Breast Cancer Research and Treatment **76:** 19–25, 2002.

Report

Breast cancers found by screening: earlier detection, lower malignant potential or both?

Miranda F. Ernst[1], Jan A. Roukema[1], Jan-Willem W. Coebergh[2,3], Ocker J. Repelaer van Driel[4], Mike W.P.M. van Beek[5], Maurice J.C. van der Sangen[6], and Adri C. Voogd[2]
[1]*Department of Surgery, St. Elisabeth Hospital, Tilburg;* [2]*Eindhoven Cancer Registry, Comprehensive Cancer Centre South, Eindhoven;* [3]*Department of Public Health, Erasmus University Medical School, Rotterdam;* [4]*Department of Surgery, Diaconessenhuis, Eindhoven;* [5]*Regional Institute of Pathology (PAMM), Eindhoven;* [6]*Department of Radiotherapy, Catharina Hospital, Eindhoven; Department of Epidemiology, University of Maastricht, Maastricht, The Netherlands (present address)*

Key words: breast carcinoma, mammography, mass screening

Summary

A population-based study was performed to compare the characteristics of clinically detected breast cancers and cancers detected by the Dutch screening program. To determine whether differences are most likely to be explained by earlier diagnosis or by the detection of biologically different cancers in the screening program, comparisons were stratified according to tumor size. Data were obtained from the population-based Eindhoven Cancer Registry. During the period 1996–1999, 568 screen-detected and 630 clinically detected invasive breast cancers were available for analysis. Compared with patients with clinically detected breast cancer, women with screen-detected breast cancer had smaller tumors ($P < 0.0001$), were more likely to have negative lymph nodes ($P < 0.0001$), tumors with a positive estrogen ($P = 0.007$) or progesterone ($P = 0.019$) receptor status and a lower mitotic activity index ($P = 0.009$). In the group with cancers $\leq$1.0 cm the screen-detected were more likely to have negative estrogen receptors ($P = 0.027$). The group with screen-detected tumors 1.1–2.0 cm across were more likely to have positive estrogen and progesterone receptors ($P = 0.005$ and $P = 0.044$, respectively) and tended to have a lower mitotic activity index ($P = 0.078$). No significant differences were found between screen-detected and clinically detected breast cancers of 2.1–3.0 cm across. After adjustments for tumor size, most of the differences between clinically detected and screen-detected breast cancers disappeared, suggesting that screen-detected breast cancers represent tumors in an earlier phase of their development, not a biologically different class.

Introduction

Patients with breast cancer detected by mammography screening have smaller tumors and are less likely to have lymph node metastases, compared to those presenting clinically [1–11]. In addition, more *in situ* cancers and tubular cancers are generally found by mammography screening [1, 2, 5, 12]. Studies comparing the malignant potential of screen-detected and clinically detected breast cancers have yielded contradictory conclusions regarding the biological nature of screen-detected cancers [1–4, 6, 8, 13]. Assuming that fast growing tumors – presenting as interval cancers – are more likely to be missed by screening, one would expect the cancers detected by screening to be less aggressive than the cancers detected clinically, provided an adjustment is made for tumor size. Lower aggressiveness of cancers found by screening than of control cancers would indicate overdiagnosis or length-time bias, but not earliness of diagnosis.

To study the biological aggressiveness of screen-detected breast cancers, we compared the pathological nodal status, estrogen and progesterone receptor status and the mitotic activity index (MAI) of 568 breast cancers detected by the Dutch screening program with those of 630 control cancers detected clinically

Table 1. Characteristics of screen-detected and clinically detected invasive breast tumors in patients of 50–69 years of age, diagnosed in the period 1996–1999 ($n = 1198$)

Characteristic	Method of detection				*P*-value
	Screen-detected ($n = 568$)		Clinically detected ($n = 630$)		
	%	No.	%	No.	
Age group					
50–59	47	269	57	358	0.0004
60–69	53	299	43	272	
Pathological tumor size, pT (cm)[a]					
≤1.0	29	158	17	100	<0.0001
1.1–2.0	52	282	41	237	
2.1–3.0	13	70	23	135	
>3.0	6	35	19	109	
Number of positive lymph nodes[b]					
0	72	404	57	323	<0.0001
1	13	70	16	93	
2 or 3	8	42	12	68	
>3	8	43	15	87	
Estrogen receptor[c]					
Positive	82	307	74	338	0.007
Negative	18	68	26	119	
Progesterone receptor[d]					
Positive	75	208	67	237	0.019
Negative	25	68	33	118	
Mitotic activity index (MAI)[e]					
<10	74	175	63	152	0.009
≥10	26	61	37	89	
Extensive intraductal component (EIC)[f]					
No	80	453	82	483	0.54
Yes	20	111	18	108	

[a] 72 missing.
[b] 68 missing.
[c] 366 missing.
[d] 567 missing.
[e] 721 missing.
[f] 43 missing.

during the same period (i.e., 1996–1999). To determine whether differences can be explained by earlier diagnosis or by the detection of biologically different cancers, comparisons were made according to tumor size.

Patients and methods

Patients

The southeast Netherlands, a region of about 2500 km^2 with a population of about 1 million inhabitants (6% of the Dutch population), is served by eight community hospitals and one Department of Radiotherapy. The region is covered by the population-based Eindhoven Cancer Registry, which has been recording data on all newly diagnosed cancer patients since 1955 according to international guidelines. Data are collected by the cancer registry from copies of the pathology reports of all 10 pathologists in three laboratories and from the medical records of the eight community hospitals and the Department of Radiotherapy.

A mammographic screening program, offering biannual screening for women 50–69 years old, was first

Table 2a. Characteristics of screen-detected and clinically detected invasive breast tumors ≤1.0 cm across in patients of 50–69 years of age, diagnosed in the period 1996–1999 ($n = 258$)

Characteristic	Method of detection				*P*-value
	Screen-detected ($n = 158$)		Clinically detected ($n = 100$)		
	%	No.	%	No.	
Age group					
50–59	46	72	64	64	0.004
60–69	54	86	36	36	
Number of positive lymph nodes[a]					
0	84	128	83	74	0.35
1	8	12	11	10	
2 or 3	7	10	2	2	
>3	2	3	3	3	
Estrogen receptor[b]					
Positive	80	75	93	65	0.027
Negative	19	18	7	5	
Progesterone receptor[c]					
Positive	82	47	85	34	0.74
Negative	18	10	15	6	
Mitotic activity index (MAI)[d]					
<10	81	48	85	34	0.64
≥10	19	11	15	6	
Extensive intraductal component (EIC)[e]					
No	78	124	72	69	0.22
Yes	22	34	28	27	

[a] 6 missing.
[b] 95 missing.
[c] 161 missing.
[d] 159 missing.
[e] 4 missing.

introduced in southeast Netherlands in 1991 and finally reached total coverage in 1996. The program is performed at five screening units, of which four are mobile.

Since 1984, detailed information has been recorded by the Eindhoven Cancer Registry on each woman diagnosed with breast carcinoma, such as type of surgery, clinical, mammographic and postoperative tumor sizes in millimeters, mammographic findings and estrogen and progesterone receptor status. In 1996 the Eindhoven Cancer Registry started documenting the mode of detection (i.e., screen- or non-screen-detected) as well as additional tumor characteristics, such as the mitotic activity index (MAI) and the presence of an extensive intraductal component (EIC). Mode of detection could be easily deduced from the clinical notes of the screening units in the medical files of the hospital to which the patients were referred for further diagnosis and treatment. However, for most patients no information could be obtained about the screening round during which the tumor had been detected.

Estrogen and progesterone receptors were determined by means of immunohistochemistry. For this study, tumors coded as 'weakly positive' in the pathology reports were considered to be positive. In all pathology laboratories, the MAI was defined as the number of mitotic figures in 10 adjacent high-power fields (HPF) [14]. The mitotic figures were counted in the most cell-rich areas of the invasive tumor margins, avoiding necrotic areas. The tumors were divided into two categories: <10 and ≥10 mitotic figures/HPF.

Table 2b. Characteristics of screen-detected and clinically detected invasive breast tumors 1.1–2.0 cm across in patients of 50–69 years of age, diagnosed in the period 1996–1999 ($n = 519$)

Characteristic	Method of detection				*P*-value
	Screen-detected ($n = 282$)		Clinically detected ($n = 237$)		
	%	No.	%	No.	
Age group					
50–59	48	134	61	144	0.003
60–69	52	148	39	93	
Number of positive lymph nodes[a]					
0	74	207	69	158	0.55
1	12	33	12	28	
2 or 3	7	21	10	24	
>3	7	20	9	20	
Estrogen receptor[b]					
Positive	84	166	72	124	0.005
Negative	16	31	28	48	
Progesterone receptor[c]					
Positive	77	114	66	86	0.044
Negative	23	34	34	44	
Mitotic activity index (MAI)[d]					
<10	75	99	64	65	0.078
≥10	25	33	36	36	
Extensive intraductal component (EIC)[e]					
No	86	240	85	200	0.76
Yes	14	40	15	36	

[a] 8 missing.
[b] 150 missing.
[c] 241 missing.
[d] 286 missing.
[e] 3 missing.

The intraductal component was considered extensive if the number of ducts with intraductal cancer in breast tissue directly adjacent to the primary tumor was ten ducts or more (EIC+). Tumors consisting predominantly of DCIS with focal areas of invasion were also classified as EIC+.

Between January 1, 1996 and December 31, 1999, 1507 patients with breast cancer were diagnosed. The patients were staged according to the TNM system of the UICC [15].

Statistics

The chi-square test was used to compare the characteristics of the tumors detected by the screening program or clinically. Stratified analyses according to tumor size were performed to adjust for the differences in tumor size between the screen-detected and the clinically detected cases.

Results

The mode of detection of the tumor was known for 1358 of the 1507 patients who were diagnosed in the period 1996–1999. Of these 1358 patients, 676 had screen-detected and 682 had clinically detected breast cancer. Of the screen-detected cancers, 108 (16%) were non-invasive, versus 52 of the clinically detected tumors (8%). All further analyses were restricted to the 1198 patients with invasive breast cancer.

The general characteristics, according to the mode of detection, are presented in Table 1. Women with

Table 2c. Characteristics of screen-detected and clinically detected invasive breast tumors 2.1–3.0 cm across in patients of 50–69 years of age, diagnosed in the period 1996–1999 ($n = 205$)

Characteristic	Method of detection				P-value
	Screen-detected ($n = 70$)		Clinically detected ($n = 135$)		
	%	No.	%	No.	
Age group					
50–59	47	33	51	69	0.59
60–69	53	37	49	66	
Number of positive lymph nodes[a]					
0	54	37	37	48	0.093
1	23	16	23	30	
2 or 3	10	7	19	24	
>3	13	9	21	27	
Estrogen receptor[b]					
Positive	77	37	70	74	0.35
Negative	23	11	30	32	
Progesterone receptor[c]					
Positive	59	24	64	58	0.52
Negative	41	17	36	32	
Mitotic activity index (MAI)[d]					
<10	55	17	56	34	0.93
≥10	45	14	44	27	
Extensive intraductal component (EIC)[e]					
No	81	57	83	111	0.80
Yes	19	13	17	23	

[a] 7 missing.
[b] 51 missing.
[c] 74 missing.
[d] 113 missing.
[e] 1 missing.

screen-detected breast cancer had smaller tumors ($P < 0.0001$), were more likely to have negative lymph nodes ($P < 0.0001$), tumors with a positive estrogen ($P = 0.007$) or progesterone ($P = 0.019$) receptor status and a lower MAI ($P = 0.009$) (Table 1).

The differences in number of positive lymph nodes, steroid receptor status, MAI and breast-conserving surgery almost all disappeared when adjustments were made for tumor size. In Tables 2a–c the characteristics are shown for screen-detected and clinically detected breast cancer according to tumor size. For screen-detected tumors ≤1.0 cm the proportion with positive estrogen receptors was lower ($P = 0.027$) (Table 2a). Screen-detected tumors 1.1–2.0 cm across were more likely to have positive estrogen and progesterone receptors ($P = 0.005$ and $P = 0.044$, respectively) and tended to have a lower MAI ($P = 0.078$) compared to clinically detected breast cancers (Table 2b). No significant differences were found between screen-detected and clinically detected breast cancers of 2.1–3.0 cm across (Table 2c).

Discussion

After adjustment for tumor size, most of the differences in nodal status, steroid receptor status, and MAI between clinically detected and screen-detected breast cancers disappeared. Thus, our results support the hypothesis that breast cancers diagnosed at screening

hardly differ biologically from those presenting clinically, but are in fact the same lesions detected at an earlier stage of their natural history. The same conclusion was drawn by other authors, based on similar findings [2, 8, 16, 17]. Moreover, biological aggressiveness and tumor size showed the same relationship in screen-detected as in clinically detected breast cancers.

The large number of screen-detected and clinically detected cancers in our study allowed us to make comparisons according to tumor size. When considering these results it should be realised that the number of patients in the subgroups became small and that the large number of tests for possible associations carries the added risk that apparently significant differences will occur by chance alone. Moreover, interpretation of the results is complicated by the fact that our screen-detected cancers are a mixture of cancers detected during the first, second and third screening round and that we were not able to make a distinction between these subgroups. It seems likely that slow growing tumors – with a long preclinical phase – will be much more common in the first screening round, whereas in later rounds more aggressive and faster growing tumors will be detected that were not yet visible on the mammogram of the first round. This hypothesis is supported by a Finnish study, which found similar results of DNA flow cytometry for cancers diagnosed in the second and third screening round and for controls, whereas cancers diagnosed in the first round had a lower malignant potential compared to controls [8]. Some studies, which only included breast cancers detected during the first round of mammographic screening (i.e., prevalent cases), found more favorable tumor characteristics after adjustment for tumor size [3, 10]; that is, for any given size, screen-detected cancers were associated with fewer lymph node metastases and were less likely to have a high MAI, a high S-phase fraction, tumor necrosis or a negative estrogen or progesterone receptor status than those detected clinically. Comparison with several other studies, which were also based largely on prevalent cases, is complicated by the fact that no adjustment for tumor size was made [1, 2, 6]. In a study of Holland et al., the proportion of patients with nodal metastases was only 17.4% in the first screening round but increased to 30% in the second round [11]. In the Dutch national screening program, however, the proportion of patients with positive lymph nodes was higher in the first screening round than in the second (27% v.s. 23%) [18]. Part of this difference might be attributed to the interval between screens, which was 3 years for the UK program and 2 years in the Dutch program.

We have no explanation for the phenomenon that screen-detected breast cancers <1 cm were more likely to have negative estrogen-receptors ($p = 0.027$) than clinically detected tumors, whereas screen-detected breast cancers 1.1–2.0 cm across were less likely to have negative estrogen-receptors than clinically detected tumors. These are the only findings which might contradict our statement that screen-detected breast cancers are of the same biological class as clinically detected cancers.

Among the patients presenting with breast cancer outside the screening program we could make no distinction between interval cancers and cancers in non-participants or lapsed participants. The participation rate of the Dutch screening program was between 70 and 80%. Nation-wide data have demonstrated that one-third of the cancers among participants of the program are detected between screening rounds [19], which would mean that of all breast cancers in the age group of 50–69 years about 25% develops in the non-participants.

Women with a positive screening mammogram but a negative outcome after further diagnostic procedures in the hospital will have undergone clinical follow-up visits. If a cancer was detected later on, it might have been classified as an interval case and not as a screen-detected case, which has probably led to some underreporting of the proportion of screen-detected cases. There is ample evidence that rapidly growing and aggressive cancers explain a substantial portion of mammographic failures [20, 21].

We agree with the conclusions of Hakama et al. that monitoring of the aggressiveness of screen-detected and clinically detected cancers can help to overcome length–time bias and overdiagnosis and that clinical indicators, mainly the size of the cancer, imply early diagnosis [8]. Effectiveness of a screening program could thus be doubted when the proportion of patients with well-differentiated tumors remains high relative to the proportion among the patients with clinically detected breast cancer; in that case increasing the proportion of screen-detected breast cancers is necessary to augment the effect of screening on mortality. According to the findings of Hakama et al., length–time bias (i.e., screen-detected cancers having a lower malignant potential than clinically detected cancers, after adjustment for tumor size) is likely to play a much bigger role in the first screening round than in subsequent rounds.

In conclusion, our results are in line with the view that breast cancers found by mammographic screening do represent tumors at an earlier stage at their development and not a biologically different class.

References

1. Cowan WK, Angus B, Henry J, Corbett IP, Reid WA, Horne CHW: Immunohistochemical and other features of breast carcinomas presenting clinically compared with those detected by cancer screening. Br J Cancer 64: 780–784, 1991
2. Cowan WK, Kelly P, Sawan A, Cunliffe WJ, Henry L, Higgs MJ, Lunt LG, Young JR, Horne CH, Angus B: The pathological and biological nature of screen-detected breast carcinomas: a morphological and immunohistochemical study. J Pathol 182: 29–35, 1997
3. Klemi PJ, Joensuu H, Toikkanen S, Tuominen J, Rasanen O, Tyrkko J, Parvinen I: Aggressiveness of breast cancers found with and without screening. Br Med J 304: 467–469, 1992
4. Klemi PJ, Toikkanen S, Rasanen O, Parvinen I, Joensuu H: Mammography screening interval and the frequency of interval cancers in a population-based screening. Br J Cancer 75: 762–766, 1997
5. Anderson TJ, Lamb J, Donnan P, Alexander FE, Huggins A, Muir BB, Kirkpatrick AE, Chetty U, Hepburn W, Smith A, Prescott RJ, Forrest P: Comparative pathology of breast cancer in a randomised trial of screening. Br J Cancer 64: 108–113, 1991
6. Crisp WJ, Higgs MJ, Cowan WK, Cunliffe WJ, Liston J, Lunt LG, Peakman DJ, Young JR: Screening for breast cancer detects tumours at an earlier biological stage. Br J Surg 80: 863–865, 1993
7. Kricker A, Farac K, Smith D, Sweeny A, McCredie M, Armstrong BK: Breast cancer in New South Wales in 1972–1995: tumor size and the impact of mammographic screening. Int J Cancer 81: 877–880, 1999
8. Hakama M, Holli K, Isola J, Kallioniemi OP, Karkkainen A, Visakorpi T, Pukkala E, Saarenmaa I, Geiger U, Ikkala J, Nieminen T, Godenhjelm K, Koivula T: Aggressiveness of screen-detected breast cancers. Lancet 345: 221–224, 1995
9. Tabar L, Duffy SW, Vitak B, Chen HH, Prevost TC: The natural history of breast carcinoma: what have we learned from screening? Cancer 86: 449–462, 1999
10. Norden T, Thurfjell E, Hasselgren M, Lindgren A, Norgren A, Bergstrom R, Holmberg L: Mammographic screening for breast cancer. What cancers do we find? Eur J Cancer 33: 624–628, 1997
11. Holland PA, Walls J, Boggis CRM, Knox F, Baildam AD, Bundred NJ: A comparison of axillary node status between cancers detected at the prevalence and first incidence screening rounds. Br J Cancer 74: 1643–1646, 1996
12. Rajakariar R, Walker R: Pathological and biological features of mammographically detected invasive breast carcinomas. Br J Cancer 71: 150–154, 1995
13. Groenendijk RPR, Bult P, Tewarie L, Peer PGM, van der Sluis RF, Ruers TJM, Wobbes T: Screen-detected breast cancers have a lower mitotic activity index. Br J Cancer 82: 381–384, 2000
14. van Diest PJ, Baak JP, Matze-Cok P, Wisse-Brekelmans EC, van Galen CM, Kurver PH, Bellot SM, Fijnheer J, van Gorp LH, Kwee WS: Reproducibility of mitosis counting in 2469 breast cancer specimens: results from the Multicenter Morphometric Mammary Carcinoma Project. Hum Pathol 23: 603–607, 1992
15. Hermanek P, Sobin LH (eds): UICC TNM Classification of Malignant Tumours. Springer-Verlag, Berlin, 198, pp 94–99
16. Tabar L, Fagerberg G, Day NE, Duffy SW, Kitchin RM: Breast cancer treatment and natural history: new insights from results of screening. Lancet 339: 412–414, 1992
17. Tabar L, Fagerberg G, Duffy SW, Day NE, Gad A, Grontoft O: Update of the Swedish two-county program of mammographic screening for breast cancer. Radiol Clin North Am 30: 187–210, 1992
18. Fracheboud J, de Koning HJ, Beemsterboer PM, Boer R, Hendriks JH, Verbeek AL, van Ineveld BM, de Bruyn AE, van der Maas PJ: Nation-wide breast cancer screening in The Netherlands: results of initial and subsequent screening 1990–1995. National Evaluation Team for Breast Cancer Screening. Int J Cancer 75: 694–698, 1998
19. Fracheboud J, de Koning HJ, Beemsterboer PM, Boer R, Verbeek AL, Hendriks JH, van Ineveld BM, Broeders MJ, de Bruyn AE, van der Maas PJ: Interval cancers in the Dutch breast cancer screening programme. Br J Cancer 81: 912–917, 1999
20. Gilliland FD, Joste N, Stauber PM, Hunt WC, Rosenberg R, Redlich G, Key CR: Biologic characteristics of interval and screen-detected breast cancers. J Natl Cancer Inst 92: 743–749, 2000
21. Porter PL, El-Bastwissi AY, Mandelson MT, Lin MG, Khalid N, Watney EA, Cousens L, White D, Taplin S, White E: Breast tumor characteristics as predictors of mammographic detection: comparison of interval- and screen-detected cancers. J Natl Cancer Inst 91: 2020–2028, 1999

Address for offprints and correspondence: Adri C. Voogd, Department of Epidemiology, University of Maastricht, P.O. Box 616, 6200 MD, Maastricht, The Netherlands; *Tel.:* +31 43 3882387; *Fax:* +31 43 3884128; *E-mail:* adri.voogd@epid.unimaas.nl