0.75*
		No	331 (97.6)	8 (2.4)	339	
		Unknown	19 (100)	0	19	
	Metastasis	Yes	23 (100)	0	23	1.00*
		No	499 (98.0)	10 (2.0)	509	
		Unknown	24 (96.0)	1 (4.0)	25	
	Morphology	Ductal	421 (97.5)	11 (2.5)	432	0.60*
		Lobular	76 (100)	0	76	
		Mixed ductal lobular	13 (100)	0	13	
		Other	36 (100)	0	36	

Progesterone receptor status	Positive	330 (98.5)	5 (1.5)	335	0.17*
	Negative	146 (96.7)	5 (3.3)	151	
	Unknown/not determined	70 (98.6)	1 (1.4)	71	
Oestrogen receptor status	Positive	422 (98.1)	8 (1.9)	430	0.69*
	Negative	89 (97.8)	2 (2.2)	91	
	Unknown/not determined	35 (97.2)	1 (2.8)	36	
Her2 receptor status	Positive	37 (100)	0	37	1.00*
	Negative	432 (97.7)	10 (2.3)	442	
	Unknown/not determined	77 (100)	0	77	

* P-values marked with an asterisk are determined using a Fisher's exact test instead of a Pearson's Chi-square test.
** Number of women diagnosed is the total number of women diagnosed with breast cancer, regardless the way of detection, i.e. screen detected, interval or no relation.

Relation of tumour to the screening program

Tumours diagnosed in women can be detected in different ways, each with a different relation to the screening program. A distinction is made between screen detected tumours, interval tumours, no relation tumours and non-screen tumours. Figure 1 shows the relations of tumours diagnosed in women aged 70 to 75 years, based on the CR cohort. In total, 2,607 tumours were detected in these women. Most of these tumours, 52.5% (N=1,369), are screen detected tumours. 16.5% (N=431) are interval tumours, 5.2% (N=136) are no relation tumours, and 25.7% (N=671) of the tumours are non-screen tumours.

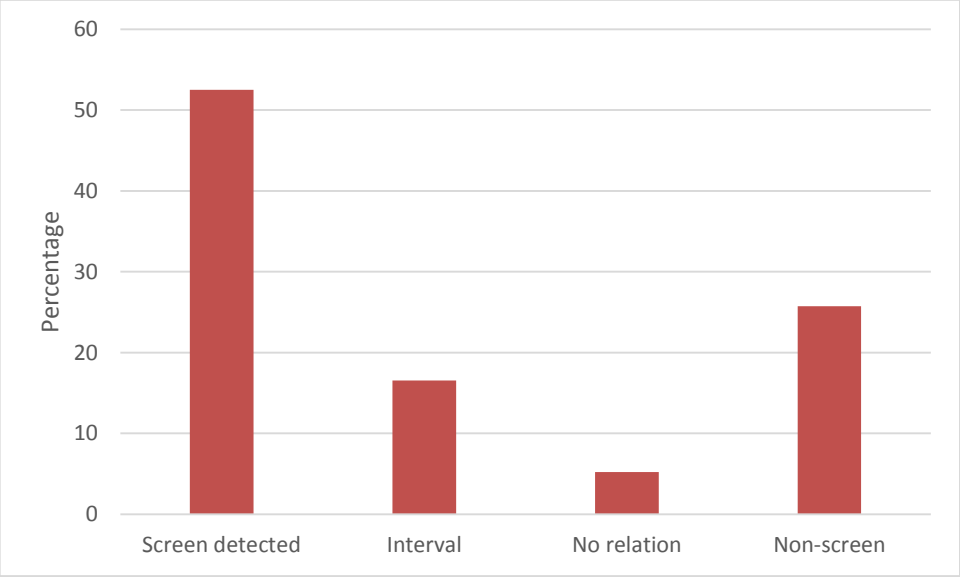


Figure 3: Way of detection of tumours, diagnosed between 1999 and 2012 in women aged between 70 and 75 years, based on the CR cohort.

In women older than 75 years, the number of screen detected and interval tumours is low; one woman (0.03%) had a screen detected tumour, 53 women (1%) had an interval tumour. 503 women (13%) had a no relation tumour, and most women, 3,257 (85%), had a non-screen tumour.

When looking at the total number of tumours detected per age, a decrease can be seen (figure 4). This decrease starts around the age of 71 and ends at the age of 76. From the age of 77 the decrease becomes an increase in the total number of tumours. After the age of 75, when women are no longer invited to participate in screening, the number of screen detected and interval tumours decrease, while the number no relation tumours increase. Also, after the age of 75 the number of non-screen

tumours increases, and at the age of 84 it merges with the blue line of the total number of tumours. This means that the total number of tumours only exists of non-screen tumours.

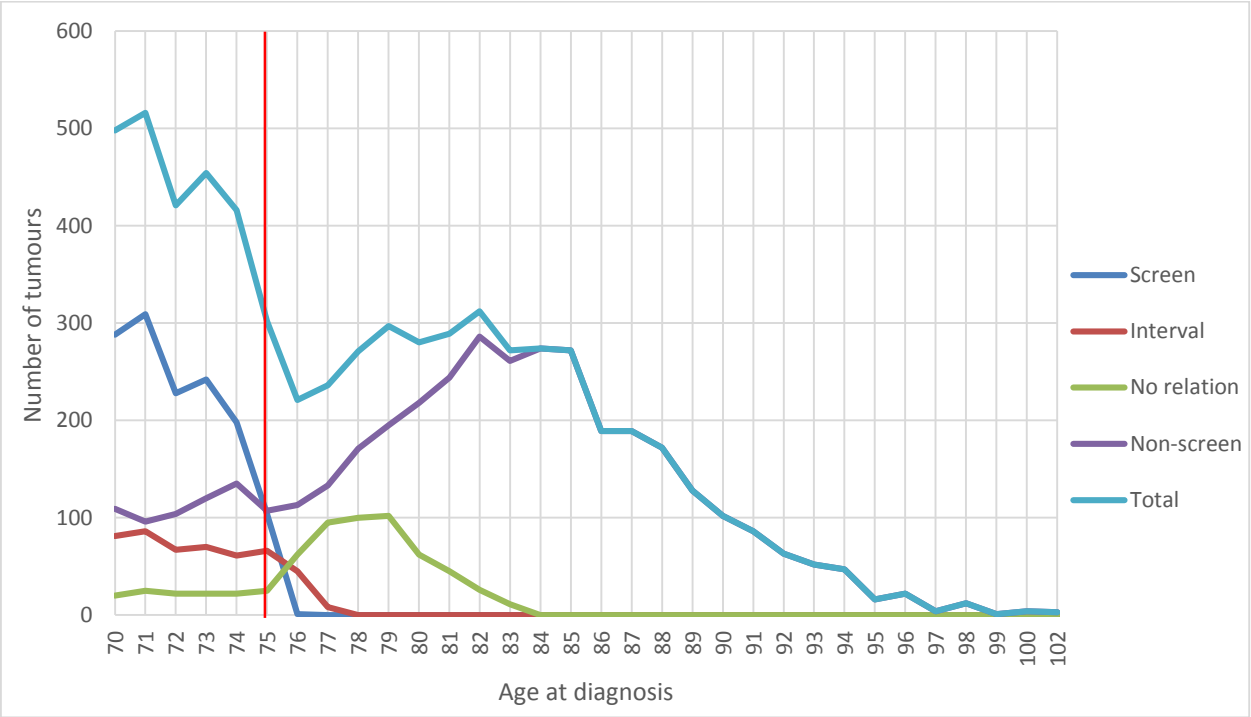


Figure 4: Way of detection and incidence of tumours per age, in women diagnosed between 1999 and 2012 in the northern region of the Netherlands, based on the CR. Invitation to participate in the screening program stops at the age of 75, as indicated by the red line at 75.

The influence of participation in women aged 70 to 75 years

To determine if participating in screening influences tumour characteristics in women aged between 70 and 75 years, tumour characteristics in women who participated in screening at least four times and women who never participated in screening were compared. Differences were found in tumour characteristics between both groups. P-values are shown in table 1.

Differences were found in tumour stage, lymph node involvement, metastasis and oestrogen and Her2 receptor statuses. It appears that women who have participated in screening more often have a lower stage tumour than women who have never participated. Of the women who participated (N=1,911), 65.2% had a T1 tumour and 11.2% had a DCIS, compared to 51.4% T1 tumours and 9.8% DCIS in women who never participated (N=646). Women who participated in screening had 2.8% T3/4 tumours, compared to 10.4% of the women who never participated. When looking at lymph node involvement and metastasis, women who participated (N=1,775 and N=1,898) more often have a negative lymph node status and less often have metastasis compared with women who never participated (N=574 and N=608): 74.6% versus 64.8%, and 1.3% versus 3.3%. Oestrogen receptor status is more often positive in women who participated (N=1,483) (86.9%) than in women who did not (N=415) (81.4%). Her2 receptor status appears to be more often positive in women who never participated in screening (11.2%) than in women who participated (7.8%). In morphology and progesterone receptor status no differences were found.

The influence of regularity of participation in women aged 70 to 75 years

For determining the influence of regularity of participation in the screening program on tumour characteristics in women aged between 70 and 75 years, tumour characteristics were compared between women who participated regularly (N=1,886) and irregularly (N=50). Women who regularly participated in screening, participated four times within 108 months, women who participated irregularly in screening, participated less than four times in 108 months. When comparing tumour characteristics between women who participated regularly and irregularly, no differences were found for all tumour characteristics between both groups. P-values can be found in table 2.

DCIS

The number of DCIS in the group of women aged 70 to 75 years, based on the CR cohort, shows no differences between women who participated in screening on a regular (N=1,886) or irregular (N=50) basis, and women who have never participated in the screening program (N=671), $\chi^2(2, N=2,607)=1.92=0.38$). However, when looking at the relation of the tumour to the screening program, there are differences in the number of DCIS, $\chi^2(3, N=2,607)=10.9=0.01$. It appears that more DCIS are found in women with screen detected tumours than in women with tumours with other relations to the screening program. 12% of the women with a screen detected tumour (N=1,369) have a DCIS, 8% of the women with a tumour detected during the interval between screen rounds (N=431), 7% of the women with no relation to screening (N=136) and 9% of the women who have never participated in the screening program (N=671).

The influence of participation in women older than 75 years

Participation of women aged 75 years and older is based on participation of these women in the screening program before they were 75 years old, since they are no longer invited to participate in screening. Comparing tumour characteristics between women who participated in the screening program (N=557) and women who never participated (N=3,257) only showed differences in tumour stage and oestrogen receptor status. Women who participated (N=547) have more lower stage tumours than women who never participated (N=3,107) (figure 5). 4.9% of the tumours detected in women who participated are DCIS, compared to 4.4% of the tumours in women who did not participate. Also the amount of T1 tumours is higher in women who participated (41.9%) compared to women who did not (31.8%), while the amount of T3/4 tumours is higher in women who never participated (16.8%) compared to women who did (8.8%) (figure 5). This is the case for most tumour stages, until the age of 84, after that age all the tumour stages of women who participated in screening are 0%. The other tumour characteristics show no differences between the two groups. P-values can be found in table 1.

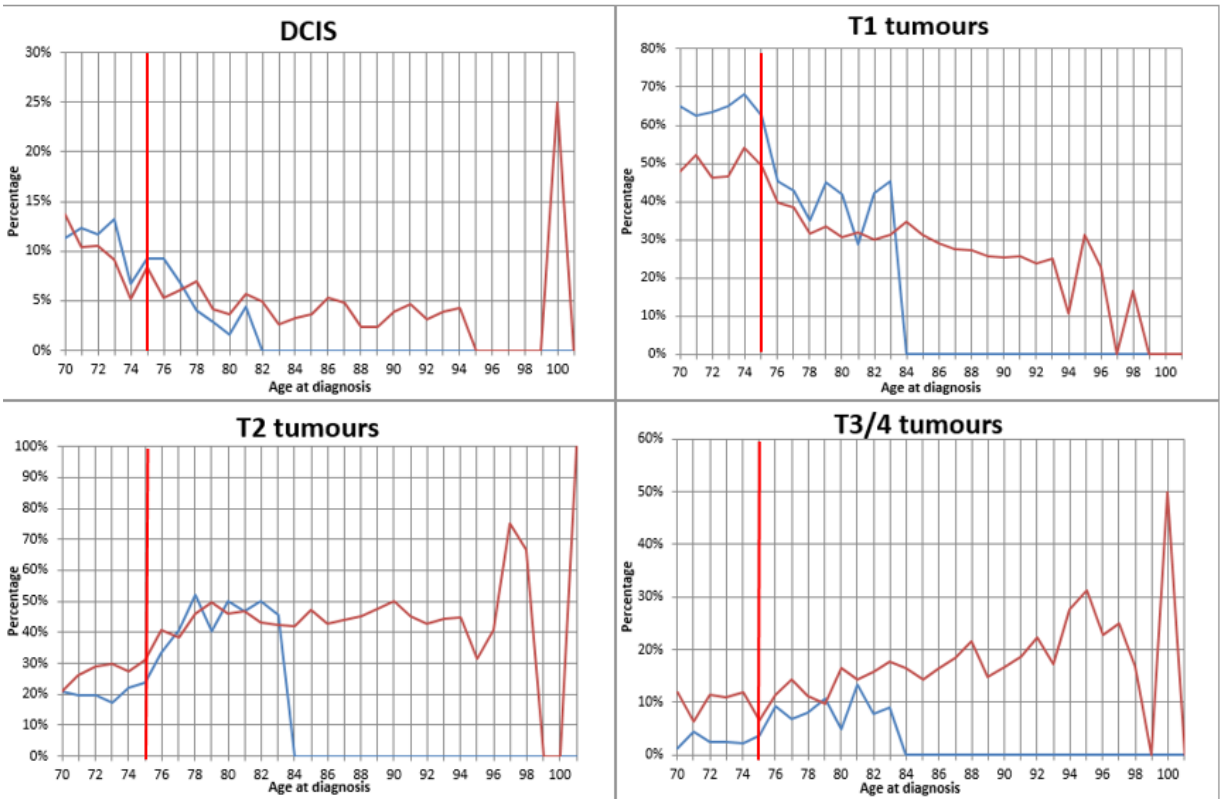


Figure 5: Tumour stage per age in women who participated in screening (blue) and women who never participated (red). The vertical red line indicates the age of 75, at which the screening program stops.

The influence of regularity of participation in women older than 75 years

To determine the effect of regularity of participation in the screening program on tumour characteristics in women over 75 years, tumour characteristics were compared between women who participated regularly (N=546) and irregularly (N=11) in the last four screening rounds they participated in. P-values are shown in table 2. Women older than 75 years are no longer invited to participate in the screening program. Therefore, to determine the regularity of participation of these women in the screening program information about screening rounds they participated in before they turned 75 years were used. When comparing the tumour characteristics between both groups, no differences were found.

Incidence of breast cancer in women screened regularly and irregularly

When comparing the number of tumours detected in women who are screened regularly (N=95,912) and irregularly (N=2,207), no differences in the number of tumours were found. 2.5% of the women who have been screened on a regular basis are diagnosed with breast cancer. Of the women who have been screened irregularly, 2.8% are diagnosed with breast cancer.

Comparing the numbers

The National Evaluation Team for Breast Cancer Screening made an evaluation of the screening program in the Netherlands. They determined for example the number of participants, number of invitations sent, and the number of screen detected and interval tumours and the distribution of tumour stages in these groups. They found that of all women invited for screening in the Netherlands, 6.2 per 1,000 women that have participated in screening were diagnosed with breast cancer through screening (5). Of these screen detected tumours, 79.0% was a DCIS or T1, of which 19.5% were DCIS

(5). T3/4 tumours made up about 1% of the tumours diagnosed, and the remainder were T2 tumours (5). 25% of the invasive tumours detected are lymph node positive (5). Less than 1% of the screen detected tumours has metastasis (5). Comparing these numbers with the numbers found in this study, shows that they are quite similar. Of the screen detected tumours 83.9% was a DCIS or a T1 tumour, of which 14.8% were DCIS. 14.0% are T2 tumours and 1.5% are T3/4 tumours. The remainder were T0 tumours. For lymph node involvement, 20.4% were positive, 70.4% are negative and the remainder is unknown. In this study, 0.4% of the screened women had metastasis, 98.9% did not. The remainder is unknown.

According to the National Evaluation Team for Breast Cancer Screening, 2.2 per 1,000 women that participated in screening in the Netherlands are classified as interval tumours (5). In women who participated in screening regularly, in this case it means they have a screen interval of less than 2.5 years between two consecutive screening rounds, 2.1 per 1,000 women are diagnosed with an interval tumour, while 2.6 per 1,000 women are diagnosed with an interval tumour if they participated irregularly (screen interval of more than 2.5 years) (5). Of the interval tumours, 50% is a DCIS or T1 tumour, 40% is a T2 tumour, and the remainder are T3/4 tumours (5). Of the invasive tumours, 45% is lymph node positive (5). 4 to 5% of the women have metastasis (5). Comparing these numbers to those in this study, shows that they are relatively similar. In this study, there is no difference in the number of interval tumours between women who participated regularly in screening (N=95,912) and women who participated irregularly (N=2,207): 0.4% of the regular women have an interval tumour and 0.2% of the irregular women, $\chi^2(1, N=98,119)=1.43=0.23$). 53.7% of the interval tumours are a DCIS or T1 tumour, 37.0% are T2 tumours, and 5.2% are T3/4 tumours. The remainder are T0 tumours. Lymph node involvement for interval tumours in this study was 31.2%, 62.6% are negative and the remainder is unknown. 3.3% of the women in this study with an interval tumour had metastasis and 92.4% was negative for metastasis. The remainder was unknown.

Discussion

It appears that participating in the breast cancer screening program positively influences tumour characteristics in women aged 70 years or older. Women who participated in screening at least 4 times appear to have better tumour characteristics (lower tumour stage, less lymph node involvement, less metastasis, more positive receptor statuses) than women who never participated in screening. This is the case for women aged between 70 and 75 years and women older than 75 years. However, for both age groups it does not seem to make a difference whether these women participate on a regular or irregular basis: there is no difference in tumour characteristics in women who were screened four times within 108 months and women screened four times in more than 108 months.

When looking at the total number of tumours diagnosed, a decrease can be seen until after the age of 75, when women are no longer invited to participate in screening. This can indicate that screening has a protective effect on the incidence of breast cancer, and that screening is effective, even for elderly women. In this study, only tumours diagnosed after the age of 70 are included. This means that no information is known about tumours detected before the age of 70. To be able to say something about the protective effect of breast cancer screening, it is important to also take tumours detected before the age of 70 into account.

After the age of 75 the number of non-screen tumours increases and at the age of 84 non-screen tumours make up the total number of tumours. Also, when comparing tumour stages in women who participated in screening and women who have never participated, at the age of 84 the total number of women who participated in screening is zero percent. One reason for this, can be that these women were already older than the maximum age for participation in screening when screening started in 1989. It is imaginable that at the beginning of the screening program, women did not see an advantage in participating. Therefore, another reason might be that these women were almost 70 years old at the time the screening program started and would only be invited for one round, and did not see any advantage to participate in only one screening round and did not participate at all.

In this study only the last four screening rounds a woman has participated in and the three intervals between them are taken into account. In this study it is assumed that participation in these screening rounds influences tumour characteristics of the tumours diagnosed in women aged older than 70 years most, and therefore are most useful in performing the analysis. The reasoning for this is that if a woman has participated at the age of 50, this participation will no longer have had any influence at the moment a woman is diagnosed with breast cancer after the age of 70.

When evaluating the influence of participation in screening on tumour characteristics, the question is to what extend screening can influence them. Tumour stage, lymph node involvement and metastasis can be influenced, because earlier detection leads to diagnosis of smaller tumours and less chance of lymph node involvement and metastasis. However, it is not very clear whether screening can influence morphology and receptor statuses. These characteristics are more fixed than the other characteristics: participation in screening is not likely to make a receptor status go from negative to positive, or morphology from lobular to ductal. Morphology, however, can change from for example only ductal to mixed ductal and lobular, due to the time between screening and diagnosis. Sometimes it can happen that receptor statuses change over time, especially with recurrent cancer (15-17). This means that for example oestrogen receptor status of a woman can be negative when she is 50 years old, and positive when she is 80 years old. However it can be questioned whether this is caused by participation

in screening and therefore if it is useful to take these characteristics into account when doing the analysis.

Comparing the data and results

The influence of participation in the screening program of individual women and the regularity of participation on tumour characteristics are taken into account in this study. By using the screen information of individual women instead of the presence of a screening program, it can be shown whether or not there is a difference in tumour characteristics if a woman participates in screening or not, and if there is a difference between participating on a regular and irregular basis. Many studies only look at the influence of the presence of a screening program on mortality of breast cancer. For example the study of De Glas et al. (11). In this study, only data on population level is used. This study also shows different results regarding screening in elderly women: screening these women leads to more lower stage breast cancer diagnosis, but has not lead to a great decrease in the number of higher stage tumours (11). Therefore, screening elderly women can lead to over-diagnosis (11). Differences in study results can be caused by the fact that different methods were used in both studies and that this study also uses information of the BOB, while the study of De Glas et al. only uses the CR. Also, this study only uses the northern region of the Netherlands. The study of De Glas et al. includes all women aged 70 to 75 years diagnosed between 1995 and 2011, while this study also takes into account women aged older than 75 years.

The number of tumours found for screen detected and interval tumours in this study were compared with the numbers found by the National Evaluation Team for Breast Cancer Screening. For both screen detected and interval tumours the percentages are relatively comparable with the percentages of the whole population of screened women in the Netherlands. Differences that are present, can be caused by the fact that this study only included women of one region of the Netherlands and only a subgroup of all the women in that region that are invited for screening and/or diagnosed with breast cancer; women aged 70 years and older.

Screening can lead to detection of more lower stage breast cancer (T1, T2 and DCIS). It is possible that these tumours otherwise would not be diagnosed. Of the total number of breast cancers diagnosed, according to the evaluation report of the National Evaluation Team for Breast Cancer Screening, 2,8% of the tumours are over-diagnosed (5). The question is whether this desirable. It can lead to unnecessary treatment and associated physical and psychological burden for women. It is important to take this into account, especially with elderly women with relatively lower health state and life expectancy. This 2.8% is (almost) the same as the incidence found in the BOB cohort: 2.5% of the women who participated regularly and 2.8% of the women who participated irregularly were diagnosed with breast cancer. It is likely that this is only a coincidence, and that there is no relation between the over-diagnosis and the incidence of breast cancer in the two age groups in the BOB cohort. However, to be sure it is better to perform some more analyses.

Interval breast cancers are detected in the 24 months between two consecutive screening rounds. These tumours are usually not visible on the screening mammogram. However, after re-evaluation of these mammograms, it appears that only in 52% of the cases nothing can be found (5, 7). This means that in 48% of the cases breast cancer was present at the moment a woman participated in screening and it was overlooked when assessing the mammograms. The actual group of interval breast cancers is smaller than is assumed. It is likely that it is also the case for the interval cancers in this study.

Unknown data

Unknown data were left out of the analysis. For some subgroups this meant that many women were left out of the analysis. This was especially the case for the receptor statuses for both women aged between 70 and 75 years and women older than 75 years. Some reasons for the missing data are the fact that for DCIS receptor statuses are not recorded in the CR (18), and not every woman has her tumour researched after diagnosis. This could influence the analysis. The results could be different if the unknown data were included in the analysis. There could be over- or underestimation of the results, especially for women older than 75 years, for whom most data are missing. It is imaginable that these women do not want to be treated anymore because of the psychological and physical burden, and therefore not want to be examined anymore. It can be possible that these women participated in screening before they were 75 years old, and are diagnosed later in a late stage of the disease, but it is unclear what the exact stage is because they are not examined. In that case, there can be overestimation of for example the effect of participation to screening on tumour stage or lymph node involvement. It can also be that those women who participated in screening have an early stage tumour and in that case there would be underestimation of the effects of screening.

Tumour stage was used as a measure for tumour size. The size of the tumour in millimetres was also available, but was not used in this study. Reason being that many of these data were missing. Reasons for the missing data are that tumour sizes only get recorded based on the information of a pathologist after surgery (18). If no surgery and no pathological research were performed, no information about tumour size was available. These missing data could be excluded from the analysis, however this would result in a small study population. Not using the tumour size could give other results regarding effectiveness of screening, because a difference in size between groups might be more likely to be found.

Due to a limited agreement for the use of data, women screened in other screening regions than the BOB, and therefore do not have a complete screening history, are left out of the analysis (N=18,730, 16.0% of all women 70 years and older and screened in the BOB region). Reasons to be left out of the analysis can be: women moving to a different region and resume the screening program there, or moving into the northern region after being screened in one of the other regions. Another reason can be that women are treated in a hospital that is in the northern region so the tumour will be registered as diagnosed in the northern region, but she was screened in another region. This means that it is possible that women, even though they were screened at least four times, are left out of the analysis. It is unknown if these 18.730 women were diagnosed with breast cancer or not, and therefore it is difficult to indicate how much this has influenced the results. For example, leaving these women out of the analyses could have led to an underestimation of the effect of regular participation in the screening program.

Determining the limit for regular and irregular participation

To make a distinction between women who have participated in screening regularly and irregularly, a limit of 108 months was used. This limit is not determined by other research or by using for example the mean time between the screening rounds. The advantage of this limit is the fact that it takes into account different events that can cause women to miss a screening round, like moving within the region, the screening unit being late, or a malfunction in the screening equipment which causes delay in the screening program. A disadvantage is that the limit might be high and classifies women as regular participants while they actually are irregular. The BOB has an indicator that focusses on the screen

interval between two consecutive screening rounds. This indicator measures how many women participated in screening within two and a half years after the previous screening (19). Two and a half years was chosen to take into account the women who participated in screening after a reminder invitation (19). Using this as a limit for determining whether a woman participated regularly or irregularly, gives a limit of 90 months for the total interval between the last four screening rounds before the diagnosis. This means that the limit used in this research is 26 months higher. To see whether using the 90 months limit for regular and irregular participation would change the results, analysis were performed using this limit as well. This did not change the results. Also only the most recent interval, the single interval between the last screening round and the second last screening round women participated in before they were diagnosed, were used in the analysis to see if the results would change. This also had no effect on the results.

Recommendations

To be able to draw conclusions on the effectiveness of the screening program on a national scale, more research is needed. For example, involving more screening regions or a national study. This study is performed in only the screening region of the BOB. This can influence the generalizability of the study. The culture and population characteristics in this region of the country are different from the culture and population characteristics of, for example, the western part of the Netherlands. By including more regions, regional differences will be reduced and make the results and conclusions of the study more generalizable.

It appears that screening in elderly women influences tumour characteristics in a positive way. Therefore, it can be stated that participation in screening is of interest in lowering tumour stage and thus using less radical treatment so that a woman will perceive less harm of treatment. However, it does not seem to differ whether a woman participates regularly or irregularly. Screening elderly women should be continued since it appears to have effect on tumour characteristics, but perhaps the program should be adjusted. For example, women after the age of 70 being invited for participation in the screening program once every three or four years instead of every two years, since it does not seem to matter if women participate regularly or irregularly. In this case, scarce health care resources, especially money, will be used in a better way.

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