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Prognostic factors in breast cancer: one fits all?

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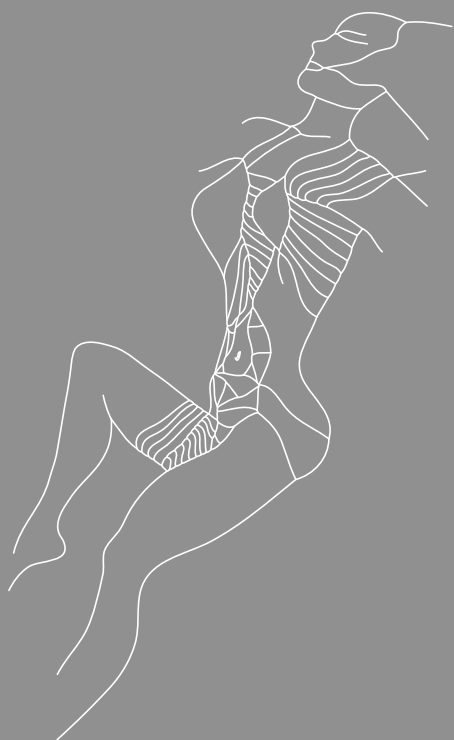
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Chapter 9

Independent prognostic value of screen detection in invasive breast cancer



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Abstract

Background

Mammographic screening has led to a proportional shift toward earlier-stage breast cancers at presentation. We assessed whether the method of detection provides prognostic information above and beyond standard prognostic factors and investigated the accuracy of predicted overall and breast cancer–specific survival by the computer tool Adjuvant! among patients with screen-detected, interval, and nonscreening-related carcinomas.

Methods

We studied 2592 patients with invasive breast cancer who were treated at the Netherlands Cancer Institute from January 1, 1990, through December 31, 2000. Overall and breast cancer–specific survival probabilities among patients with mammographically screen-detected ($n = 958$), interval ($n = 417$), and nonscreening-related ($n = 1217$) breast carcinomas were compared. Analyses were adjusted for clinicopathologic characteristics and adjuvant systemic therapy. Because of gradual implementation of population-based screening in the Netherlands, analyses were stratified a priori according to two periods of diagnosis. All statistical tests were two-sided.

Results

Screen detection was associated with reduced mortality (adjusted hazard ratio for all-cause mortality = 0.74, 95% confidence interval = 0.63 to 0.87, $p < 0.001$, and adjusted hazard ratio for breast cancer–specific mortality = 0.62, 95% confidence interval = 0.50 to 0.78, $p < 0.001$, respectively) compared with nonscreening-related detection. The absolute adjusted reduction in breast cancer–specific mortality was 7% at 10 years. The prognostic value of the method of detection was independent of the period of diagnosis and was similar across tumor size and lymph node status categories, indicating its prognostic value beyond stage migration. Adjuvant! underestimated breast cancer–specific survival in patients with screen-detected (-3.2%) and interval carcinomas (-5.4%).

Conclusions

Screen detection was found to be independently associated with better prognosis for overall and breast cancer–specific survival and to provide prognostic information beyond stage migration among patients with invasive breast cancer. We propose that the method of detection should be taken into account when estimating individual prognosis.

Introduction

Breast cancer mortality has decreased during the last several decades because of both the introduction of mammographic screening and the improvement and more extensive use of adjuvant systemic therapy.¹⁻⁷ Several studies have shown that breast cancer screening leads to a reduction of breast cancer mortality for the entire population.⁸⁻¹¹ However, it is still unclear how much the method of detection affects the prognosis of individual patients and whether the method of detection should be used as a prognostic factor to improve individualized treatment.

Breast cancers detected by screening mammography are often at an earlier stage of development than those detected after the patient has displayed symptoms of disease.¹²⁻¹⁷ This stage shift at diagnosis is a reflection of screening-related lead-time bias (*i.e.*, the time between detection of the tumor by mammography and the moment the tumor would have been detected in the absence of screening).¹⁸⁻²⁰ Lead-time bias automatically lengthens survival duration, thereby causing at least part of the observed improved outcome of patients with screen-detected tumors. Another phenomenon that contributes to the improved outcome of patients with a screen-detected tumor is length bias.¹⁹ Carcinomas detected by screening are not a random sample of cancers in the population but, instead, may contain a disproportionately large proportion of slow-growing tumors that tend to be associated with better survival, even in the absence of screening. If the method of detection has prognostic value that is independent of known prognostic factors (such as tumor size and lymph node status), it could potentially improve the prediction of outcome and the selection of patients for adjuvant systemic therapy and should therefore be incorporated in decision-making tools and guidelines.

Therefore, another important question is whether prognostic tools (such as the web-based program Adjuvant!) that are based on an unknown mixture of screen-detected and nonscreening-related carcinomas predict outcome of patients with screen-detected breast cancer accurately. To our knowledge, the study by Wishart *et al.*²¹ was the only study that has evaluated whether one of the currently available prediction models (*i.e.*, the Nottingham Prognostic Index) is adequate for screen-detected breast cancers. In addition, to our knowledge, none of the earlier studies by others⁸⁻¹¹ that examined the prognostic value of the method of detection on prognosis evaluated both the most important and least biased outcomes: overall and breast cancer-specific survival.²² Therefore, we assessed whether the method of detection (*i.e.*, screen-detected carcinomas, interval carcinomas, or nonscreening-related carcinomas) provided independent prognostic information for the individual patient in a comprehensive way. In addition, we investigated whether outcomes predicted by the web-based computer tool Adjuvant! were accurate, independent of the method of detection.²³⁻²⁵

Patients and Methods

Patient Selection

Women who were treated for invasive breast cancer at the Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital (NKI-AVL) from January 1, 1990, through December 31, 2000, and aged 50–69 years were selected from a database that we constructed for a previous study.²³ The following selection criteria were used: 1) a diagnosis of invasive unilateral breast carcinoma; 2) a known tumor size of T1 (≤ 2 cm), T2 (2–5 cm), or T3 (> 5 cm); 3) a known lymph node status of negative (pN0) or positive (pN1 = 1–3, pN2 = 4–9, or pN3 > 9 positive lymph nodes); 4) no distant metastases; 5) primary surgery; 6) complete axillary lymph node staging; and 7) administration of radiation therapy according to national guidelines. Patients with previous malignancies and patients who received neoadjuvant therapy were not included. A total of 2861 patients fulfilled the selection criteria and were initially included in the analysis. No ethical review was required according to the Dutch legislation.²³

Breast Cancer Screening in the Netherlands

The Dutch screening program started April 1, 1990, in a number of zip code regions, and all women aged 50–69 years in those regions were invited to participate in the screening program. Zip code regions were selected on the basis of availability of screening units, and regions were added as soon as a supplementary screening unit became available until full coverage was achieved in 1997.^{26–27} Women were invited for biennial mammography through a personal letter that included a scheduled appointment for mammography that could be changed on request. Nonattendants received a reminder after 2–3 months.²⁷ Screening mammograms were performed in independent and (mostly) mobile screening units (3–8 units per region). No screening mammographies were performed outside the national screening program. Information about screening mammography or diagnostic mammography was recorded in separate systems in the screening facility or in the hospital. Screening was extended to women aged 70–75 years in 1998. The national participation rate of the fully implemented Dutch screening program is between 70% and 80%.^{26–27}

Method of Detection

Information about the method of detection was retrieved from the database of the Comprehensive Cancer Center Amsterdam and was available for 2592 of 2861 patients. The Comprehensive Cancer Center Amsterdam is a regional cancer registry that receives this information from the Dutch national screening facilities. Patients with an unknown method of detection ($n = 269$) were excluded (*Figure 1*). Breast cancer–specific survival in this

group was similar to that in the group of patients with a known method of detection (n = 2592) (data not shown).

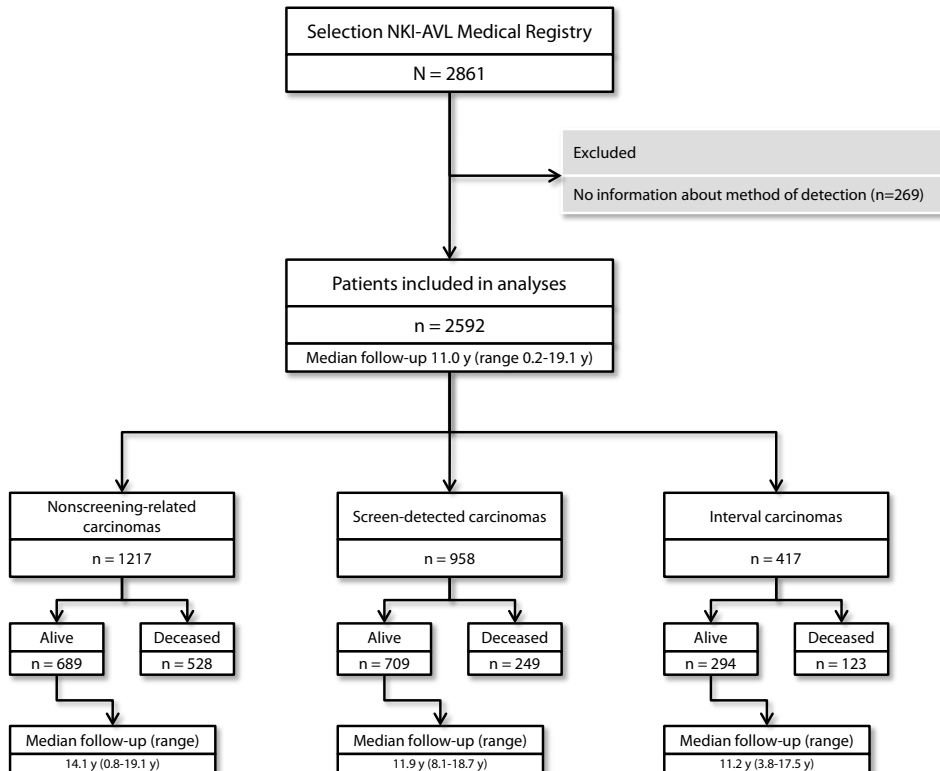


Figure 1. Flow diagram for patient selection and median follow-up by method of detection. NKI-AVL = Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital.

We classified three types of breast carcinomas on the basis of method of detection: 1) screen-detected carcinomas, defined as carcinomas that were mammographically detected in the first or subsequent screening rounds (n = 958); 2) interval carcinomas, defined as symptomatic carcinomas that were diagnosed within 24 months of a negative screening (n = 417); and 3) nonscreening-related carcinomas, defined as symptomatic carcinomas in patients who were not participating in the screening program (n = 1217). Among the 958 patients with a screen-detected carcinoma, 510 (53%) were detected in the first screening round (*i.e.*, prevalent carcinomas) and 443 (46%) in a subsequent screening round (*i.e.*, incident carcinomas); this information was missing for five patients. Overall survival and breast cancer-specific survival among the 510 patients with breast carcinomas that were

detected in the first screening round was similar to those in patients with breast carcinomas that were detected in second or subsequent screening rounds (*Supplementary Figure 1 and Supplementary Table 1*), so we pooled data from patients with screen-detected prevalent carcinomas and from patients with screen-detected incident carcinomas. Ninety-six patients had symptomatic carcinomas detected more than 24 months after a negative screening (interval range = 25–83 months). Disease outcomes for these 96 patients were similar to that for patients with nonscreening-related carcinomas, and so we pooled data from the 96 patients with symptomatic carcinomas detected more than 24 months after a negative screening and that from the 1121 patients with nonscreening-related cancers. Because of the stepwise implementation of the screening, the group of patients who were diagnosed with nonscreening-related breast carcinomas could presumably represent different groups of patients in each period of diagnosis. That is, there could have been a larger self-selected group of nonparticipants in the nonscreening group in the later years of diagnoses (1997–2000) compared with the early years of diagnoses (1990–1996), during which the nonparticipants were mostly noninvited persons. Therefore, we stratified our results into two periods of diagnosis: 1990–1996 and 1997–2000.

Pathology Data

Data on histology, tumor size, tumor grade, number of positive lymph nodes, estrogen-receptor status (*Table 1*), and HER2 status were retrieved from the NKI-AVL's Department of Clinical Chemistry, personal logbook of NKI-AVL pathologist, Dutch Network and National Database for Pathology, and the Medical Registry of the NKI-AVL, as previously described.²³ Tumors were classified into categories of stage according to the International Union Against Cancer TNM classification and were classified by the differentiation grade according to methods previously described by Bloom and Richardson.²⁸

Adjuvant Treatment

Information about adjuvant systemic therapy was obtained for each patient in this study from the NKI-AVL Medical Registry. In general, the use of adjuvant systemic therapy in the Netherlands increased, especially during the past decade.⁷ Since the introduction of a consensus guideline for adjuvant systemic therapy by the Dutch Breast Cancer Platform (NABON) in 2000, adjuvant systemic therapy was recommended for patients with lymph node–positive breast cancer and for a selection of patients with lymph node–negative breast cancer, according to tumor size and grade.²⁹ Before the introduction of this guideline, adjuvant systemic therapy was mainly recommended for lymph node–positive disease, tamoxifen was recommended for postmenopausal patients, and chemotherapy was recommended for premenopausal patients. In our study cohort of 2592 patients, 1150 (44.4%) did not receive adjuvant systemic therapy, 164 (6.3%) received chemotherapy, 1105 (42.6%) received hormonal therapy, and 173 (6.7%) received both chemotherapy and

hormonal therapy. Trends in the usage of adjuvant systemic therapy in our study cohort are depicted in *Supplementary Figure 2*.

Outcome data

Outcome data were obtained from the NKI-AVL Medical Registry (date of first local, regional, or distant recurrence; second malignancies; and/or contralateral breast cancer and date of last follow-up or death). These outcome data were further completed by linking patient records to the Dutch municipal registry, which contains the date of death or emigration for all Dutch citizens. For patients who were not registered as having died or emigrated, the date of last follow-up was recorded as February 1, 2009 (*i.e.*, 2 months before the date of linkage). Cause of death was partially retrieved from the Medical Registry and partially from individual patient files, with 418 breast cancer-specific deaths and 94 deaths from other causes being identified. Patients without a known cause of death ($n = 388$) were considered to have died of breast cancer if they were diagnosed with distant metastases during follow-up ($n = 77$ breast cancer-specific deaths; $n = 311$ other causes).

Predicted Outcomes by Adjuvant!

To evaluate the influence of the method of detection on algorithms for outcome prediction, we compared 10-year observed overall survival and breast cancer-specific survival with those that had been predicted by Adjuvant! (Batch processor version 8.0; Adjuvant! Incorporation, San Antonio, TX). Adjuvant! is a web-based computer tool that calculates individual outcomes by entering the patient's age, co-morbidity, tumor size, tumor grade, number of positive axillary lymph nodes, estrogen receptor status, and adjuvant systemic therapy. For this study, predicted outcomes were calculated by entering clinicopathologic data for each individual patient in the Adjuvant!, version 8.0 batch processor, including HER2 status. The Adjuvant! processor was run by one of the authors (P. M. Ravdin), while blinded to patient outcomes. The model's estimation of prognosis is calculated based on 10-year observed overall survival of women diagnosed with breast cancer between January 1, 1988, and December 31, 1992, in the United States and recorded in the Surveillance, Epidemiology, and End Results database.²⁵ The estimations of treatment efficacy by this tool are mainly calculated from the proportional risk reductions derived from the Early Breast Cancer Trialists' Collaborative Group 1998 meta-analyses, which was recently updated with the meta-analyses data from 2005.³⁰⁻³¹ Because we could not retrieve reliable data about co-morbidity, we used the default assumption of 'minor health problems.' In our study, 1447 patients had complete data for all factors that were used to predict outcome by the Adjuvant! model. Grade was unknown for 394 tumors, and estrogen receptor status was unknown for 931 tumors; for these tumors, grade and estrogen receptor status were entered in the model as 'unknown.' Given that Adjuvant! calculates predicted outcomes at 10 years, we evaluated its accuracy in a subgroup of patients who could have had at least 10 years of follow-up (*i.e.*, the 2329 patients who were diagnosed before the year 2000).

Table 1. Association between clinicopathological characteristics of patients with breast cancer and method of detection*†

| Characteristic | Nonscreening-related carcinoma | | Screen-detected carcinoma | | P | Interval carcinoma | | P |
|--------------------------|--------------------------------|------------|---------------------------|---------|--------|--------------------|--|--------|
| | No. (%) | No. (%) | No. (%) | No. (%) | | | | |
| Year of diagnosis | | | | | <0.001 | | | <0.001 |
| 1990–1996 | 932 (76.6) | 514 (53.7) | 168 (40.3) | | | | | |
| 1997–2000 | 285 (23.4) | 444 (46.3) | 249 (59.7) | | | | | |
| Age, y | | | | | <0.001 | | | 0.02 |
| 50–59 | 715 (58.8) | 492 (51.4) | 272 (65.2) | | | | | |
| 60–70 | 502 (41.2) | 466 (48.6) | 145 (34.8) | | | | | |
| Histology† | | | | | 0.03 | | | 0.16 |
| IDC | 928 (76.3) | 708 (73.9) | 302 (72.4) | | | | | |
| ILC | 144 (11.8) | 100 (10.4) | 64 (15.3) | | | | | |
| ID/LC | 54 (4.4) | 72 (7.5) | 25 (6.0) | | | | | |
| Others | 91 (7.5) | 78 (8.1) | 26 (6.2) | | | | | |
| Tumor size‡ | | | | | <0.001 | | | 0.18 |
| pT1 | 609 (50.0) | 727 (75.9) | 224 (53.7) | | | | | |
| pT2 | 561 (46.1) | 224 (23.4) | 172 (41.2) | | | | | |
| pT3 | 47 (3.9) | 7 (0.7) | 21 (5.0) | | | | | |
| Nodal status§ | | | | | <0.001 | | | 0.05 |
| pN0 | 567 (46.6) | 635 (66.3) | 189 (45.3) | | | | | |
| pN1 | 419 (34.4) | 218 (22.8) | 136 (32.6) | | | | | |
| pN2 | 169 (13.9) | 75 (7.8) | 55 (13.2) | | | | | |
| pN3 | 62 (5.1) | 30 (3.1) | 37 (8.9) | | | | | |
| Stage | | | | | <0.001 | | | 0.36 |
| I | 379 (31.1) | 543 (56.7) | 134 (32.1) | | | | | |
| II | 585 (48.1) | 308 (32.2) | 185 (44.4) | | | | | |
| III | 253 (20.8) | 107 (11.2) | 98 (23.5) | | | | | |

| Characteristic | Nonscreening-related carcinoma | | Screen-detected carcinoma | | P |
|---|--------------------------------|------------|---------------------------|---------|--------|
| | No. (%) | No. (%) | No. (%) | No. (%) | |
| Grade | | | | | 0.06 |
| 1 | 173 (17.9) | 275 (32.4) | 57 (15.0) | | |
| 2 | 491 (50.7) | 426 (50.2) | 179 (47.0) | | |
| 3 | 305 (31.5) | 147 (17.3) | 145 (38.1) | | |
| Unknown II | 248 | 110 | 36 | | |
| ER status | | | | | 0.05 |
| Positive | 558 (77.2) | 510 (81.6) | 224 (71.6) | | |
| Negative | 165 (22.8) | 115 (18.4) | 89 (28.4) | | |
| Unknown II | 494 | 333 | 104 | | |
| Adjuvant systemic therapy | | | | | <0.001 |
| None | 476 (39.1) | 533 (55.6) | 141 (33.8) | | |
| Chemo only | 92 (7.6) | 42 (4.4) | 30 (7.2) | | |
| Hormonal therapy only | 581 (47.7) | 341 (35.6) | 183 (43.9) | | |
| Chemo and hormonal | 68 (5.6) | 42 (4.4) | 63 (15.1) | | |
| All-cause mortality | | | | | <0.001 |
| Alive at last follow-up | 689 (56.6) | 709 (74.0) | 294 (70.5) | | |
| Death | 528 (43.4) | 249 (26.0) | 123 (29.5) | | |
| Breast cancer-specific mortality | | | | | 0.004 |
| Alive or no breast cancer-related death | 909 (74.7) | 848 (88.5) | 340 (81.5) | | |
| Breast cancer-related death | 308 (25.3) | 110 (11.5) | 77 (18.5) | | |
| Total | 1217 (100) | 958 (100) | 417 (100) | | |

* ER = estrogen receptor, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma; ID/LC = invasive ductolobular carcinoma.

† Associations between clinicopathological characteristics and method of detection were tested by chi-square statistics for the comparisons screen-detected versus non-screening-related carcinomas, and interval versus non-screening-related carcinomas. All statistical tests were two-sided.

‡ pT1 ≤2 cm; pT2 = 2–5 cm; pT3 >5 cm; § pN0 = lymph node-negative; pN1 = 1–3 positive lymph nodes; pN2 = 4–9 positive lymph nodes; pN3 >9 positive lymph nodes.

¶ Patients with unknown characteristics were not included in P value calculations, therefore percentages for these groups were not depicted in the table.

Statistical Analyses

Primary endpoints were overall survival, as measured from the time of diagnosis to death from any cause, or breast cancer–specific survival, as measured from the time of diagnosis to breast cancer–specific death. Patients who were still alive or who had died of other causes were censored on the date of the last follow-up or death. Kaplan–Meier survival analyses, log-rank tests, and univariate Cox proportional hazard ratios (HRs) were calculated to estimate differences in survival (mortality HRs) among patients with screen-detected, interval, or nonscreening-related breast carcinomas. To adjust for lead-time and length bias, multivariable Cox proportional hazard models were used to calculate the independent prognostic value of the method of detection after adjustment for age, tumor size, axillary lymph node status, tumor grade, estrogen receptor status, and adjuvant systemic therapy. In addition, to minimize lead-time bias, we evaluated disease outcome for screen-detected and nonscreening-related tumors, stratified for lymph node status and for tumor size. The proportional hazard assumption for the Cox model was evaluated by visual examination of the log minus log curves. Data are presented as hazard ratios with 95% confidence intervals (CIs). For the estimation of the absolute difference in survival, directly adjusted Cox survival curves were generated.

To assess the value of Adjuvant!, we calculated the observed overall survival and breast cancer–specific survival from Kaplan–Meier survival analyses for each subgroup by the method of detection and stratified by period of diagnosis. For the same datasets, the average predicted overall survival and breast cancer–specific survival percentages were calculated from individual predicted outcomes by Adjuvant!. Observed and average predicted outcomes were compared with a one-sample *t* test by assuming that the predicted outcomes were constant. All *P* values are two-sided, and a *P* value of less than .05 was considered statistically significant. Analyses were performed with SPSS, version 15.0 (SPSS, Inc, Chicago, IL) and STATA, version 11.1 (StataCorp, College Station, TX). The study was reported according to the STROBE statement.³²

Results

Baseline Characteristics and Stage Distribution

Analyses included 2592 patients (*Figure 1*), of whom 1614 were diagnosed with breast cancer between January 1, 1990, and December 31, 1996, and 978 patients were diagnosed between January 1, 1997, and December 31, 2000. As a consequence of the stepwise implementation of breast cancer screening in the Netherlands, breast carcinomas of most patients who were diagnosed before 1997 were detected outside the screening program. This group of patients diagnosed between January 1, 1990, and December 31, 1996,

included 932 (58%) nonscreening-related breast carcinomas, 514 (32%) screen-detected carcinomas, and 168 (10%) interval carcinomas. Between January 1, 1997, and December 31, 2000, most patients were diagnosed with screen-detected or interval breast carcinomas; specifically, there were 444 (45%) screen-detected carcinomas, 285 (29%) nonscreening-related carcinomas, and 249 (26%) interval carcinomas (*Figure 2*).

Baseline characteristics of patients in this study are summarized in *Table 1*. Screen detection of breast cancer was statistically significantly associated with older age, smaller tumor size, lymph node–negative disease, low grade, estrogen receptor–positive tumors, and less frequent administration of adjuvant systemic therapy compared with nonscreening-related detection. There was essentially no difference in tumor size between interval carcinomas and nonscreening-related carcinomas (23 versus 24 mm). However, interval carcinomas were more likely to occur in younger women and were slightly more often lymph node–positive and estrogen receptor negative (*Table 1*). The distribution of stage by method of detection was similar for patients diagnosed with breast cancer between 1990 and 1996, and patients diagnosed with breast cancer between 1997 and 2000 (data not shown). During median follow-up of 11 years (range = 0.2–19.1 years), 900 (35%) of 2592 patients died, of whom 495 (19%) died of breast cancer (*Table 1*).

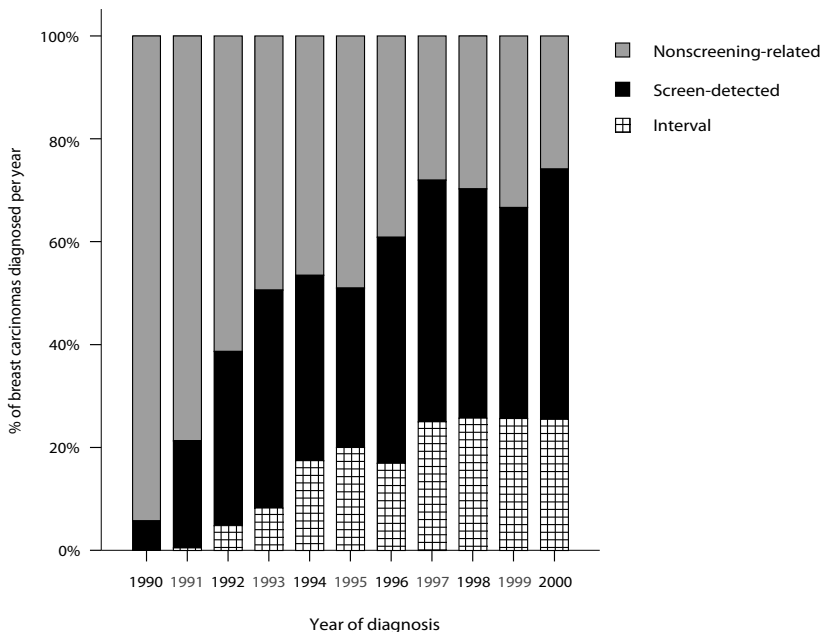
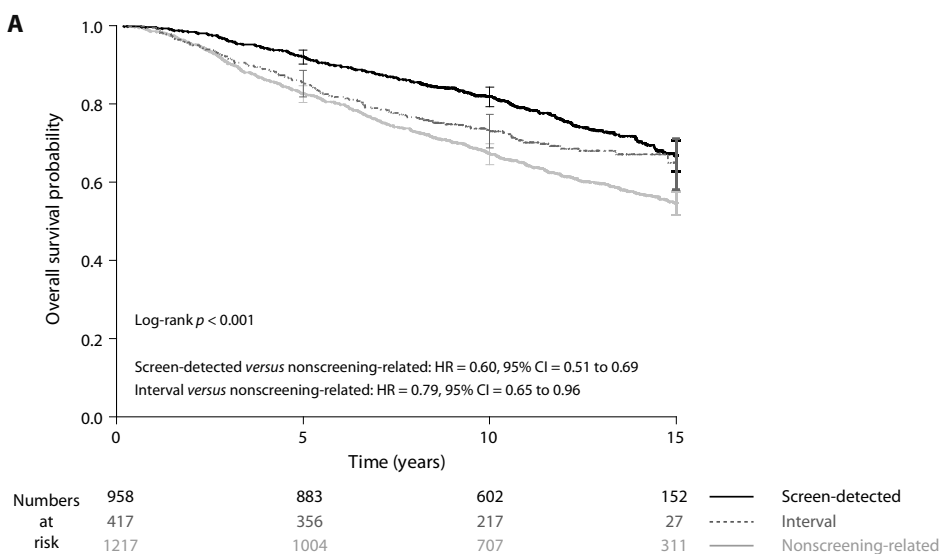


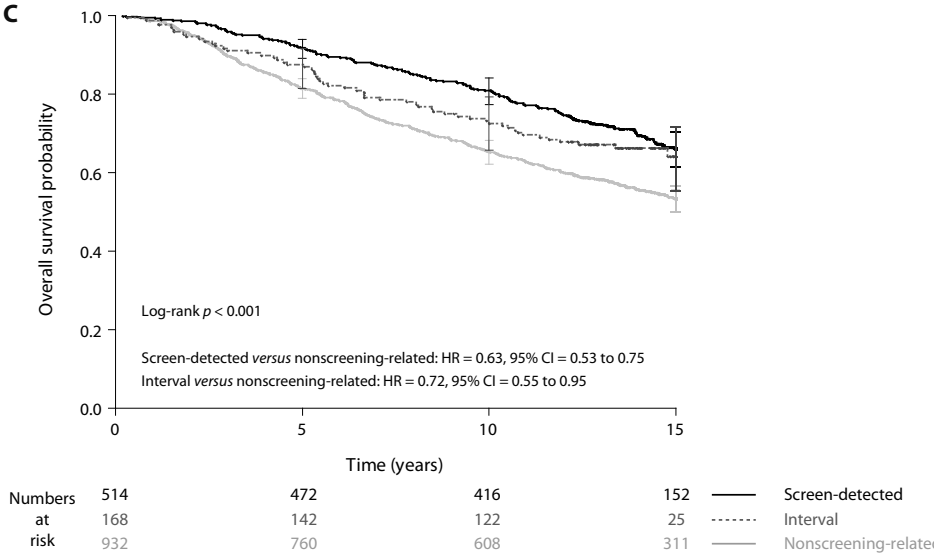
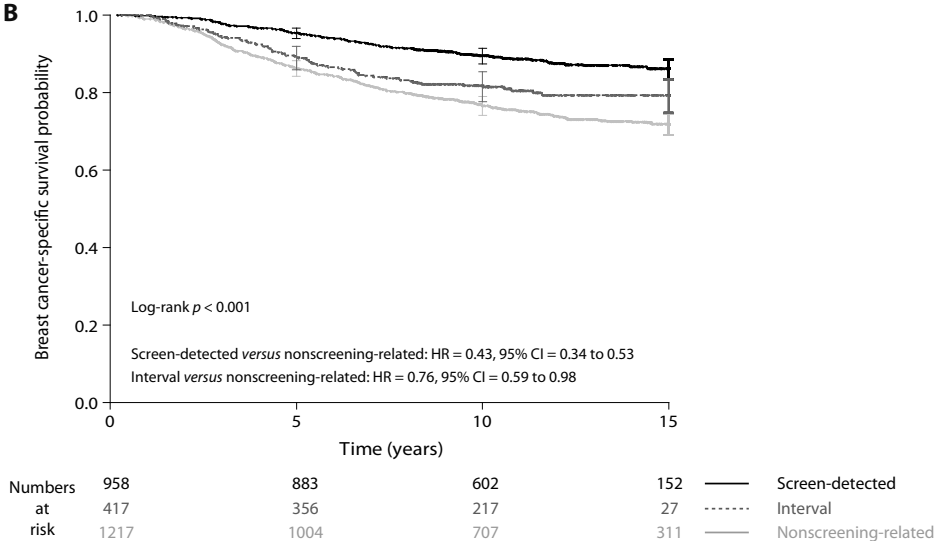
Figure 2. Method of detection by year of diagnosis: 1990–1996 (implementation of screening), 1997–2000 (full coverage of screening). Screening information was retrieved from the Dutch national screening facility. Screen detected (black bars), interval (hatched bars), non-screening related (gray bars).

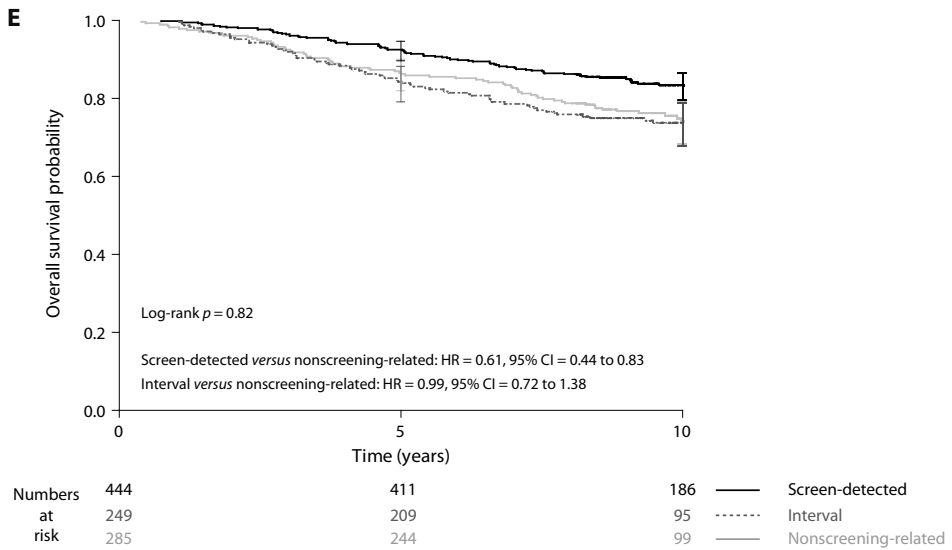
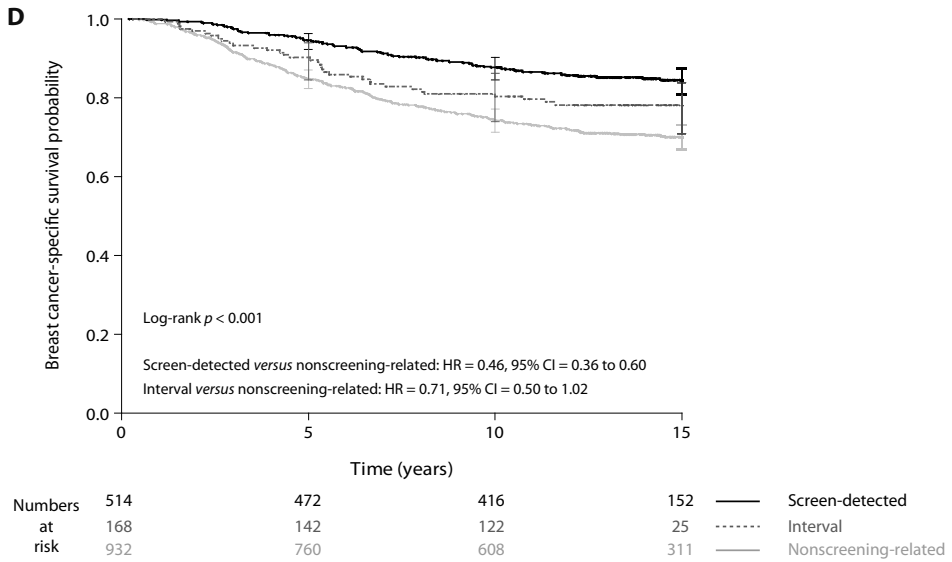
Overall and Breast Cancer–Specific Survival by Method of Detection

Patients with screen-detected carcinomas had statistically significantly better overall survival and breast cancer–specific survival than patients with nonscreening-related carcinomas (for all-cause mortality, univariate HR = 0.60, 95% CI = 0.51 to 0.69, $p < 0.001$; for breast cancer–specific mortality, univariate HR = 0.43, 95% CI = 0.34 to 0.53, $p < 0.001$) (Figure 3, A and B). Similar patterns were observed for all-cause mortality and for breast cancer–specific mortality in patients diagnosed between 1990 and 1996, and between 1997 and 2000 (Figure 3, C–F).

In a multivariable model that was adjusted for age at diagnosis, tumor size, tumor grade, lymph node status, estrogen receptor status, and adjuvant systemic therapy (Table 2), screen detection was still independently associated with increased survival for patients diagnosed with breast cancer between 1990 and 1996 (for all-cause mortality, adjusted HR = 0.77, 95% CI = 0.64 to 0.92, $p = 0.005$; for breast cancer–specific mortality, adjusted HR = 0.66, 95% CI = 0.50 to 0.86, $p = 0.002$). The favorable outcome of screen-detected carcinomas was of similar magnitude in patients diagnosed more recently (for all-cause mortality, adjusted HR = 0.73, 95% CI = 0.52 to 1.02, $p = 0.07$; for breast cancer–specific mortality, adjusted HR = 0.63, 95% CI = 0.40 to 1.01, $p = 0.05$) but with less statistical significance. Overall, screen detection was associated with reduced mortality (adjusted HR for all-cause mortality = 0.74, 95% CI = 0.63 to 0.87, $p < 0.001$; adjusted HR for breast cancer–specific mortality = 0.62, 95% CI = 0.50 to 0.78, $p < 0.001$) compared with nonscreening-related detection. The absolute reduction in breast cancer–specific mortality at 10 years of follow-up between the screen-detected and nonscreening-related carcinomas was 7% (adjusted survival rates were 86% versus 79%, respectively; unadjusted differences were 13% with survival rates of 89% for screen-detected carcinomas and 76% for nonscreening-related carcinomas).







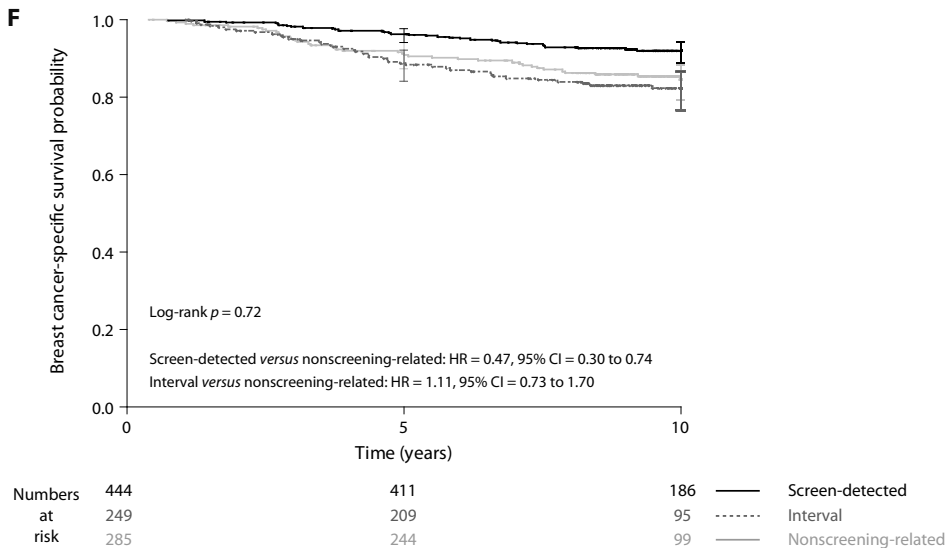


Figure 3. Kaplan–Meier curves for overall survival and breast cancer-specific survival by method of detection. Log-rank p -values and univariate hazard ratios (HRs) for all-cause mortality and breast cancer-specific mortality with corresponding 95% confidence intervals (CIs) at 5, 10, and 15 years are shown (error bars).

A) Overall survival for all patients ($n = 2592$).

B) Breast cancer-specific survival for all patients ($n = 2592$).

C) Overall survival for patients diagnosed in 1990–1996 ($n = 1614$).

D) Breast cancer-specific survival for patients diagnosed in 1990–1996 ($n = 1614$).

E) Overall survival for patients diagnosed in 1997–2000 ($n = 978$).

F) Breast cancer-specific survival for patients diagnosed in 1997–2000 ($n = 978$). Interval carcinomas were diagnosed 24 months or less after a negative screening. Non-screening-related carcinomas were symptomatic cancer in patients who had not been screened or were screened more than 24 months before detection of breast cancer. Numbers of patients at risk are shown below each graph.

Furthermore, diagnosis of an interval carcinoma between 1990 and 1996 was independently associated with better survival (for all-cause mortality, adjusted HR = 0.71, 95% CI = 0.54 to 0.96, $p = 0.02$; for breast cancer-specific mortality, adjusted HR = 0.70, 95% CI = 0.49 to 1.01, $p = 0.05$) compared with nonscreening-related detection. Conversely, diagnosis of an interval carcinoma between 1997 and 2000 was not associated with survival (for all-cause mortality, adjusted HR = 0.89, 95% CI = 0.63 to 1.24, $p = 0.48$; for breast cancer-specific mortality, adjusted HR = 0.91, 95% CI = 0.59 to 1.40, $p = 0.66$) (Table 2).

We also found that the interaction term between the method of detection and lymph node status was statistically significant in multivariable models for all-cause mortality ($p = 0.045$) and breast cancer-specific mortality ($p = 0.009$). However, in the model including the interaction term, screen detection was still associated with all-cause and breast cancer-specific mortality, with similar HRs for screen-detected cancers (all-cause mortality, adjusted HR = 0.70, 95% CI = 0.56 to 0.87, $p = 0.001$; breast cancer-specific mortality, adjusted HR = 0.51, 95% CI = 0.36 to 0.72, $p < 0.001$) and somewhat lower HRs for interval cancers (all-cause mortality, adjusted HR = 0.48, 95% CI = 0.33 to 0.71, $p < 0.001$; and breast cancer-specific mortality, adjusted HR = 0.27, 95% CI = 0.14 to 0.51, $p < 0.001$).

Table 2. Multivariable Cox proportional hazard analyses for all-cause mortality and breast cancer-specific mortality for all patients, patients who were diagnosed in the period of implementation of screening (1990-1996), and patients who were diagnosed in the period when screening reached full coverage (1997–2000)*.

| Characteristics | All-cause mortality | | Breast cancer-specific mortality | |
|---|---------------------|---------------------|----------------------------------|---------------------|
| | <i>P</i> | HR (95% CI) | <i>P</i> | HR (95% CI) |
| Year of diagnosis 1990–2000 | | | | |
| Method of detection | | | | |
| Screen-detected <i>versus</i> nonscreening-related | <0.001 | 0.74 (0.63 to 0.87) | <0.001 | 0.62 (0.50 to 0.78) |
| Interval carcinoma <i>versus</i> nonscreening-related | 0.009 | 0.76 (0.62 to 0.93) | 0.02 | 0.73 (0.56 to 0.94) |
| Age (per year) | <0.001 | 1.05 (1.04 to 1.06) | 0.15 | 1.01 (1.00 to 1.03) |
| pT† | | | | |
| pT2 (<i>versus</i> pT1) | <0.001 | 1.51 (1.30 to 1.75) | <0.001 | 1.75 (1.43 to 2.14) |
| pT3 (<i>versus</i> pT1) | <0.001 | 1.80 (1.30 to 2.50) | 0.02 | 1.65 (1.09 to 2.49) |
| pN‡ | | | | |
| pN1 (<i>versus</i> pN0) | <0.001 | 1.44 (1.16 to 1.77) | 0.003 | 1.56 (1.17 to 2.07) |
| pN2 (<i>versus</i> pN0) | <0.001 | 2.32 (1.82 to 2.97) | <0.001 | 3.01 (2.18 to 4.15) |
| pN3 (<i>versus</i> pN0) | <0.001 | 4.40 (3.25 to 5.94) | <0.001 | 6.30 (4.36 to 9.10) |
| Grade | | | | |
| II (<i>versus</i> I) | 0.01 | 1.34 (1.06 to 1.69) | <0.001 | 2.31 (1.51 to 3.55) |
| III (<i>versus</i> I) | <0.001 | 2.31 (1.79 to 2.96) | <0.001 | 4.59 (2.95 to 7.13) |
| Grade unknown (<i>versus</i> I) | <0.001 | 1.54 (1.19 to 1.99) | <0.001 | 3.03 (1.93 to 4.76) |
| ER status | | | | |
| ER negative (<i>versus</i> ER positive) | 0.04 | 1.24 (1.01 to 1.53) | 0.06 | 1.29 (0.99 to 1.68) |
| ER unknown (<i>versus</i> ER positive) | 0.15 | 1.11 (0.96 to 1.29) | 0.23 | 1.13 (0.92 to 1.39) |
| Chemotherapy (yes <i>versus</i> no) | 0.14 | 0.83 (0.65 to 1.06) | 0.02 | 0.71 (0.53 to 0.95) |
| Hormonal therapy (yes <i>versus</i> no) | 0.02 | 0.78 (0.65 to 0.95) | 0.10 | 0.80 (0.62 to 1.04) |

Table 2. Continued

| Characteristics | All-cause mortality | | Breast cancer-specific mortality | |
|---|---------------------|---------------------|----------------------------------|---------------------|
| | <i>P</i> | HR (95% CI) | <i>P</i> | HR (95% CI) |
| Year of diagnosis: 1990–1996 | | | | |
| Method of detection | | | | |
| Screen-detected <i>versus</i> nonscreening-related | <0.005 | 0.77 (0.64 to 0.92) | 0.002 | 0.66 (0.50 to 0.86) |
| Interval carcinoma <i>versus</i> nonscreening-related | 0.02 | 0.71 (0.54 to 0.96) | 0.05 | 0.70 (0.49 to 1.01) |
| Age (per year) | <0.001 | 1.04 (1.03 to 1.06) | 1.0 | 1.00 (0.98 to 1.02) |
| pT† | | | | |
| pT2 (<i>versus</i> pT1) | <0.001 | 1.54 (1.30 to 1.82) | <0.001 | 1.86 (1.47 to 2.35) |
| pT3 (<i>versus</i> pT1) | 0.003 | 1.79 (1.22 to 2.62) | 0.04 | 1.64 (1.01 to 2.67) |
| pN‡ | | | | |
| pN1 (<i>versus</i> pN0) | 0.04 | 1.31 (1.02 to 1.69) | 0.08 | 1.37 (0.97 to 1.95) |
| pN2 (<i>versus</i> pN0) | <0.001 | 2.23 (1.67 to 2.98) | <0.001 | 3.00 (2.06 to 4.37) |
| pN3 (<i>versus</i> pN0) | <0.001 | 4.13 (2.86 to 5.95) | <0.001 | 6.13 (3.93 to 9.55) |
| Grade | | | | |
| II (<i>versus</i> I) | 0.07 | 1.28 (0.99 to 1.66) | 0.004 | 2.00 (1.25 to 3.18) |
| III (<i>versus</i> I) | <0.001 | 2.15 (1.62 to 2.85) | <0.001 | 3.91 (2.43 to 6.30) |
| Grade unknown (<i>versus</i> I) | 0.02 | 1.40 (1.06 to 1.84) | <0.001 | 2.49 (1.54 to 4.02) |
| ER status | | | | |
| ER negative (<i>versus</i> ER positive) | 0.41 | 1.12 (0.86 to 1.47) | 0.93 | 1.02 (0.73 to 1.42) |
| ER unknown (<i>versus</i> ER positive) | 0.47 | 1.06 (0.90 to 1.25) | 0.67 | 0.95 (0.76 to 1.19) |
| Chemotherapy (yes <i>versus</i> no) | 0.11 | 0.75 (0.53 to 1.07) | 0.03 | 0.64 (0.43 to 0.97) |
| Hormonal therapy (yes <i>versus</i> no) | 0.17 | 0.85 (0.67 to 1.07) | 0.16 | 0.80 (0.58 to 1.10) |

Continued ►

Table 2. Continued

| Characteristics | All-cause mortality | | Breast cancer-specific mortality | |
|---|---------------------|---------------------|----------------------------------|----------------------|
| | <i>P</i> | HR (95% CI) | <i>P</i> | HR (95% CI) |
| Year of diagnosis: 1997–2000 | | | | |
| Method of detection | | | | |
| Screen-detected <i>versus</i> nonscreening-related | 0.07 | 0.73 (0.52 to 1.02) | 0.05 | 0.63 (0.40 to 1.01) |
| Interval carcinoma <i>versus</i> nonscreening-related | 0.48 | 0.89 (0.63 to 1.24) | 0.66 | 0.91 (0.59 to 1.40) |
| Age (per year) | <0.001 | 1.06 (1.04 to 1.09) | 0.005 | 1.05 (1.02 to 1.09) |
| pT† | | | | |
| pT2 (<i>versus</i> pT1) | 0.05 | 1.36 (1.00 to 1.85) | 0.22 | 1.29 (0.86 to 1.93) |
| pT3 (<i>versus</i> pT1) | 0.10 | 1.71 (0.91 to 3.20) | 0.43 | 1.39 (0.61 to 3.16) |
| pN‡ | | | | |
| pN1 (<i>versus</i> pN0) | 0.006 | 1.71 (1.16 to 2.51) | 0.02 | 1.89 (1.12 to 3.18) |
| pN2 (<i>versus</i> pN0) | 0.001 | 2.27 (1.39 to 3.71) | 0.01 | 2.29 (1.20 to 4.37) |
| pN3 (<i>versus</i> pN0) | <0.001 | 4.71 (2.75 to 8.07) | <0.001 | 6.04 (3.07 to 11.87) |
| Grade | | | | |
| II (<i>versus</i> I) | 0.06 | 1.64 (0.97 to 2.75) | 0.02 | 4.24 (1.31 to 13.78) |
| III (<i>versus</i> I) | <0.001 | 2.86 (1.62 to 5.07) | 0.001 | 7.24 (2.15 to 24.40) |
| Grade unknown (<i>versus</i> I) | 0.02 | 2.33 (1.12 to 4.83) | 0.08 | 3.68 (0.86 to 15.87) |
| ER status | | | | |
| ER negative (<i>versus</i> ER positive) | 0.14 | 1.34 (0.91 to 1.98) | 0.003 | 2.09 (1.28 to 3.42) |
| ER unknown (<i>versus</i> ER positive) | 0.73 | 0.91 (0.52 to 1.58) | 0.83 | 0.91 (0.39 to 2.12) |
| Chemotherapy (yes <i>versus</i> no) | 0.99 | 1.00 (0.67 to 1.49) | 0.46 | 1.21 (0.73 to 2.00) |
| Hormonal therapy (yes <i>versus</i> no) | 0.10 | 0.73 (0.51 to 1.06) | 0.38 | 1.25 (0.76 to 2.04) |

* All analyses were done with the use of the Cox proportional hazard model. All statistical tests were two-sided.

CI = confidence interval; ER = estrogen receptor; HR = hazard ratio.

† pT = pT1 ≤2 cm; pT2 = 2–5 cm; pT3 >5 cm. ‡ pN = pN0 = lymph node-negative; pN1 = 1–3 positive lymph nodes; pN2 = 4–9 positive lymph nodes; pN3 >9 positive lymph nodes.

In 1998, screening in the Netherlands was extended to woman aged 70–75 years. Including those patients in this analysis resulted in 180 additional breast cancer patients, including 74 (41%) screen-detected breast cancers, 14 (8%) interval breast cancers, and 92 (51%) nonscreening-related breast cancers. When we included this age group in the survival analysis, the difference in outcomes between screen-detected and nonscreening-related

carcinomas was even larger for breast cancer-specific mortality (unadjusted HR = 0.35, 95% CI = 0.23 to 0.52, $p < 0.001$ and adjusted HR = 0.49, 95% CI = 0.32 to 0.75, $p < 0.001$) (Supplementary Table 2).

Screen-detected breast carcinomas were smaller (mean size 17 versus 24 mm; $p < 0.001$) and more often (66.3% versus 46.6%) had a lymph node-negative status compared with nonscreening-related carcinomas, reflecting the well-known stage shift caused by screening (Table 1). In addition to the multivariable analyses, we compared breast cancer-specific survival between patients with screen-detected carcinomas and patients with nonscreening-related carcinomas as stratified by tumor size and by lymph node status. Because the differences in breast cancer-specific survival between screen-detected and nonscreening-related carcinomas were similar in both periods of diagnosis (1990–1996 and 1997–2000), we pooled patients with such carcinomas to increase sample sizes for subgroup analyses by tumor size and lymph node status. Patients with screen-detected cancers had better breast cancer-specific survival than patients with nonscreening-related tumors within each stratum of tumor size, with the most pronounced difference in tumors of 10 mm or less in diameter (for breast cancer-specific mortality, unadjusted HR = 0.28, 95% CI = 0.11 to 0.71, $p = 0.007$; adjusted HR = 0.35, 95% CI = 0.13 to 0.96, $p = 0.04$) (Supplementary Table 3 and Supplementary Figure 3, A–D). In analyses stratified by lymph node status, better breast cancer-specific survival was associated with screen-detected tumors in both patients with lymph node-negative and patients with lymph node-positive breast cancer (in lymph node-negative patients, unadjusted HR for breast cancer-specific mortality = 0.40, 95% CI = 0.28 to 0.56, $p < 0.001$; in lymph node-positive patients, unadjusted HR = 0.59, 95% CI = 0.45 to 0.79, $p < 0.001$). After adjustment for other prognostic factors (including age, tumor size, grade, estrogen receptor status and adjuvant systemic therapy), screen detection was strongly and statistically significantly associated with improved breast cancer-specific survival among patients with lymph node-negative disease, but this association was weaker and non-statistically significant among patients with lymph node-positive disease (in lymph node-negative patients, adjusted HR for breast cancer-specific mortality = 0.51, 95% CI = 0.36 to 0.73, $p < 0.001$; in lymph node-positive patients, adjusted HR = 0.79, 95% CI = 0.59 to 1.06, $p = 0.12$) (Supplementary Table 4 and Supplementary Figure 3, E–F). The observed survival difference of patients with lymph node-positive screen-detected carcinomas was to a larger extent associated with stage shift and period of diagnosis; that is, lymph node-positive patients with screen-detected breast cancer were statistically significantly more likely to be diagnosed in 1997–2000 and to have smaller and better differentiated tumors than lymph node-positive patients whose breast cancer was not detected by screening ($p < 0.001$) (data not shown). Screen detection was also independently associated with breast cancer-specific survival among systemically untreated patients (adjusted HR = 0.48, 95% CI = 0.32 to 0.71, $p < 0.001$).

Table 3. Adjuvant predicted and observed 10-year overall survival and breast cancer-specific survival for all patients diagnosed before 2000, for patients diagnosed in the period of implementation of screening (1990–1996), and for patients diagnosed in the period when screening reached full coverage (1997–1999)*.

| Period of diagnosis and method of detection | No. Patients (%) | 10-year overall survival | | | 10-year breast cancer-specific survival | | | P | |
|--|------------------|--------------------------|---|------|---|---|---------------------|------|-------|
| | | Adjuvant predicted, % | Observed, Predicted – observed % (95% CI) | P | Adjuvant predicted, % | Observed, Predicted – observed % (95% CI) | P | | |
| Method of detection, year of diagnosis: 1990–1999 | | | | | | | | | |
| Nonscreening related | 1149 (64.9) | 69.2 | 66.6 (63.9 to 69.3) | 2.6 | 0.06 | 76.5 | 75.7 (73.2 to 78.2) | 0.8 | 0.54 |
| Screen-detected | 830 (46.9) | 77.6 | 82.0 (79.5 to 84.5) | -4.4 | <0.001 | 86.1 | 89.3 (87.1 to 91.5) | -3.2 | 0.004 |
| Interval carcinoma | 350 (19.8) | 68.7 | 72.4 (67.7 to 77.1) | -3.7 | 0.12 | 75.5 | 80.9 (76.6 to 85.2) | -5.4 | 0.02 |
| Method of detection, year of diagnosis: 1990–1996 (implementation of screening) | | | | | | | | | |
| Nonscreening related | 932 (57.7) | 68.6 | 65.3 (62.2 to 68.4) | 3.3 | 0.04 | 76.2 | 74.3 (71.4 to 77.2) | 1.9 | 0.21 |
| Screen-detected | 514 (31.8) | 76.7 | 80.9 (77.6 to 84.2) | -4.2 | 0.01 | 85.5 | 87.7 (84.8 to 90.6) | -2.2 | 0.14 |
| Interval carcinoma | 168 (10.4) | 68.9 | 73.2 (66.5 to 79.9) | -4.3 | 0.21 | 75.9 | 80.9 (74.8 to 87.0) | -5.0 | 0.11 |
| Method of detection, year of diagnosis: 1997–1999 (full coverage of screening) | | | | | | | | | |
| Nonscreening related | 217 (22.2) | 71.9 | 72.3 (66.2 to 78.4) | -0.4 | 0.90 | 78.2 | 81.7 (76.2 to 87.2) | -3.5 | 0.21 |
| Screen-detected | 316 (32.3) | 79.2 | 83.8 (79.7 to 87.9) | -4.6 | 0.03 | 87.0 | 92.1 (89.0 to 95.2) | -5.1 | 0.002 |
| Interval carcinoma | 182 (18.6) | 68.6 | 71.7 (65.0 to 78.4) | -3.1 | 0.36 | 75.3 | 80.8 (74.9 to 86.7) | -5.5 | 0.007 |

* Analyses were done with the use of one sample ttests. All statistical tests were two-sided. CI = confidence interval.

Adjuvant! Predictions

To evaluate the influence of the method of detection on an algorithm for outcome prediction, we compared 10-year observed overall survival and breast cancer–specific survival with 10-year overall survival and breast cancer–specific survival that had been predicted by Adjuvant!. Adjuvant! predicted the outcome among patients with nonscreening-related carcinomas accurately, that is, the predicted survival of patients with a nonscreening-related carcinoma was within 2% of the observed survival and/or non-statistically significantly different in all but one group: Adjuvant! overestimated overall survival in patients with a nonscreening-related carcinoma diagnosed between 1990 and 1996 with 3.3% ($p=0.04$). However, Adjuvant! predictions underestimated overall survival and breast cancer–specific survival among patients with screen-detected and interval carcinomas. Prediction of breast cancer–specific survival was underestimated by Adjuvant! for patients with screen-detected and interval carcinomas by -3.2% and -5.4%, respectively. Among patients with screen-detected carcinomas, in particular, Adjuvant! underestimated survival for all periods of diagnosis (*Table 3*). In addition, Adjuvant! underestimated breast cancer–specific survival in patients younger than 50 years whose breast cancer was diagnosed more recently (1997–2000) with -3.0%, reflecting the observed 22% reduction in breast cancer–specific survival, whereas Adjuvant! predictions for patients younger than 50 years diagnosed between 1990 and 1996 were accurate (*Supplementary Table 5*).²³

Discussion

We found that screen detection was independently associated with better breast cancer–specific survival, as shown in multivariable analyses and analyses stratified for tumor size and lymph node status, and provided prognostic information beyond stage migration for patients with invasive breast cancer. These results are in agreement with previous studies.^{9,11,21} Therefore, the method of detection should be taken into account when selecting patients for adjuvant systemic therapy and withholding chemotherapy for women with screen-detected carcinoma could be considered. We also analyzed the accuracy of predicted disease outcome by the computer tool Adjuvant! as stratified by the method of detection.²⁵ When we compared outcomes from this study with outcomes predicted by Adjuvant! for the same patients, we found that predicted breast cancer–specific survival by Adjuvant! was underestimated for all three groups, with the most pronounced and statistically significant differences in patients with screen-detected and interval breast carcinomas.

The true independent prognostic value of the method of detection for individual breast cancer patients may remain a matter of dispute. This dispute may not be settled unless a precise method for assessing tumor advancement is developed. Nonetheless, we

have obtained consistent evidence in this study that the method of detection was an independent prognostic factor beyond stage shift for disease outcome in patients with invasive breast carcinomas, with increased survival being associated with screen-detected carcinomas.

However, the question remains whether models and guidelines for adjuvant systemic therapy that were developed in an (partially) unscreened population are applicable to patients with screen-detected carcinomas and whether the use of these models and guidelines may lead to overtreatment in these patients. Our data indicate that current models for determining prognosis in breast cancer patients may be improved by including the method of detection. In our study, the general underestimation of survival outcome by Adjuvant! for patients diagnosed with breast cancer in 1997 through 1999 may be attributed in part to improved salvage therapy and adjuvant systemic therapy.³³⁻³⁵ We observed a reduction in breast cancer-specific mortality for patients younger than 50 years who were recently diagnosed, which supports this hypothesis. However, the underestimations of overall and breast cancer-specific survival by Adjuvant! were most pronounced in patients with screen-detected carcinomas, indicating that although improved therapy will influence the model's prediction, the method of detection should be taken into account when selecting patients for adjuvant systemic therapy.

It is well established and confirmed by our study that screened populations have a larger proportion of smaller, lymph node-negative, lower grade, and estrogen receptor-positive tumors than nonscreened populations. Stratification by tumor size reduces the magnitude of lead-time bias that is caused by stage shift, although it may not completely eliminate lead-time bias because shift within a stage can still occur (*e.g.*, more T1ab tumors with a diameter of ≤ 1 cm in the pT1 category of ≤ 2 cm tumors). We found that, even within strata of less than 10-mm tumors and of 10- to 20 mm tumors, screen-detected carcinomas were associated with better breast cancer-specific survival than non-screened carcinomas. Stratification by lymph node status showed that, despite the prognostic value of screen detection being similar among patients with lymph node-negative and lymph node-positive disease, screen detection was independently associated with breast cancer-specific survival especially for patients with no lymph node metastases at diagnosis and that the observed survival difference of patients with lymph node-positive screen-detected carcinomas was to a larger extent associated with stage shift and period of diagnosis.

When studying the effect of screening on mortality at the population level, both lead-time (stage shift) and length bias (less-aggressive tumors) can cause a spurious improvement of survival in the screened population. When investigating the independent prognostic value of the method of detection on the prediction of outcome for an individual patient, screen-detected carcinomas appear to have a more favorable tumor biology (*e.g.*, to be at a low grade at diagnosis) and are subject to potential overdiagnosis.³⁶ A different natural history of screen-detected carcinomas has also been postulated by others.^{37,38} Moreover, we found that, even after adjustment for known prognostic factors and within strata of tumor size,

method of detection had independent prognostic value. This result could indicate that we were not able to completely correct for length bias with the prognostic factors that were available; however, we argue that it is exactly this remaining unexplained difference in tumor biology beyond stage shift (length bias) that is important in the prediction of outcome for the individual patient.

Although the prognostic value of screen detection was similar among patients diagnosed in 1990–1996 and those diagnosed in 1997–2000, there were several reasons to stratify our data analyses according to period of diagnosis. First, because the stepwise implementation of screening in the Netherlands, patients diagnosed with nonscreening-related breast carcinomas in 1990–1996 were predominantly women who had not been invited for screening in a certain geographic region, whereas patients diagnosed with nonscreening-related breast carcinomas after 1996 were more likely to have been a specific subset of patients who decided not to participate in the breast cancer screening program for various reasons. Patients diagnosed from 1990 to 1996 were expected to be a random selection of patients that, consequently, can be viewed as a unique control group of nonscreening-related cancers. Patients diagnosed after 1996 are subject to selection biases, such as worse accessibility to adequate treatment facilities or lower socioeconomic status, which will influence both participation rate and outcome. In addition, as shown by Kalager *et al.*,¹⁰ organized screening programs also result in a survival benefit for patients outside the screening program that can be attributed to increased awareness and optimization of breast cancer care. This effect may dilute the prognostic value of screen detection, especially in more recent years (1997–2000) when the coverage of screening was complete. The possibility that both screening and improved adjuvant systemic therapy contributed to the reduction in breast cancer mortality from 1990 to 2010 with similar magnitude further emphasizes the necessity for comparisons during the same period between patients with screen-detected carcinomas and those with nonscreening-related carcinomas.³⁹

The observed intermediate survival among patients with interval breast cancers was consistent with previous studies.^{40–42} Interval breast carcinomas are a heterogeneous group of tumors consisting of true interval carcinomas (*i.e.*, rapidly growing tumors), occult carcinomas, and tumors that were missed on previous screening mammography (*i.e.*, slowly growing tumors).⁴³ The latter group of tumors could be related to breast density and thus associated with younger age at diagnosis, which we did observe. Although general baseline tumor characteristics did not differ much between interval cancers and nonscreening-related cancers, patients with interval carcinomas received adjuvant systemic therapy more often. However, we found that, in the adjuvant-untreated group specifically, survival was similar between patients with interval carcinomas and patients with a screen-detected carcinoma (data not shown). In addition, increased patient awareness as a result of the screening program and self-selection could have resulted in a better outcome for interval carcinomas.

One of the strengths of our study was that information about whether a tumor was detected in the first screening round (*i.e.*, was a prevalent carcinoma) or in a subsequent screening round (*i.e.*, was an incident carcinoma) was available. Another strength was that both overall survival and breast cancer–specific survival could be evaluated and that outcome data were collected in a manner that was blinded to the method of detection, thereby eliminating potential problems of differential bias in ascertainment and coding of cause of death (*i.e.*, the sticky-diagnosis and slippery-linkage biases, respectively).⁴⁴ In addition, patients in this study cohort had a substantial follow-up.

As a consequence of the conservative adjuvant systemic therapy guidelines that were used during the time patients in this study cohort were treated for breast cancer, a large proportion of patients received no chemo and/or hormonal therapy (*Supplementary Figure 2*). Although most patients with early-stage breast cancer currently receive some form of adjuvant systemic therapy, the estimated prognosis (*i.e.*, disease outcome without adjuvant systemic therapy) is important for the decision whether or not to treat patients with adjuvant systemic therapy. We found that method of detection has independent prognostic value, with screen detection associated with better survival. Thus, withholding chemotherapy for women with screen-detected carcinoma could be considered; however, these results require validation in an independent series of patients.

There have been several randomized clinical screening trials^{8,9,11} that have investigated the association between screening and outcome. These studies have identified a reduction of 25%–35% in breast cancer mortality that is associated with screen detection, which was sustained, though attenuated, after adjustment for prognostic factors. Notwithstanding the outcome of the randomized clinical trials, these results are not simply applicable to the general and diverse population that is participating in breast cancer screening. Shen *et al.*¹¹ studied patients who were included in trials that were conducted in 1963–1966 and 1980–1985, thus representing different birth cohorts from those of women who are currently at risk of breast cancer. In addition, they missed important clinicopathologic information (*e.g.*, exact tumor size and tumor grade). Although Joensuu *et al.*⁹ had detailed information and could adjust distant disease-free survival for tumor size, number of positive lymph nodes, tumor grade, and hormone receptor status, there were only 443 patients with a screen-detected carcinoma. Wishart *et al.*²¹ have shown that screen-detected carcinomas were associated with better overall survival than symptomatic breast cancer. The prognostic value of screen detection remained statistically significant after correction for stage shift defined by the Nottingham Prognostic Index, but no data on breast cancer–specific survival were included. Although Wishart *et al.*²¹ analyzed 5604 patients, the control group (*i.e.*, symptomatic breast cancer patients) consisted of a mixture of patients with potentially very different survival rates, that is, true interval carcinomas, patients with interval carcinomas diagnosed more than 3 years after a negative mammographic screening, and patients who did not participate in the screening program.

This study had several limitations. Information was not available for tumor markers, such as HER2 (for the majority of patients) or Ki67. However, it is not likely that the remaining difference in outcome between screen-detected and nonscreening-related tumors can be explained merely by these factors.⁴⁵ In general, patients were treated according to guidelines available at that time; however, other factors (*e.g.*, co-morbidity or HER2 status) could have influenced choice of treatment. Residual confounding by indication was shown by the increased risk of death after chemotherapy or hormonal treatment in carcinomas diagnosed in 1997–2000 (*Table 2*), although hazard ratios of treatment were non-statistically significant. Several studies^{46–48} have shown that gene expression profiles can account for a substantial part of the unexplained variance in prognosis. Therefore, the independent prognostic value of method of detection after adjustment for gene expression in a tumor remains to be determined.

In summary, we have shown that screen detection was consistently associated with disease outcome and provided prognostic information beyond stage migration among patients with invasive breast cancer. As a consequence, we propose that method of detection should be used in combination with traditional markers of tumor burden and aggressiveness to estimate prognosis for each patient, and to guide their decision to receive adjuvant systemic therapy.

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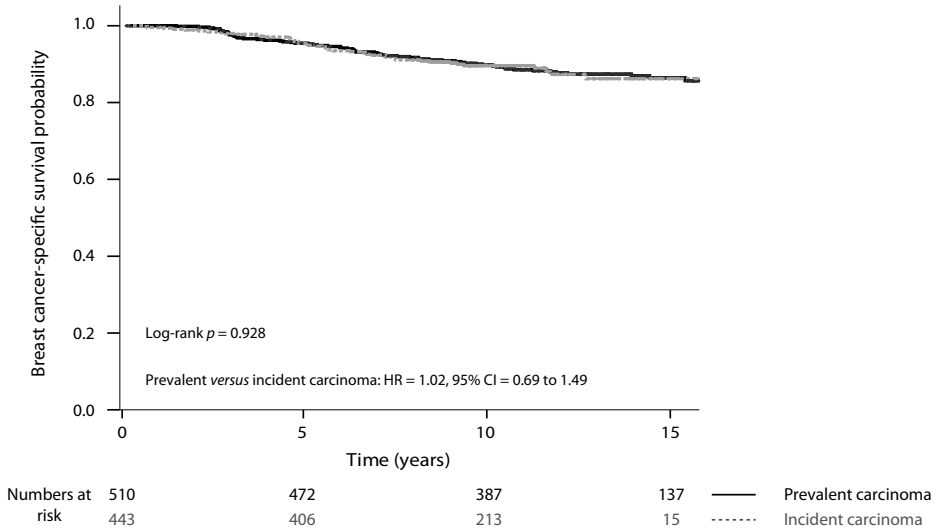
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Supplements Chapter 9



Supplementary Figure 1. Breast cancer-specific mortality in 953 women diagnosed with a screen-detected carcinoma between 1990 and 2000. Kaplan–Meier curves for breast cancer-specific survival and the univariate hazard ratio (HR) with its 95% confidence interval (CI) for prevalent versus incident carcinomas are shown.

Kaplan–Meier survival analysis, log-rank test, and univariate Cox proportional hazard ratio (HRs) were calculated to estimate differences in survival among patients with prevalent carcinoma (*i.e.*, detected in the first screening round) and patients with incident carcinomas (*i.e.*, detected in a second or subsequent screening round).

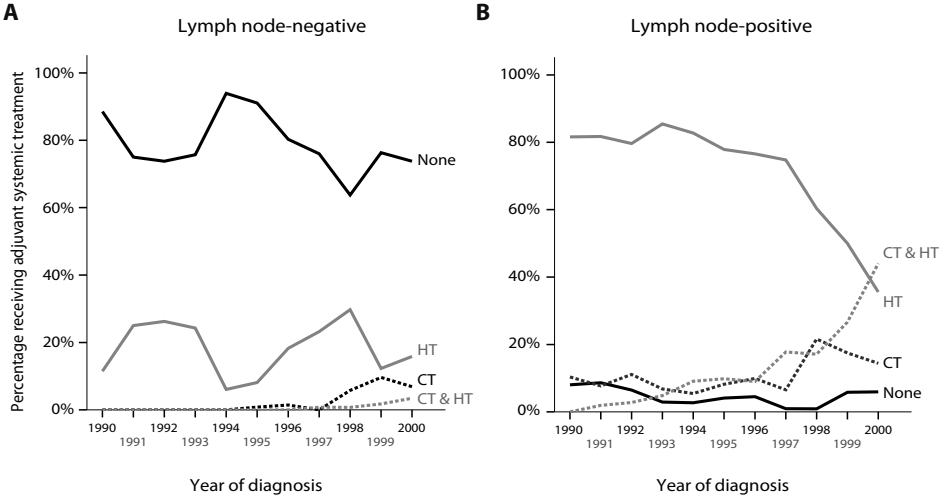
Supplementary Table 1. Multivariable Cox proportional hazard regression analyses for breast cancer-specific mortality in patients with breast cancer detected in the first screening round (*i.e.*, prevalent carcinoma) (n = 510) and patients with breast cancer detected in a second or subsequent screening round (*i.e.*, incident carcinoma) (n = 443)*.

| Characteristics | Breast cancer-specific mortality | |
|---|----------------------------------|----------------------|
| | P | HR (95% CI) |
| Incident versus prevalent carcinoma | 0.85 | 0.95 (0.58 to 1.56) |
| Period of diagnosis (1990–1996 versus 1997–2000) | 0.01 | 0.87 (0.79 to 0.97) |
| Age (per year) | 0.15 | 1.03 (0.99 to 1.06) |
| pT† | | |
| pT2 (versus pT1) | 0.04 | 1.58 (1.02 to 2.46) |
| pT3 (versus pT1) | 0.04 | 3.87 (1.04 to 14.32) |
| pN‡ | | |
| pN1 (versus pN0) | 0.09 | 1.71 (0.92 to 3.18) |
| pN2 (versus pN0) | 0.002 | 2.83 (1.45 to 5.55) |
| pN3 (versus pN0) | <0.001 | 6.21 (2.85 to 13.56) |
| Grade | | |
| II (versus I) | 0.002 | 3.13 (1.51 to 6.49) |
| III (versus I) | <0.001 | 5.90 (2.65 to 13.16) |
| Unknown (versus I) | 0.41 | 1.47 (0.59 to 3.70) |
| ER status | | |
| ER negative (versus ER positive) | 0.16 | 1.51 (0.85 to 2.69) |
| ER unknown (versus ER positive) | 0.10 | 0.65 (0.40 to 1.08) |
| Chemotherapy (yes versus no) | 0.81 | 0.92 (0.47 to 1.82) |
| Hormonal therapy (yes versus no) | 0.58 | 0.86 (0.50 to 1.49) |

* All statistics were calculated with the use of the Cox proportional hazard model. All statistical tests were two-sided.

CI = confidence interval; ER = estrogen receptor; HR = hazard ratio.

† pT = pT1 ≤ 2 cm; pT2 = 2–5 cm; pT3 > 5 cm. ‡ pN = pN0 = lymph node-negative; pN1 = 1–3 positive lymph nodes; pN2 = 4–9 positive lymph nodes; pN3 > 9 positive lymph nodes.



Supplementary Figure 2. Trends in the treatment of patients with adjuvant systemic therapy in our study cohort of 2592 breast cancer patients aged 50 to 69 years, diagnosed between 1990 and 2000, stratified by nodal status.

CT = chemotherapy; HT = hormonal therapy.

Supplementary Table 2. Multivariable Cox proportional hazard regression analyses for breast cancer-specific mortality in patients diagnosed between 1997 and 2001, including 180 patients who were aged 70–75 years*.

| Characteristics | Breast cancer-specific mortality | |
|--|----------------------------------|----------------------|
| | <i>P</i> | HR (95% CI) |
| Method of detection | | |
| Screen-detected <i>versus</i> nonscreening-related | <0.001 | 0.49 (0.32 to 0.75) |
| Interval <i>versus</i> nonscreening-related | 0.41 | 0.85 (0.57 to 1.26) |
| Age (per year) | 0.006 | 1.04 (1.01 to 1.07) |
| pT† | | |
| pT2 (<i>versus</i> pT1) | 0.01 | 1.62 (1.11 to 2.37) |
| pT3 (<i>versus</i> pT1) | 0.05 | 2.02 (1.01 to 4.04) |
| pN‡ | | |
| pN1 (<i>versus</i> pN0) | 0.005 | 1.99 (1.24 to 3.20) |
| pN2 (<i>versus</i> pN0) | 0.009 | 2.16 (1.21 to 3.86) |
| pN3 (<i>versus</i> pN0) | <0.001 | 5.90 (3.19 to 10.92) |
| Grade | | |
| II (<i>versus</i> I) | 0.02 | 3.56 (1.28 to 9.93) |
| III (<i>versus</i> I) | 0.002 | 5.61 (1.93 to 16.32) |
| Unknown (<i>versus</i> I) | 0.20 | 2.28 (0.64 to 8.07) |
| ER status | | |
| ER negative (<i>versus</i> ER positive) | 0.002 | 2.00 (1.28 to 3.11) |
| ER unknown (<i>versus</i> ER positive) | 0.80 | 1.11 (0.51 to 2.42) |
| Chemotherapy (yes <i>versus</i> no) | 0.66 | 1.11 (0.69 to 1.80) |
| Hormonal therapy (yes <i>versus</i> no) | 0.42 | 1.20 (0.77 to 1.87) |

* All statistics were calculated with the use of the Cox proportional hazard model. All statistical tests were two-sided.

CI = confidence interval; ER = estrogen receptor; HR = hazard ratio.

† pT = pT1 ≤ 2 cm; pT2 = 2–5 cm; pT3 > 5 cm. ‡ pN = pN0 = lymph node-negative; pN1 = 1–3 positive lymph nodes; pN2 = 4–9 positive lymph nodes; pN3 > 9 positive lymph nodes.

Supplementary Table 3. Multivariable Cox proportional hazard regression analyses for breast cancer-specific mortality stratified by tumor size*.

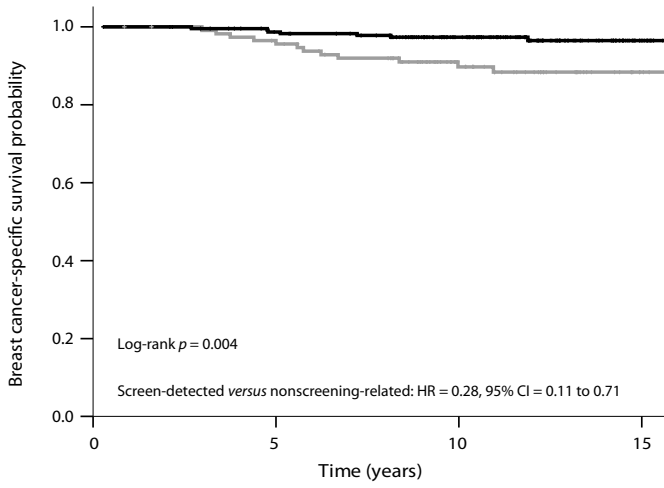
| Characteristics | Tumor size of ≤10 mm | | | Tumor size of 11–20 mm | | | Tumor size of 21–30 mm | | | Tumor size 31–50 mm | | |
|---|----------------------|------------------------|--------|------------------------|--------|----------------------|------------------------|----------------------|---|---------------------|--|--|
| | P | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | | |
| Method of detection: Screen-detected versus nonscreening-related | 0.04 | 0.35 (0.13 to 0.96) | 0.10 | 0.74 (0.52 to 1.05) | 0.002 | 0.53 (0.36 to 0.79) | 0.08 | 0.57 (0.31 to 1.07) | | | | |
| Age (per year) | 0.92 | 1.00 (0.93 to 1.09) | 0.88 | 1.00 (0.97 to 1.04) | 0.79 | 1.00 (0.98 to 1.03) | 0.14 | 1.03 (0.99 to 1.08) | | | | |
| pN† | | | | | | | | | | | | |
| pN1 (versus pN0) | 0.68 | 1.49 (0.23 to 9.67) | 0.97 | 1.01 (0.58 to 1.77) | 0.06 | 1.57 (0.98 to 2.51) | 0.87 | 0.94 (0.42 to 2.06) | | | | |
| pN2 (versus pN0) | 0.21 | 4.43 (0.43 to 46.16) | 0.007 | 2.39 (1.27 to 4.48) | <0.001 | 3.01 (1.77 to 5.14) | 0.13 | 1.92 (0.83 to 4.48) | | | | |
| pN3 (versus pN0) | 0.02 | 37.92 (1.75 to 822.85) | 0.10 | 2.64 (0.84 to 8.34) | <0.001 | 8.65 (4.60 to 16.25) | 0.001 | 4.38 (1.85 to 10.38) | | | | |
| Grade | | | | | | | | | | | | |
| II (versus I) | 0.51 | 1.51 (0.45 to 5.09) | 0.009 | 2.33 (1.24 to 4.39) | 0.20 | 1.75 (0.75 to 4.07) | 0.69 | 1.52 (0.20 to 11.68) | | | | |
| III (versus I) | 0.69 | 1.54 (0.19 to 12.26) | <0.001 | 5.91 (3.02 to 11.57) | 0.01 | 3.13 (1.32 to 7.41) | 0.37 | 2.53 (0.33 to 19.14) | | | | |
| Unknown (versus I) | 0.38 | 1.84 (0.48 to 7.11) | 0.002 | 2.97 (1.47 to 6.01) | 0.05 | 2.44 (1.01 to 5.89) | 0.41 | 2.35 (0.31 to 18.03) | | | | |
| ER status | | | | | | | | | | | | |
| ER negative (versus ER positive) | 0.66 | 1.46 (0.27 to 7.80) | 0.48 | 1.21 (0.72 to 2.04) | 0.38 | 1.25 (0.76 to 2.06) | 0.25 | 1.49 (0.75 to 2.95) | | | | |
| ER unknown (versus ER positive) | 0.49 | 0.68 (0.23 to 2.05) | 0.13 | 1.35 (0.92 to 1.97) | 0.81 | 1.04 (0.73 to 1.49) | 0.21 | 1.41 (0.83 to 2.41) | | | | |
| Chemotherapy (yes versus no) | 0.67 | 1.53 (0.22 to 10.84) | 0.81 | 0.92 (0.48 to 1.77) | 0.03 | 0.55 (0.32 to 0.94) | 0.16 | 0.56 (0.26 to 1.25) | | | | |
| Hormonal therapy (yes versus no) | 0.64 | 0.67 (0.13 to 3.49) | 0.93 | 0.98 (0.59 to 1) | 0.34 | 0.80 (0.51 to 1.26) | 0.07 | 0.55 (0.29 to 1.05) | | | | |

* All statistics were calculated using the Cox proportional hazard model and were two-sided.

CI = confidence interval; ER = estrogen receptor; HR = hazard ratio.

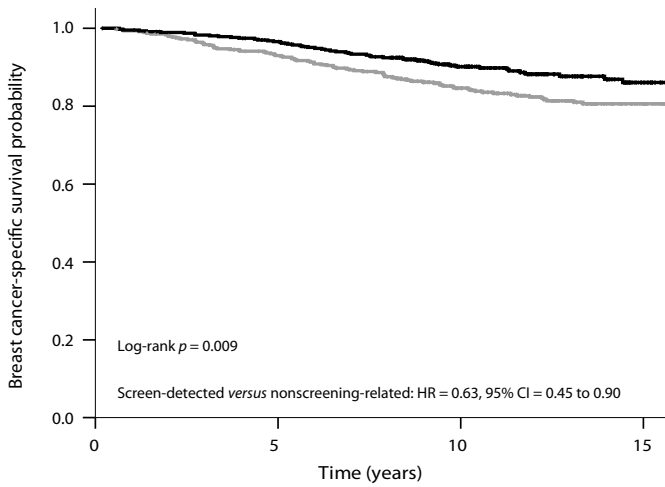
† pN: pN0 = lymph node-negative; pN1 = 1–3 positive lymph nodes; pN2 = 4–9 positive lymph nodes; pN3 > 9 positive lymph nodes.

A



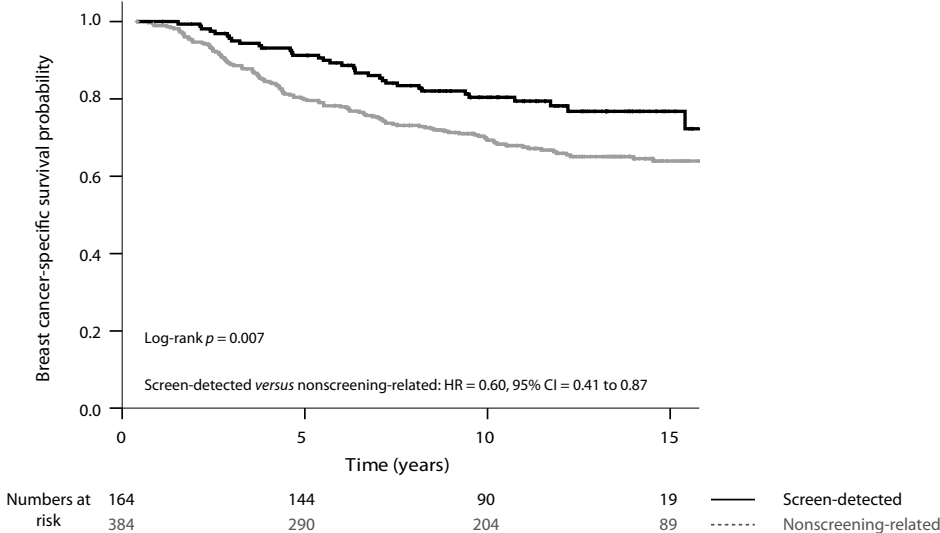
| | | | | | | |
|-----------------|-----|-----|-----|----|-------|----------------------|
| Numbers at risk | 238 | 225 | 163 | 46 | — | Screen-detected |
| | 116 | 109 | 72 | 36 | | Nonscreening-related |

B

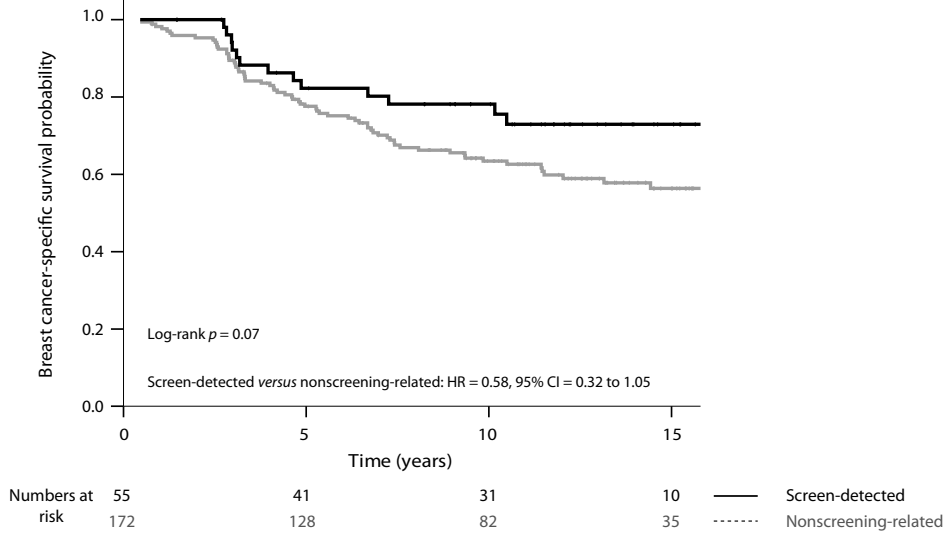


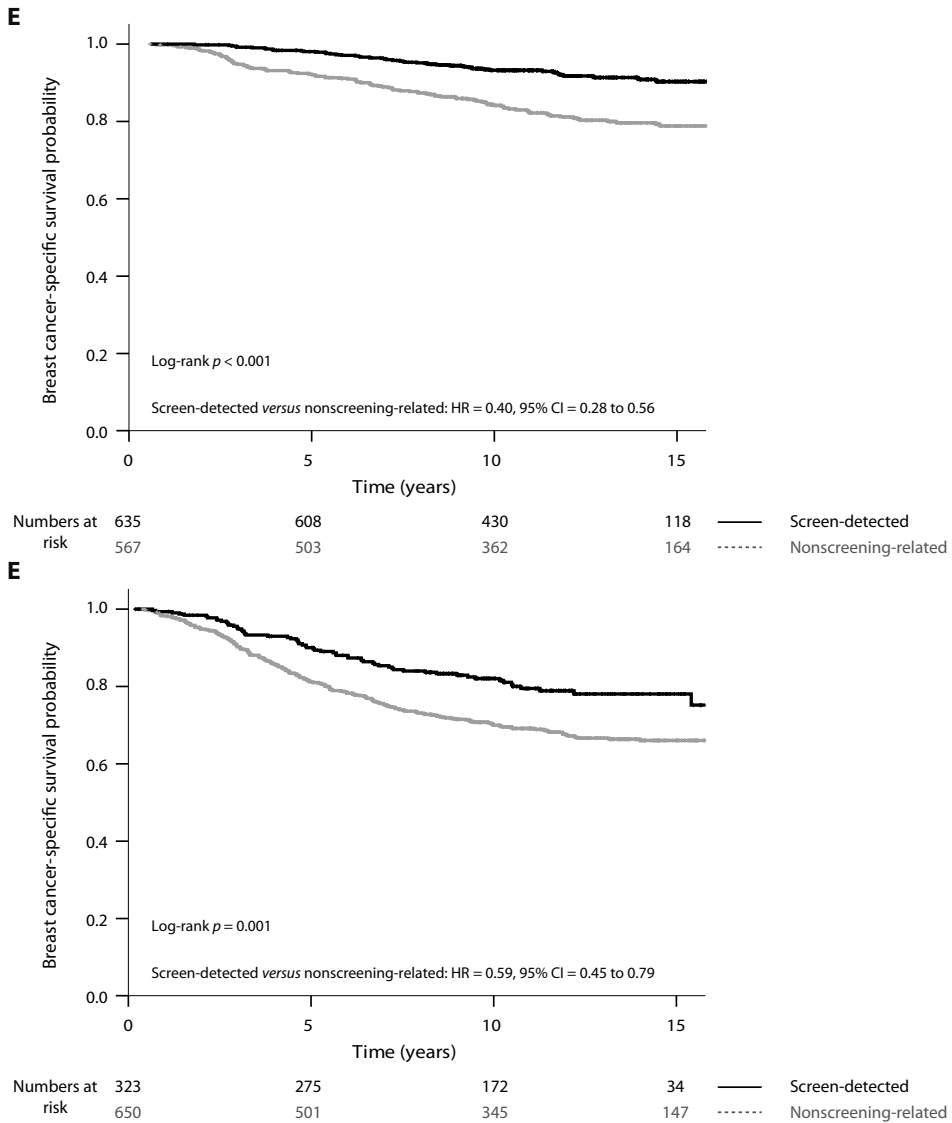
| | | | | | | |
|-----------------|-----|-----|-----|-----|-------|----------------------|
| Numbers at risk | 476 | 450 | 305 | 74 | — | Screen-detected |
| | 484 | 432 | 320 | 139 | | Nonscreening-related |

C



D





Supplementary Figure 3. Breast cancer-specific survival by method of detection. Kaplan–Meier curves for breast cancer-specific survival and univariate hazard ratios (HRs) for breast cancer-specific mortality.

- A)** Patients with tumors of 10 mm or less.
- B)** Patients with tumors of 11–20 mm.
- C)** Patients with tumors of 21–30 mm.
- D)** Patients with tumors of 31–50 mm.

E) Patients with lymph node-negative breast cancer.

F) Patients with lymph node-positive breast cancer.

NRS = Non-screening-related carcinomas, symptomatic cancer in patients who had not been screened or were screened more than 24 months before detection of breast cancer. SD = Screen-detected carcinomas.

The number of patients at risk is shown below each graph. For 32 patients, no exact tumor size was available (only pT stage), and so they were excluded from the analyses shown in Figure 3, A–D. Kaplan-Meier survival analyses, log-rank tests, and univariate Cox proportional hazard ratios (HRs) were calculated to estimate differences in survival among patients with screen-detected carcinoma and patients with non-screening-related carcinoma.

Supplementary Table 4. Multivariable Cox proportional hazard regression analyses for breast cancer-specific mortality stratified by lymph node status*.

| Characteristics | Lymph node-negative | | Lymph node-positive | |
|--|---------------------|----------------------|---------------------|---------------------|
| | P | HR (95% CI) | P | HR (95% CI) |
| Method of detection: screen-detected versus non-screening-related | <0.001 | 0.51 (0.36 to 0.73) | 0.12 | 0.79 (0.59 to 1.06) |
| Age (per year) | 0.26 | 1.02 (0.99 to 1.05) | 0.77 | 1.00 (0.98 to 1.03) |
| pT† | | | | |
| pT2 (versus pT1) | <0.001 | 1.87 (1.32 to 2.65) | <0.001 | 2.00 (1.51 to 2.67) |
| pT3 (versus pT1) | 0.08 | 3.62 (0.88 to 14.95) | 0.009 | 2.05 (1.20 to 3.49) |
| Grade | | | | |
| Grade II (versus grade I) | 0.002 | 2.45 (1.38 to 4.35) | 0.05 | 1.98 (0.99 to 3.94) |
| Grade III (versus grade I) | <0.001 | 4.08 (2.11 to 7.87) | <0.001 | 4.62 (2.31 to 9.25) |
| Grade unknown (versus grade I) | <0.001 | 3.35 (1.82 to 6.16) | 0.001 | 3.19 (1.57 to 6.49) |
| ER status | | | | |
| ER negative (versus ER positive) | 0.26 | 1.36 (0.80 to 2.32) | 0.18 | 1.29 (0.89 to 1.88) |
| ER unknown (versus ER positive) | 0.30 | 0.82 (0.57 to 1.19) | 0.02 | 1.38 (1.05 to 1.81) |
| Chemotherapy (yes versus no) | 0.90 | 1.06 (0.45 to 2.46) | 0.15 | 0.75 (0.50 to 1.11) |
| Hormonal therapy (yes versus no) | 0.20 | 0.76 (0.49 to 1.16) | 0.70 | 0.92 (0.62 to 1.38) |

* All statistics were calculated using the Cox proportional hazard model and were two-sided.

CI = confidence interval; ER = estrogen receptor; HR = hazard ratio.

† pT: pT1 ≤ 2 cm; pT2 = 2–5 cm; pT3 > 5 cm.

Supplementary Table 5. Adjuvant! 10-year observed and predicted breast cancer-specific survival for patients younger than 50 years by period of diagnosis*.

| Period of diagnosis | No. patients (%) | 10-year breast cancer-specific survival | | | |
|---------------------|------------------|---|----------------------|----------------------|----------|
| | | Adjuvant! predicted, % | Observed, % (95% CI) | Predicted – observed | <i>P</i> |
| 1990–1996 | 1381 (70.0) | 77.3 | 77.5 (75.3 to 79.7) | 0.2 | 0.86 |
| 1997–2000 | 592 (30.0) | 79.3 | 82.3 (79.2 to 85.4) | -3.0 | 0.06 |

* All statistics were calculated by one sample *t* tests and were two-sided.

CI = confidence interval.