A difficult balancing act : Informing breast cancer patients about adjuvant systemic therapy

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Chapter 3

Accuracy of the online prognostication tools PREDICT and Adjuvant! for early-stage breast cancer patients younger than 50 years

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Abstract

Importance
Online prognostication tools such as PREDICT and Adjuvant! are increasingly used in clinical practice by oncologists to inform patients and guide treatment decisions about adjuvant systemic therapy. However, their validity for young breast cancer patients is debated.

Objective
To assess first, the prognostic accuracy of PREDICT's and Adjuvant! 10-year all-cause mortality, and second, its breast cancer-specific mortality estimates, in a large cohort of breast cancer patients diagnosed <50 years.

Design
Hospital-based cohort.

Setting
General and cancer hospitals.

Participants
A consecutive series of 2,710 patients without a prior history of cancer, diagnosed between 1990-2000 with unilateral stage I-III breast cancer aged <50 years.

Main outcome measures
Calibration and discriminatory accuracy, measured with C-statistics, of estimated 10-year all-cause and breast cancer-specific mortality.

Results
Overall, PREDICT's calibration for all-cause mortality was good (predicted versus observed) $mean_{difference}$: -1.1% (95%CI: -3.2% to 0.9%) (P= 0.28)). PREDICT tended to underestimate all-cause mortality in good prognosis subgroups (range $mean_{difference}$: -2.9% to -4.8%), overestimated all-cause mortality in poor prognosis subgroups (range $mean_{difference}$: 2.6% to 9.4%), and underestimated survival in patients < 35 by -6.6%. Overall, PREDICT overestimated breast cancer-specific mortality by 3.2% (95%CI: 0.8% to 5.6%) (P= 0.007)); and also overestimated it seemingly indiscriminately in numerous subgroups (range $mean_{difference}$: 3.2% to 14.1%). Calibration was poor in the cohort of patients with the lowest and those with the highest mortality probabilities. Discriminatory accuracy was moderate-to-good for all-cause mortality in PREDICT (0.71 (95%CI: 0.68 to 0.73)) and the results were similar for breast cancer-specific mortality. Adjuvant!'s calibration and discriminatory accuracy for both all-cause and breast cancer-specific mortality were in line with PREDICT's findings.

Conclusions
Although imprecise at the extremes, PREDICT's estimates of 10-year all-cause mortality seem reasonably sound for breast cancer patients <50 years; Adjuvant! findings were similar. Prognostication tools should be used with caution due to the intrinsic variability of their estimates, and because the threshold to discuss adjuvant systemic treatment is low. Thus, seemingly insignificant mortality over- or underestimations of a few percentages can significantly impact treatment decision-making.

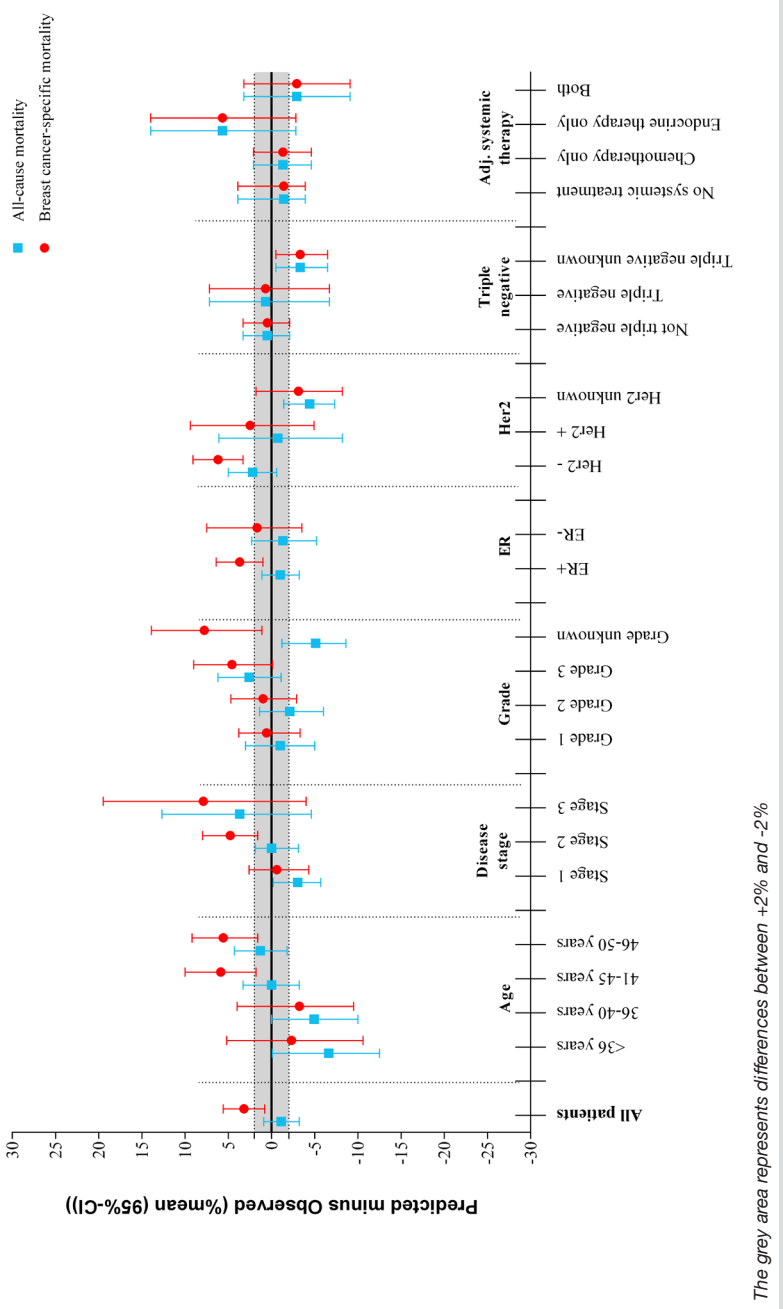
Introduction

In 2015, a total of 14,449 women were diagnosed with invasive breast cancer in The Netherlands, of which 20% were younger than 50 years at diagnosis (1). Available evidence strongly suggests that breast tumors are more aggressive in young (especially those <40 years) than in post-menopausal women (2-5). This is partly due to the over-representation of aggressive biological features (e.g., estrogen receptor (ER) negative, grade 3 in young patients (2-5). Yet, even after controlling for known biological factors indicative of tumor aggressiveness, young age in itself remains an independent predictor of poor cancer-specific survival, and strongly correlates with the risks of local recurrence and contralateral breast cancer (4,6,7). Therefore, pending better molecular characterization of tumors in young women, young age itself and classical tumor characteristics, remain important prognosticators.

Accurate quantification of long-term disease outcome and potential adjuvant systemic treatment benefit could help oncologists and patients in tailoring treatment decisions, also considering the potential side-effects of and possibly reduced quality of life during/after systemic therapy. Furthermore, adequately informing patients about such probabilities as well as the side-effects of treatment could empower them to choose the treatment option that best fits their preferences. Adjuvant! (8,9) and PREDICT (10,11) are online prognostication tools, that provide personalized 10-year all-cause and/or breast cancer-specific mortality estimates for the adjuvant treatment setting. Both tools base their predictions on patient (e.g., age) and tumor (e.g., size, nodal status, ER-status, and grade) characteristics.

Clinicians reported common use of Adjuvant! during consultations with patients (12,13); PREDICT's average user access is 10,000 per month as per February 2016, and currently probably higher as Adjuvant! has been offline for some time. Further, the Dutch national breast cancer guideline based its treatment recommendations on Adjuvant!'s estimates and leading British and American guidelines endorsed Adjuvant!'s use to quantify prognosis (14-16). Adjuvant! and PREDICT have mainly been externally validated in North American and European populations, but also in Asian populations (17-19). Generally, their estimates seem accurate for Western patients diagnosed between 50-65 years (17-19). A recent analysis within the POSH study of about 600 women diagnosed <40 years with ≥10-year follow-up has shown that overall PREDICT overestimated all cause 10-year mortality by 8%, and that in women aged 31- 35 years at diagnosis it underestimated all-cause mortality by 5%18. Overall, the evidence on Adjuvant! and PREDICT's performance in young patients is not strong, as the number of young patients (with sufficient follow-up) included in the validation studies was small; but it suggests that both tools significantly underestimate mortality in patients diagnosed <50 years, with the largest discrepancies observed in patients diagnosed ≤35 years (17-21). These

findings are concerning; especially as Adjuvant! already adjusts its mortality estimates for ER-positive breast cancer patients ≤35 years by a factor of 1.5 (9). In view of the limited evidence on their performance in patients <50 years, and the impact that these tools can have on oncologists' and patients' decision-making, our primary aim was to assess the prognostic accuracy of PREDICT and Adjuvant!'s 10-year all-cause mortality estimates in a large cohort of young breast cancer patients, and secondarily to assess the prognostic accuracy of their breast cancer-specific mortality estimates.



The grey area represents differences between +2% and -2%

Figure 1 Overview of mean difference between PREDICT's estimates and observed all-cause and breast cancer specific mortality by prognostic factors

Methods

Patient selection

We used data from a hospital-based cohort of consecutive females diagnosed <50 years of age with invasive breast cancer, identified through medical registries of participating hospitals or the Netherlands Cancer Registry. We selected all patients diagnosed between 1990-2000 with unilateral stage I-III breast cancer without a previous cancer diagnosis (except non melanoma skin cancer), for whom complete data on tumor size, nodal status, receipt of adjuvant systemic therapy, and follow-up was available (Appendix Figure 1; Appendix A).

Procedures

Data collection has been described previously (22), in short: information about diagnosis and treatment, e.g., histological tumor grade, stage, adjuvant chemotherapy and endocrine systemic treatment (before summer 2005 no adjuvant trastuzumab was administered), estrogen (ER) and progesterone receptor status (PR), Her2-neu, and angiolymphatic invasion were gathered from original pathology reports and/or determined using reviews of whole slides and staining of tumors in tissue micro arrays. Follow-up data, such as date of last follow-up, vital status, and cause of death were obtained from the medical registries from the participating hospitals and/or linkage with the Dutch municipal registry through the Netherlands Cancer Registry (last follow-up update in 2013). Patients with unknown vital status (N=16) and follow-up time ≤10 years (N=21) were excluded (Appendix Figure 1; Appendix A).

Predicted all-cause and breast cancer-specific mortality were calculated for each patient individually by entering prognosticators in PREDICT (version-1.3) and Adjuvant! (version-8.0) batch processors, with blinding to patient outcomes. After the calculation of the mortality estimates, we received a revision of the systemic therapy data which showed that for N=219 patients whether they had received systemic therapy or not, and to a lesser extent which type of systemic therapy they had received had been misclassified. We recalculated PREDICT's estimates, but not for Adjuvant!, since the latter tool was no longer available. In essence, the direction of the difference did not change, nor did our conclusions.

Adjuvant! requires data on comorbidity, which was not available, therefore we set comorbidity to minor problems (default setting). Patients <50 years at diagnosis are unlikely to have significant comorbidities, consequently the setting used will give average outcomes reflecting the general health of our sample. KI67-status was set to unknown, and mode of disease detection was set to symptomatic, in the PREDICT analyses. Also, we used the Prognostic Factor Impact Calculator incorporated in Adjuvant! to take Her2-status into account in the calculation of the all-cause and breast cancer-specific

mortality probabilities. We assumed a relative risk for high vs. low risk group of 1.5 and that on average 20% of patients had Her2-positive disease (23-25). For patients without Her2 overexpression we used the low risk probability estimates, for those with Her2 overexpression we used the high risk estimates and for those with unknown Her2-status we used the unadjusted estimates automatically generated by Adjuvant!.

Statistical analysis

PREDICT's batch processor cannot calculate prognostic estimates if ER-status is unknown, thus patients with unknown ER-status were excluded from all analyses of PREDICT's estimates, leaving 2,073 and 1,076 patients in the all-cause and breast cancer-specific mortality analyses respectively. In the all-cause mortality analyses of Adjuvant! all 2,710 patients that met the inclusion criteria were included. In the breast cancer-specific mortality analyses, hospitals for which cause of death data was missing were excluded leaving 1,535 patients in the analyses.

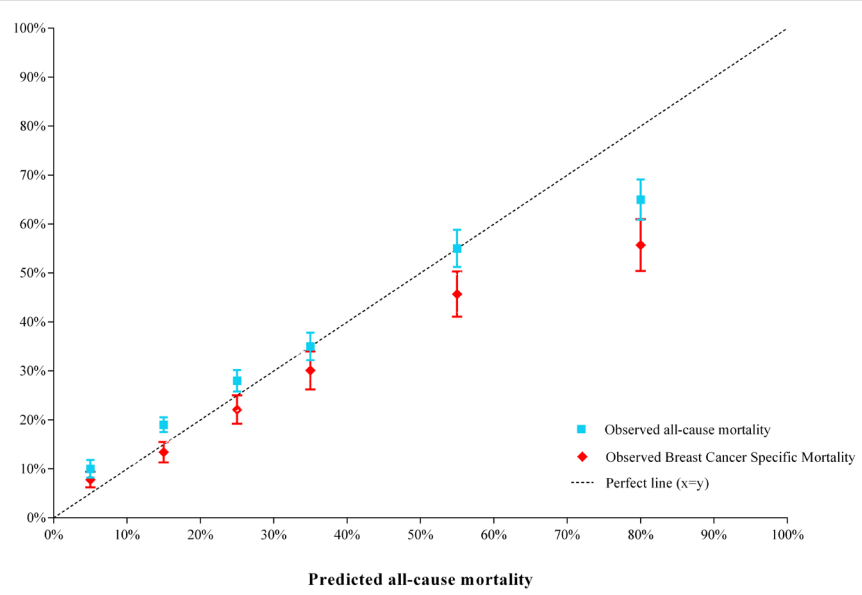


Figure 2 Observed vs. PREDICT estimates of 10-year all-cause and breast cancer specific mortality

We compared the average observed and the average predicted 10-year all-cause and breast cancer-specific mortality using one-sample T-tests for proportions. We used a

1,000 resamples bootstrap for calculation of the 95%-confidence interval, and bootstrap p-values were directly calculated from the bootstrap sampling using the percentiles and simple sampling method. The prognostication tool's average predicted mortality was the fixed value (i.e., assumed to be true based on the model used), and the average observed mortality the comparison variable. We compared the concordance between the observed and predicted estimates for the whole population and for subgroups of relevant prognostic characteristics, which were determined a priori.

Additionally, we evaluated model calibration by plotting averages of observed versus predicted mortality, grouped by deciles of predicted outcomes. If there were <100 patients in a decile, it was merged with adjacent decile(s) to ensure sufficiently large numbers in all deciles. The slope of the fitted line was compared with the slope of the line indicating a perfect relationship (y=x). We evaluated discriminatory accuracy using receiver-operator curves (ROC) and corresponding c-indices derived by calculating the area under the curve (AUC). All analyses were performed in SPSS version 20.0 software.

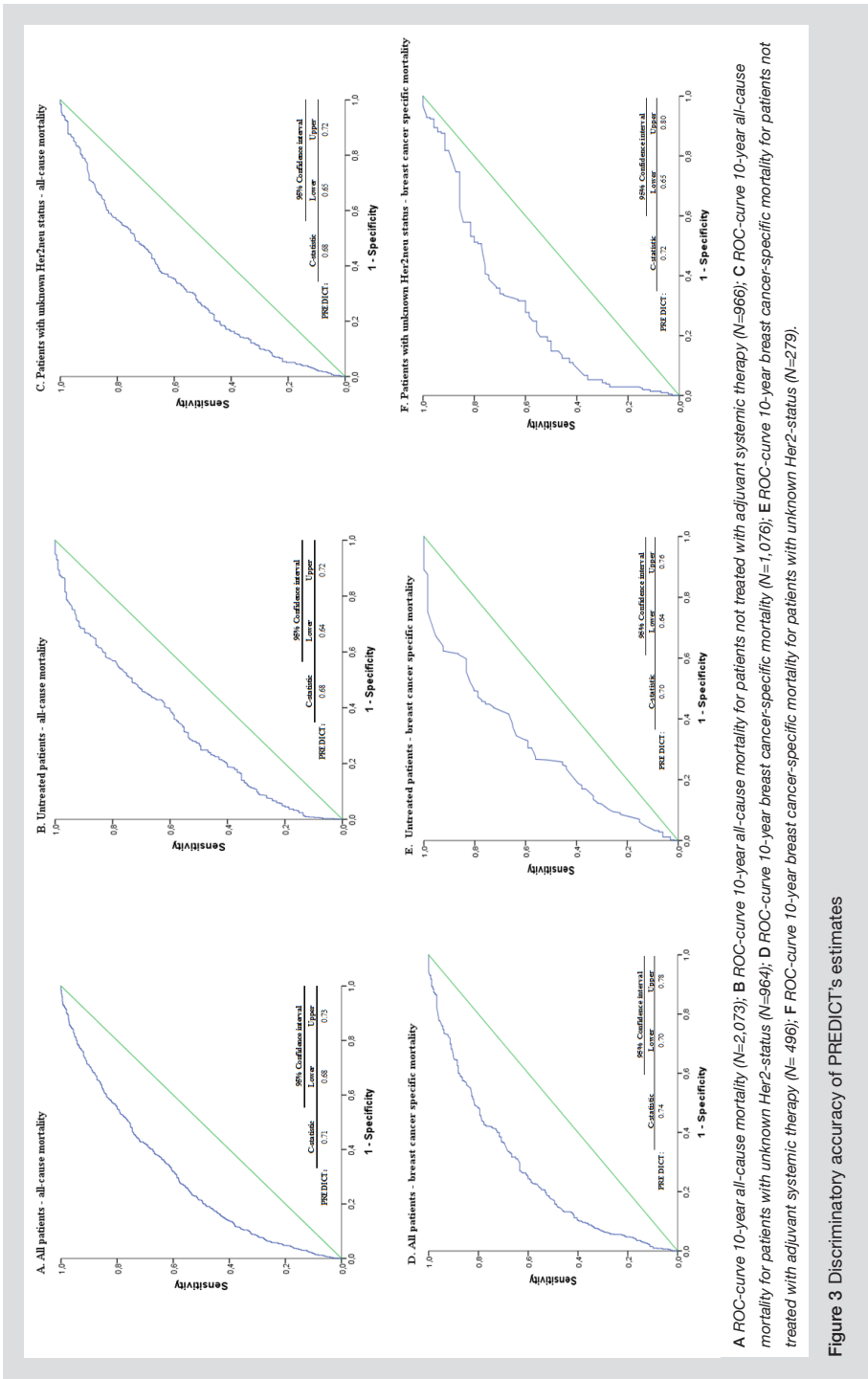
Results

Patients in the all-cause mortality analyses had a mean age of 42 years (range: 22-50) and an average of 13.5 years follow-up (Appendix Table 1). Overall, 61% of patients had stage II disease (Appendix Table 2), and on average patients ≤40 years more often had ER-negative, grade 3 and/or node-positive disease compared to those who were 41-50 years at diagnosis.

Calibration of 10-year all-cause mortality for the whole population
Calibration was assessed using the mean difference between predicted an observed mortality. PREDICT tended to underestimate all-cause mortality, but the overall difference was not statistically significant (-1.1, 95%-CI: -3.2 to 0.9; P=0.28) (Figure 1; Appendix Table 3). Adjuvant! also underestimated all-cause mortality (-2%, 95%-CI: -3.7 to -0.3; P=0.02) (Appendix Table 4). The PREDICT batch processor did not allow for inclusion of patients with unknown ER-status, therefore these patients were excluded (N= 637 (23.5%). However, Adjuvant!'s expected mortality did not change when we excluded the patients with unknown ER-status (27.0% versus 26.7%).

Calibration of 10-year all-cause mortality for key prognostic subgroups
PREDICT underestimated all-cause mortality in the two youngest age groups by -6.6% to -4.9 (Figure 1; Appendix Table 3). It also underestimated mortality in subgroups of patients with good prognosis, e.g., stage I, T1, and N0 disease, the mean range of difference was between -2.9% to -4.8%. PREDICT tended to overestimate mortality for poor prognosis subgroups (e.g., N1, stage III, T3) by 2.6% to 9.4%. PREDICT also overestimated mortality in the Her2-negative subgroup by 2.2%. Adjuvant!'s performance was comparable to PREDICT's (Appendix Figure 2; Appendix Table 4). Neither PREDICT nor Adjuvant! take angiolymphatic invasion into account, but we did evaluated the prognosis estimates for subgroups in our dataset. Both tools underestimated mortality in patients with extensive angiolymphatic invasion (range mean difference: -4.0% to -9.3%) (Appendix Tables 3-4).

Calibration of 10-years breast cancer-specific mortality estimates
PREDICT overestimated breast cancer-specific mortality by 3.2% (95%-CI: 0.8 to 5.6; P=0.007) (Figure 1; Appendix Table 3). Adjuvant!'s estimates did not significantly differ from observed breast cancer-specific mortality (P=0.23) (Appendix Figure 3; Appendix Table 4). However, both PREDICT and Adjuvant! seemed to indiscriminately overestimate rates across subgroups (range mean difference: 3.0% to 14.1%) (Figure 1; Appendix Figure 3; Appendix Table 3-4).



A *ROC-curve 10-year all-cause mortality (N=2,073);* **B** *ROC-curve 10-year all-cause mortality for patients not treated with adjuvant systemic therapy (N=966);* **C** *ROC-curve 10-year all-cause mortality for patients with unknown Her2-status (N=964);* **D** *ROC-curve 10-year breast cancer-specific mortality (N=1,076);* **E** *ROC-curve 10-year breast cancer-specific mortality for patients not treated with adjuvant systemic therapy (N= 496);* **F** *ROC-curve 10-year breast cancer-specific mortality for patients with unknown Her2-status (N=279).*

Figure 3 Discriminatory accuracy of PREDICT's estimates

Calibration curves

The calibration curves for PREDICT and Adjuvant! were similar, and showed that overall both tools' predictions of all-cause mortality were accurate for patients with 20% to 40% mortality probability (Figure 2; Appendix Figure 4). However, the fit was inferior in the cohort of patients with the best (<20% mortality probability) and poorest (>40% mortality probability) prognosis (Figure 2; Appendix Figure 4). We found a similar pattern for breast cancer-specific mortality probability estimates for both tools (Figure 2; Appendix Figure 4).

Discriminatory accuracy

PREDICT's discriminatory accuracy for all-cause (C-statistic: 0.71) and breast cancer-specific mortality (C-statistic: 0.74) was moderate in the whole population (Figure 3: panel-A, panel-D). To assess the discriminatory accuracy in the absence of a treatment effect, we ran these analyses in untreated patients. Patients with relatively good prognosis were overrepresented in this subgroup; there were more patients with ER-positive (72%), grade 1 (22%), T1 tumors (62%), N0 status (85%) and stage I (58%) disease (compared to whole cohort: see Appendix-Table 2). The discriminatory accuracy in the subgroup of untreated patients was moderate (Figure 3: panel-B, panel-E). Adjuvant!'s discriminatory accuracy is in line with PREDICT in the whole population and in the cohort of untreated patients (Appendix Figure 5).

In our analyses we accounted for Her2-status, which is not automatically done by Adjuvant!. To gauge Adjuvant!'s discriminatory accuracy in a subgroup where we did not use this adjustment, we ran these analyses in patients with unknown Her2-status. Adjuvant! and PREDICT discriminatory accuracy for all-cause and breast cancer-specific mortality in this subgroup was also moderate (Figure 3: panel-C, panel-F; Appendix Figure 5).

Discussion

The prognostic accuracy of PREDICT and Adjuvant!'s 10-year all-cause and breast cancer-specific mortality estimates were evaluated in a large cohort of Dutch patients diagnosed <50 years of age between 1990 and 2000. We mainly focus on PREDICT's results as Adjuvant! has been offline for some time, therefore we were unable to update it estimates after receiving new data about adjuvant systemic therapy. However, the updated data about adjuvant systemic therapy did not lead to differences in the direction of the under- or overestimation by PREDICT, therefore, we used the Adjuvant! results to substantiate our findings in PREDICT. Overall, PREDICT tended to underestimate all-cause mortality, but the difference was not statistically significant. It did significantly underestimated all-cause mortality for patients ≤40 years by up to -6.6%. Further, PREDICT underestimated all-cause mortality for patients with good prognosis, and overestimated it for those with poor prognostic characteristics. Adjuvant!'s calibration and discriminatory accuracy in our population was in line with PREDICT's. Although the absolute differences observed were small, they might nonetheless be clinically relevant. Given that the minimum treatment benefit generally required to be eligible for adjuvant systemic treatment is only 3-5%, an absolute overestimation of treatment benefit of 2% may already affect treatment decisions, and reflects a relative overestimation of almost 30%.

Many young patients (especially those ≤35 years) with favorable prognostic characteristics (e.g., N0 or T1) had a high tumor grade. This could partly explain PREDICT's (and Adjuvant!'s) underestimation of all-cause mortality in the good prognosis subgroups. Also, it has been described that tumors in young patients have a greater tendency to metastasize, even in case of favorable prognostic characteristics (4). Given the high probability of poor outcomes in patients ≤40 years, it has been argued that most or all are candidates for adjuvant chemotherapy, solely based on age at diagnosis (4). Indeed, treating all patients diagnosed ≤40 years with adjuvant chemotherapy seems to be the tendency in clinical practice, which inevitably means that a substantial proportion of patients only experience side-effects and no treatment benefit. Current guidelines (14-16) stipulate that independent of intrinsic tumor subtype, all breast cancer patients ≤35 years with tumors >1cm should receive chemotherapy, and for those who are Her2neu-positive (irrespective of age) chemotherapy in combination with trastuzumab is also indicated in case of tumors 5-10 mm (T1b). The first international consensus guidelines for the treatment of breast cancer in patients ≤40 years, however, strongly advocated that age should not be the sole reason to prescribe more aggressive treatment and that tumor biology should be the overriding factor (26). This underscores the importance of well-validated tools including all relevant tumor characteristics.

Contrary to our findings that both prognostication tools tended to overestimate all-cause

mortality in subgroups with poor prognosis, we found that both tools underestimate all-cause mortality especially for patients with extensive angiolymphatic invasion by as much as 9.3%. Currently, neither tool takes angiolymphatic invasion into account. This is perhaps understandable as angiolymphatic invasion is one of the features that pathologists have difficulty scoring in a reproducible manner, which has somewhat limited its usefulness when assessing prognosis. However, in view of our findings, it might be relevant to investigate whether this factor adds prognostic information.

Further, PREDICT (and Adjuvant!) tended to underestimate the impact of endocrine therapy on survival. As relatively few young patients have ER-positive breast cancer, and before 1995 endocrine therapy was not administered to premenopausal patients, they are probably underrepresented in the trials on which the treatment effect estimates are based. However, nowadays substantially more young patients are treated with adjuvant systemic therapy (Appendix Figure 6), including endocrine therapy in case of hormone-positive disease, as there is evidence that endocrine therapy is equally effective in young/premenopausal and older/postmenopausal patients (27). Our findings highlight that these tools need to be updated from time to time, as is currently the case for Adjuvant!.

In this young age group, all-cause mortality is likely a close representation of breast cancer-specific mortality. Based on our smaller dataset with known cause of death, PREDICT significantly overestimated breast cancer-specific mortality, and it (like Adjuvant!) seemed to generally indiscriminately overestimate breast cancer-specific mortality across subgroups. For a large proportion of our population, data on cause of death was not available, limiting the number of patients available for the breast cancer-specific mortality analyses and leading to wide confidence intervals in many subgroup analyses. Also, where cause of death was known, for 37% of patients in our sample it was classified as not breast cancer-related. Considering that these were young women, it seems unlikely that such a large proportion of patients would have pre-existing comorbid conditions, i.e., competing causes of death. It seems more likely that cause of death was not missing at random, and/or at least for a proportion of these breast cancer patients and/or the late effects of treatment were the true underlying cause of death. Indeed, bias through misclassification of cause of death is a well-known problem when assessing cancer-specific mortality (28-30). Moreover, differences may exist between health care provided in the Netherlands versus the United States and United Kingdom. Therefore, our cancer-specific mortality findings should be interpreted cautiously.

A clear strength of our study is our large cohort with complete data about tumor size, nodal status and receipt of adjuvant therapy. However, a weakness is that mode of disease detection (PREDICT) was missing (but population-based screening starts at 50

years), and that Her2neu and KI67-status were not routinely determined at diagnosis, and Her2-status was only assessed by immunohistochemistry. Also, we excluded patients diagnosed prior to 1990, which reduced our sample size considerably. We opted to exclude these patients from our analyses as patients diagnosed during this time period had significantly poorer survival compared to those diagnosed between 1990-2000. Therefore, the findings in this subgroup would not be comparable to those of currently diagnosed/treated patients. Further, we cannot disentangle the effect of adjuvant systemic treatments on outcome, as treatment decisions were not or not always based on PREDICT (or Adjuvant!) estimates, but on local treatment guidelines and patient preferences. Yet, since half of our population did not receive adjuvant systemic treatment, they can be viewed as a proxy for a validation unbiased by treatment effect. In this subgroup PREDICT (like Adjuvant!) performed well with regard to all-cause mortality. Additionally, some of the differences observed between the tools might be due to differences in exposure to risk factors and/or factors associated with poor survival between the populations in which they were developed (31-33), i.e., British for PREDICT and American for Adjuvant!. Finally, in order to allow for sufficient follow-up time we used a cohort of patients diagnosed up to 2000 in which absolute survival might not completely reflect that of recently diagnosed patients (Appendix Figure 7).

PREDICT's all-cause mortality estimates seem reasonably sound for young breast cancer patients, but further adjustments are especially needed for patients ≤40 years and for those in the best and poorest prognosis subgroups. Our data underscores that it is important to remain aware of the fact that these tools provide average estimates which in certain patients and patient groups might not be accurate, also in view of the variability of the disease. These estimates, therefore, are intended to supplement, and not to replace clinical judgement and doctor-patient communication, when advising patients about adjuvant systemic therapy.

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Appendix A supplemental information on the methods used

Number of patients per participating hospital

Included patients were treated between 1990 and 2000 at the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital (N=683), Erasmus Medical Center-Daniel den Hoed Clinic (N=320), which are cancer centers; Leiden University Medical Center (N=205), an academic hospital; and Medisch Spectrum Twente Hospital (N=839), PAMM Laboratories (N=221), Albert Schweitzer Hospital (N=191), Rijnland Hospital (N=86), Viecuri Hospital (N=74), Diaconessenhuis Leiden (N=50), and Elkerliek Hospital (N=41), which are regional hospitals.

An update of the clinical and follow-up data revealed that 19 patients included in the current study were 50 years at diagnosis, and therefore did not meet the eligibility criterion of below 50 years. This shift in age was due to adjustment of the date of diagnosis (histological confirmation). Given the small number of patients concerned and the fact that the results remained the same irrespective of whether these patients were included or not, we decided to keep them in the analyses.

Procedures

Data categorization: age at diagnosis (continuous), tumor size (continuous for PREDICT and for Adjuvant! categorized as: 0.0-1.0 cm, 1.1-2.0 cm, 2.1-3.0 cm, 3.1-5.0 cm or >5.0 cm), tumor grade (categorized as: Grade 1, Grade 2, Grade 3 or undefined if missing), number of positive axillary lymph nodes (continuous for PREDICT and for Adjuvant! categorized as: 0 positive nodes, 1-3 positive nodes, 4-9 positive nodes or >9 positive nodes), ER-status (categorized as: positive, negative or undefined if missing).

For Adjuvant! if tumor diameter (in mm) was missing, patients were categorized using pathological T-stage if available (T1 was categorized as having a tumor of 1.1-2.0 cm, T2 was categorized as having a tumor of 3.1-5.0 cm and T3 was categorized as having a tumor of >5.0 cm). For Adjuvant! patients with missing data on the number of positive axillary lymph nodes were categorized using pathological N-stage if available (N0 was categorized as having 0 positive nodes, N1 was categorized as having 1-3 positive nodes, N2 was categorized as having 4-9 positive nodes and N3 was categorized as having >9 positive nodes). We used weighed mean imputed values to calculate PREDICT survival estimates for missing values of grade (imputed value: 2.25), tumor size in mm (if pT1a-b: 5mm; pT1c: 1.5mm; pT2: 40mm; pT3: 50mm), and number of positive axillary lymph nodes (if pN1: 2 positive nodes; pN2: 7 positive nodes; pN3: 10 positive nodes). The T, N, and M were determined according to Dutch guidelines at the time of diagnosis; for combining these three factors in the stage variable, the AJCC TNM staging guidelines of 2002 were used.

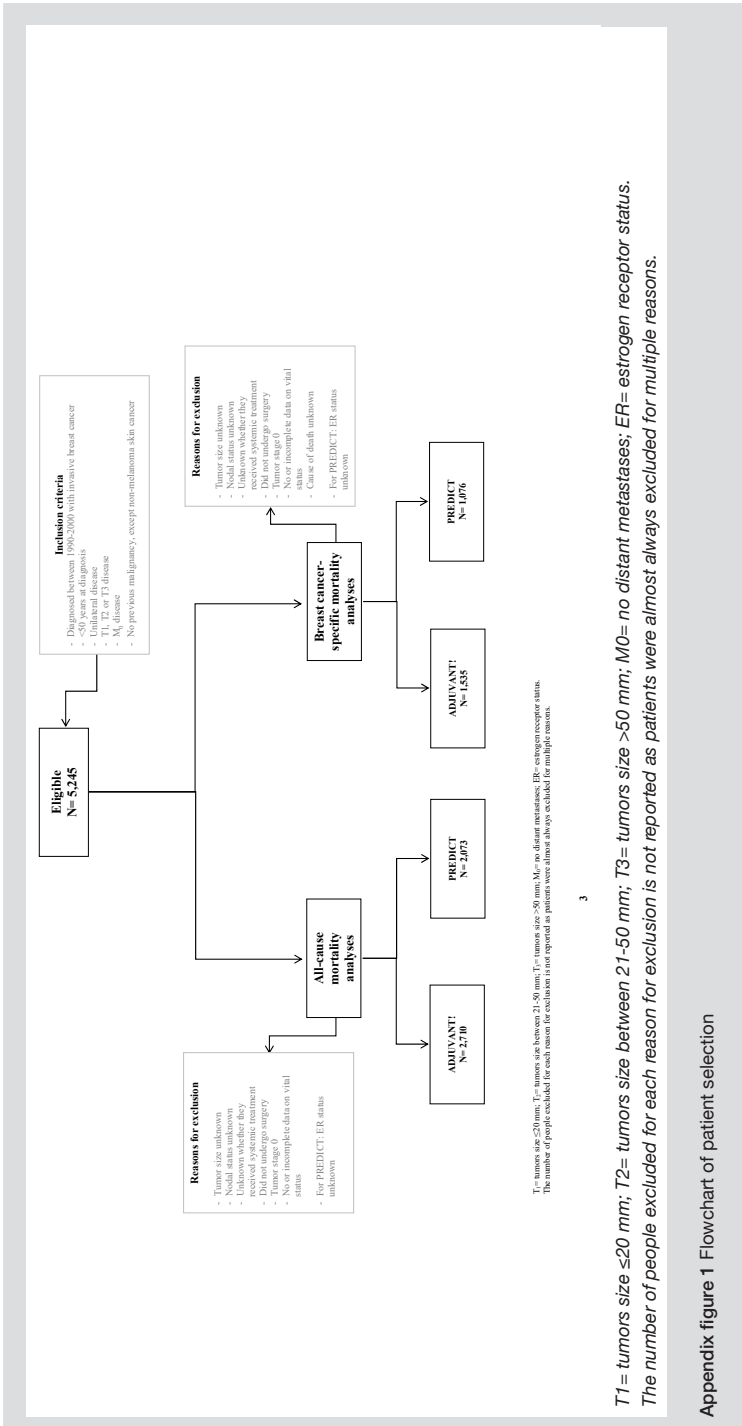
According to the clinical cut-off points endorsed in the Dutch breast cancer guideline for immunohistochemical staining of receptors, a tumor was considered receptor negative using the following cut-offs: ER= ≤10%; PR= ≤10%; Her2-score= 0 or 1+)) (21;26;27). Receptor status data was included from Tissue Micro Arrays (TMA) if data from pathology reports was not available, for ER the data source was N_{TMA}= 757 and $N_{pathology\ reports}$= 1316, and for Her2 data source was N_{TMA}= 817 and $N_{pathology\ reports}$= 308. Patients with a tumor that did not express ER, PR and Her2 were considered to have a triple negative tumor. Within the time period that patients in this cohort had been diagnosed (i.e. 1990-2000), it was not yet standard practice to routinely assess cell-surface Her2 protein expression by immunohistochemistry (Her2-status missing for N= 1,639 (60%)). Her2 was mostly included from analyses of TMA using Her2 immunohistochemistry, however, the number of copies of the Her2-gene was not quantified using an in situ hybridization technique (e.g., FISH, CISH or SISH) for patients with an equivocal Her2 immunohistochemistry (i.e. 2+ score) to definitively determine Her2-status (N= 60 (2%)). We opted to include patients with equivocal Her2 immunohistochemistry in our analyses and treat them as having Her2-negative disease, based on Kaplan-Meier curves analyses that showed that their survival pattern was similar to those with immunohistochemistry Her2-negative disease (data not shown).

Angiolymphatic-invasion, i.e., tumor formation in blood and/or lymph blood vessels, was only available for reviewed tumor H&E slides. A breast pathologist (H. Peterse, NKI-AVL) scored the tumors as follows: 0=none, 1=1-3 vessels in the whole slide, 2=more than three vessels in the whole slide.

Adjuvant systemic treatment was categorized as: none, first generation (if treated with cyclophosphamide - methotrexate - fluorouracil (CMF), cyclophosphamide - doxorubicin or epirubicin (AC or EC) (four cycles) or if type chemotherapy regime was unknown and the patient also received endocrine therapy) and second generation (if treated with fluorouracil (5FU) - doxorubicin or epirubicin - cyclophosphamide (FEC or FAC) (six cycles), others). In the Adjuvant! analysis sample (N=2,710), in total 1,058 patients received first generation chemotherapy and 47 patients received second-generation chemotherapy. In the PREDICT analysis sample (N=2,073), in total 800 patients received first generation chemotherapy and 24 patients received second-generation chemotherapy. In this population, endocrine treatment only consisted of Tamoxifen.

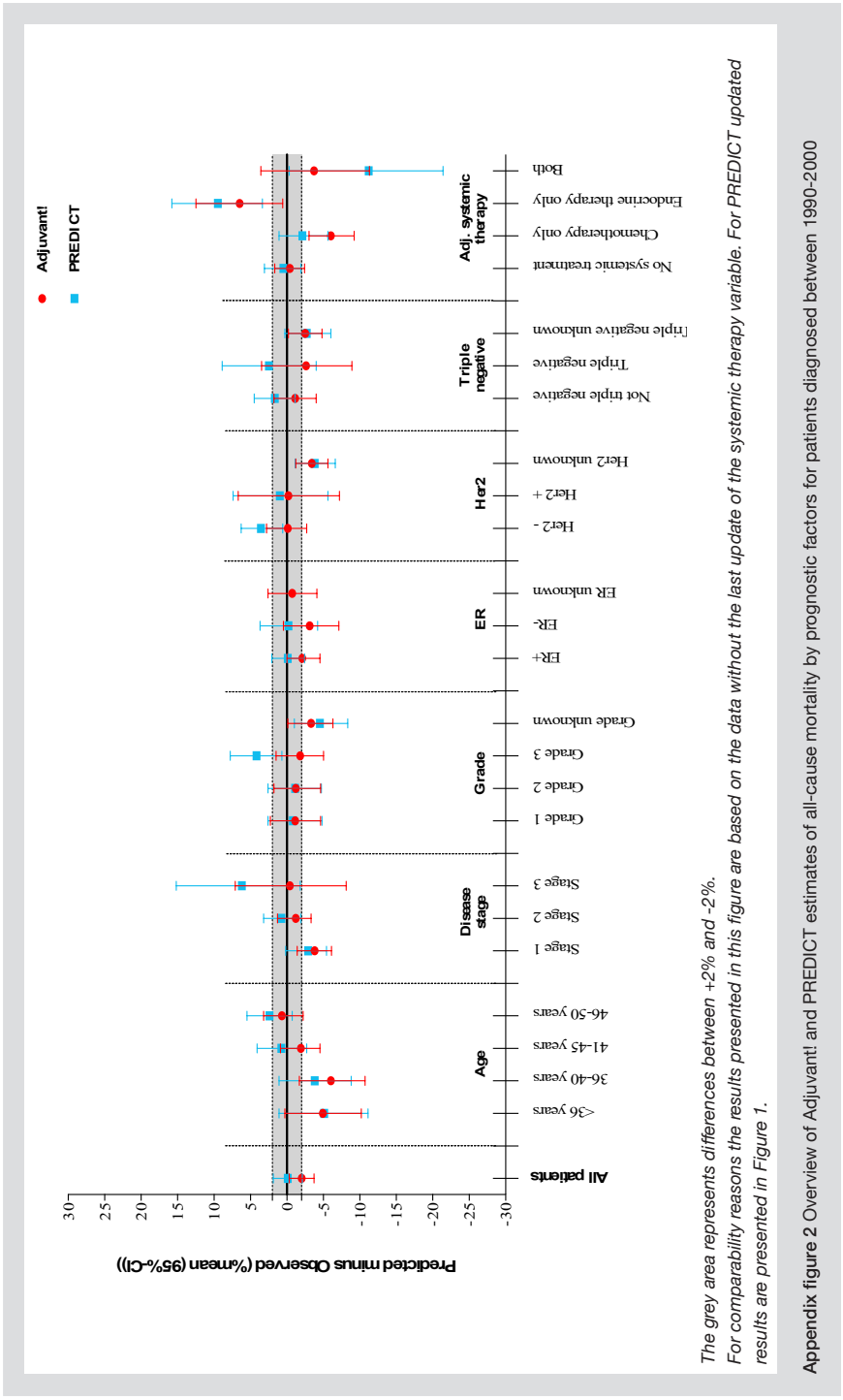
Analyses

The following hospitals had no data on cause of death and were thus excluded from the breast cancer-specific mortality estimates, namely: Elkerliek (N=41), Viecuri (N=74), PAMM Laboratories (N=221) and Medisch Spectrum Twente (N=839).



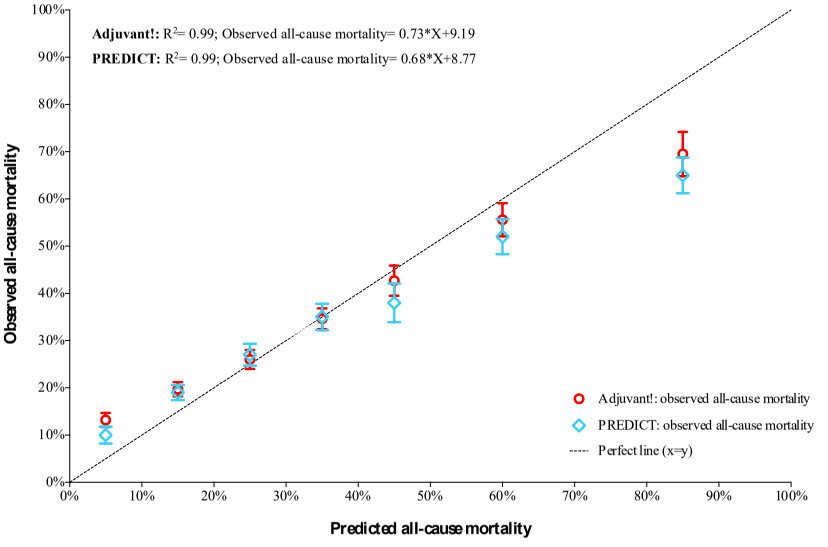
T1= tumors size ≤20 mm; T2= tumors size between 21-50 mm; T3= tumors size >50 mm; M0= no distant metastases; ER= estrogen receptor status.
The number of people excluded for each reason for exclusion is not reported as patients were almost always excluded for multiple reasons.

Appendix figure 1 Flowchart of patient selection



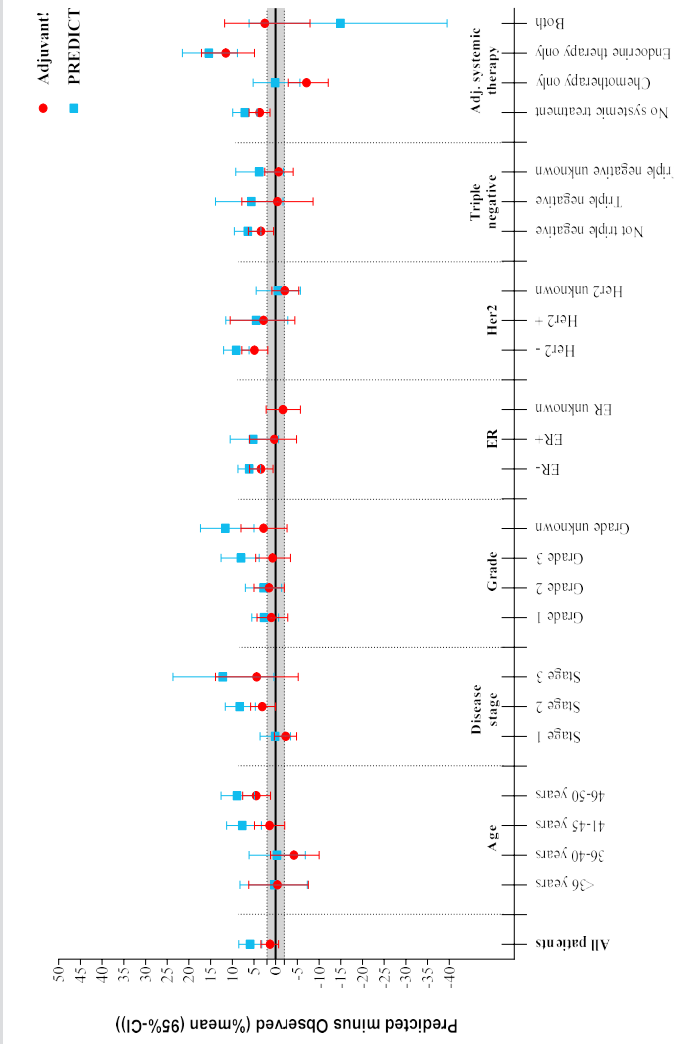
The grey area represents differences between +2% and -2%.
For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable. For PREDICT updated results are presented in Figure 1.

Appendix figure 2 Overview of Adjuvant! and PREDICT estimates of all-cause mortality by prognostic factors for patients diagnosed between 1990-2000



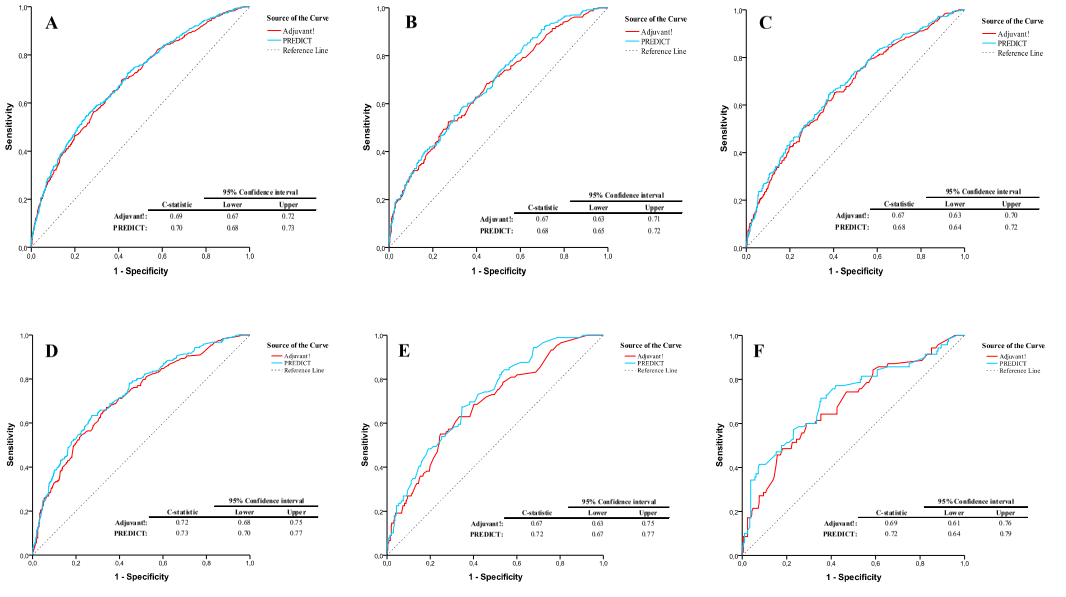
The grey area represents differences between +2% and -2%.
For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable. For PREDICT updated results are presented in Figure 1.

Appendix figure 3 Overview of Adjuvant! and PREDICT's estimates of breast cancer-specific mortality by prognostic factors for patients diagnosed between 1990-2000



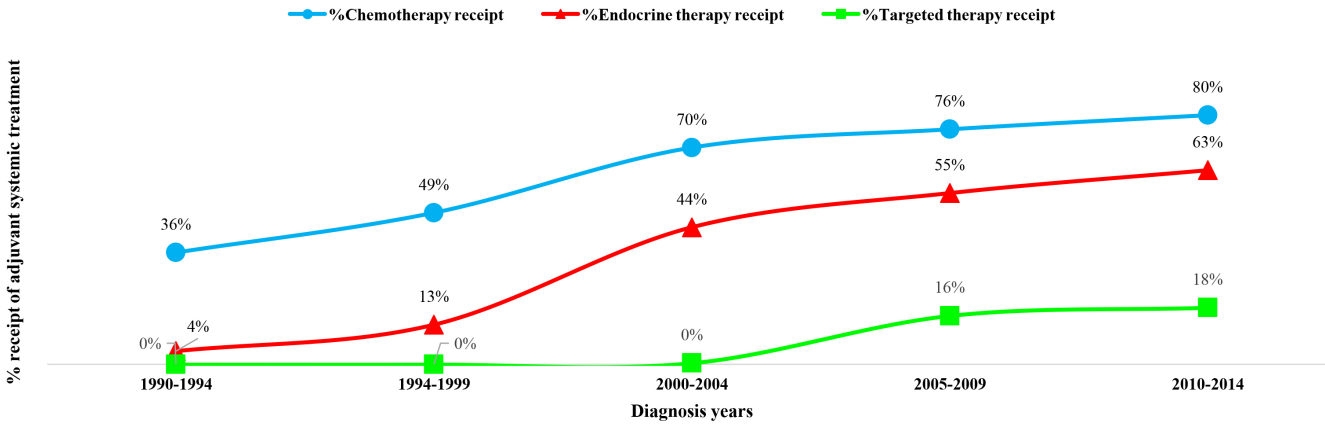
The analysis of Adjuvant!'s calibration contains N= 1,535 patients, and in the PREDICT analysis we included N= 1,076 patients. Deciles with <100 patients were merged, namely 40% to 60% and 60% to 100%. Error bars are standard errors (SE). For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable. For PREDICT updated results are presented in Figure 2.

Appendix figure 4 Observed vs. Predicted 10-year all-cause and breast cancer-specific mortality for patients diagnosed between 1990-2000 (without updated adjuvant systemic therapy receipt data)



All ROC-curves are based on patients diagnosed between 1990 up to 2000 included in the PREDICT analyses (N=2,073). For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable. For PREDICT updated results are presented in Figure 3.
A *ROC-curve 10-year all-cause mortality (N=2,073);* **B** *ROC-curve 10-year all-cause mortality for patients not treated with adjuvant systemic therapy (N=1,061);* **C** *ROC-curve 10-year all-cause mortality for patients with unknown Her2-status (N=964);* **D** *ROC-curve 10-year breast cancer-specific mortality (N=1,076); E ROC-curve 10-year breast cancer-specific mortality for patients not treated with adjuvant systemic therapy (N= 591); F ROC-curve 10-year breast cancer-specific mortality for patients with unknown Her2-status (N=279).*

Appendix figure 5 Discriminatory accuracy of Adjuvant! and PREDICT in patients diagnosed between 1990-2000

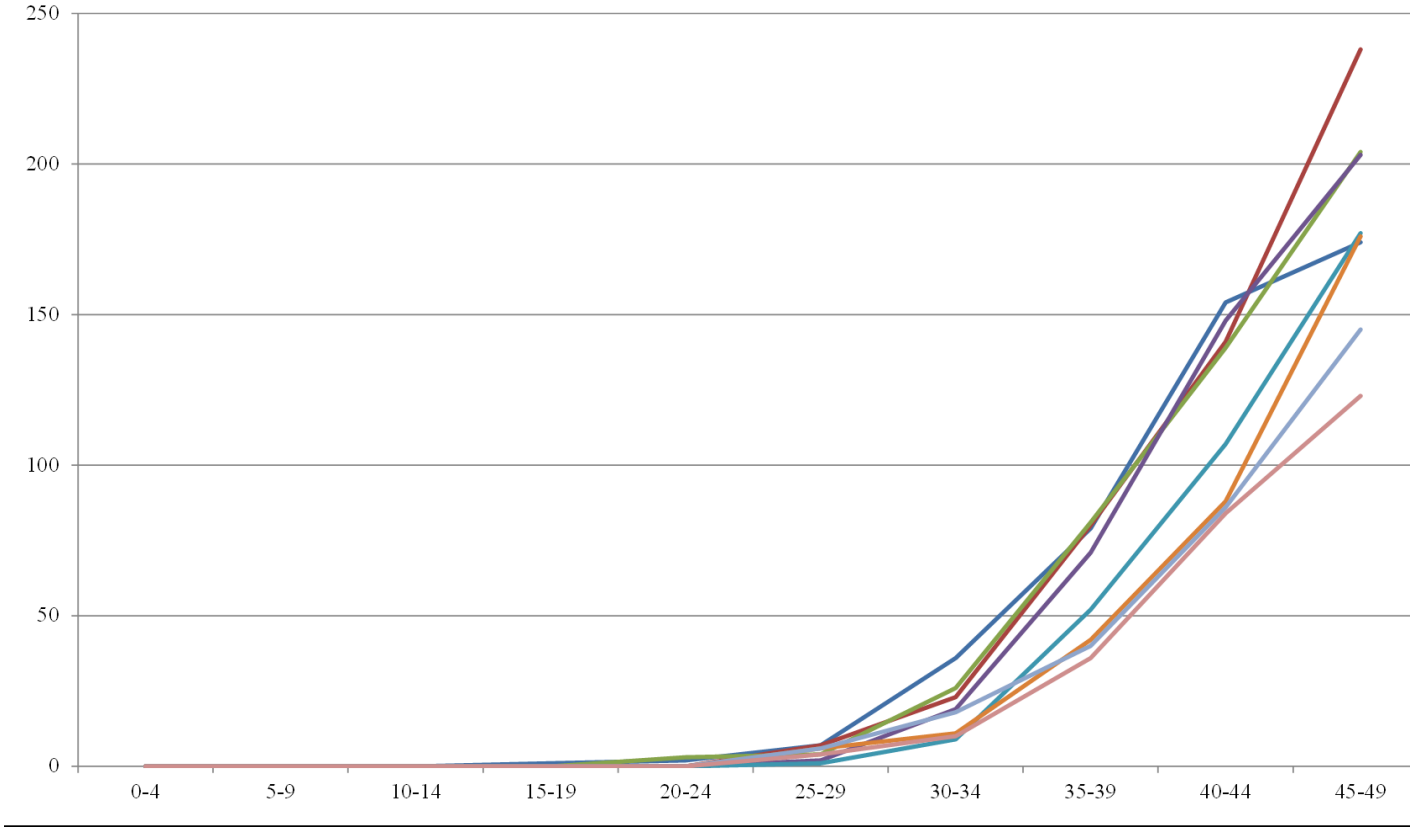


Source: Netherlands Cancer Registry, managed by Netherlands Comprehensive Cancer Organisation (IKNL)© March 2016

Appendix Figure 6 Netherlands Cancer Registry data on the trends in use of adjuvant systemic therapy among stage I-III breast cancer patients aged <50 years diagnosed between 1990-2014

		Total number of patients who received:								
Diagnosis years	*Total population*	*Neo-adjuvant chemotherapy*	*Adjuvant chemotherapy*	*Neo-adjuvant and adjuvant chemotherapy*	*Neo-adjuvant endocrine therapy*	*Adjuvant endocrine therapy*	*Neo-adjuvant and adjuvant endocrine therapy*	*Neo-adjuvant targeted therapy*	*Adjuvant targeted therapy*	*Neo-adjuvant and adjuvant targeted therapy*
1990-1994	10.269	109	3.582	9	4	438	0	0	0	0
1994-1999	11.451	207	5.357	29	18	1.449	0	0	0	0
2000-2004	12.907	599	8.374	42	18	5.684	4	1	58	0
2005-2009	13.983	1.555	8.933	101	30	7.674	14	239	1.888	72
2010-2014	13.887	3.215	7.749	184	71	8.592	25	633	1.722	191

Source: Netherlands Cancer Registry, managed by Netherlands Comprehensive Cancer Organisation (IKNL)© March 2016



Source: Netherlands Cancer Registry, managed by Netherlands Comprehensive Cancer Organisation (IKNL) © January 2016

Appendix figure 7 Netherlands Cancer Registry data on mortality rates among breast cancer patients for the period 1990-2014

Appendix Table 1 Overview of subsets used in the analyses

	Adjuvant! analyses		PREDICT analyses	
	Subset diagnosed between 1990-2000		Subset diagnosed between 1990-2000	
	all-cause mortality	*breast cancer-specific mortality*	*all-cause mortality*	*breast cancer-specific mortality*
Number of patients:	2,710	1,535	2,073	1,076
Mean FUP in years (SE):	13.5 (0.12)	8.7 (0.07)	13.5 (0.14)	8.6 (0.08)
FUP range in years:	0 to 23	0 to 10	0 to 23	0 to 10
Mean age in years (SE):	42 (0.10)	43 (0.14)	42 (0.12)	43 (0.17)
Age in years (range):	23 to 50	23 to 50	23 to 50	23 to 50
Number of patients per age category (%):				
<35	328 (12)	189 (12)	254 (12)	132 (12)
36-40	447 (17)	255 (17)	353 (17)	183 (17)
41-45	936 (35)	538 (35)	716 (35)	379 (35)
46-50	999 (37)	553 (36)	750 (36)	382 (36)
Number of patients per stage (%):				
1	925 (34)	534 (35)	690 (33)	365 (34)
2	1,614 (60)	891 (58)	1,256 (61)	638 (59)
3	171 (6)	110 (7)	127 (6)	73 (7)
unknown	0	0	0	0

Appendix Table 2 Distribution of prognostic characteristics by age at diagnosis for patients diagnosed between 1990-2000 (N (row%))

	≤35 years N_{col}= 254	36-40 years N_{col}= 353	41-45 years N_{col}= 716	46-50 years N_{col}= 750	N_{row}	P*
ER-status						
ER +	127 (9)	225 (16)	517 (36)	581 (40)	1,450	**<0.001**
ER -	127 (20)	128 (21)	199 (32)	169 (27)	623	
Unknown	0	0	0	0	0	
Her2-status						
Her2 -	105 (12)	155 (17)	307 (34)	331 (37)	898	0.093
Her2 +	36 (17)	41 (19)	70 (33)	64 (30)	211	
Unknown	113	157	339	355	964	
Tumor grade						
Grade 1	16 (6)	36 (14)	88 (34)	121 (46)	261	
Grade 2	46 (9)	86 (17)	180 (35)	206 (40)	518	**<0.001**
Grade 3	123 (17)	145 (20)	246 (34)	215 (30)	729	
Unknown	69	86	202	208	565	
Tumor size						
0.1-1.0 cm	29 (11)	47 (19)	86 (34)	92 (36)	254	
1.1-2.0 cm	85 (11)	132 (17)	279 (35)	300 (38)	796	
2.1-3.0 cm	54 (12)	85 (18)	168 (36)	162 (35)	469	0.326
3.1-5.0 cm	64 (15)	63 (15)	142 (33)	159 (37)	428	
>5 cm	22 (18)	26 (21)	41 (33)	37 (29)	126	
Unknown	0	0	0	0	0	

ER= estrogen receptor; Her2= Her2neu receptor
This table is based on the patients included in the PREDICT analyses (N= 2,073). It is based on updated adjuvant systemic treatment data. In the new data patients were mainly reallocated to having received systemic treatment instead of not having done so, and having received chemotherapy instead of only endocrine therapy.
If row percentage does not add up to 100%, this is due to the rounding at the first decimal.
*P-values for Chi-square tests (not including unknown).

Appendix Table 2 continued Distribution of prognostic characteristics by age at diagnosis for patients diagnosed between 1990-2000 (N (row%))

	≤35 years N_{col}= 254	36-40 years N_{col}= 353	41-45 years N_{col}= 716	46-50 years N_{col}= 750	N_{row}	P*
Positive nodes						
0	122 (12)	149 (15)	372 (37)	360 (36)	1,003	
1-3	77 (11)	134 (19)	220 (32)	258 (37)	689	**0.046**
4-9	36 (13)	49 (18)	98 (36)	90 (33)	273	
>9	19 (18)	21 (19)	26 (24)	42 (39)	108	
Unknown	0	0	0	0	0	
Disease stage						
Stage 1	72 (10)	108 (16)	260 (38)	250 (36)	690	
Stage 2	164 (13)	216 (17)	413 (33)	463 (37)	1,256	0.085
Stage 3	18 (14)	29 (23)	43 (34)	37 (29)	127	
Unknown	0	0	0	0	0	
Surgery						
Breast conserving	104 (10)	192 (18)	377 (36)	380 (36)	1,053	**0.032**
Mastectomy	150 (15)	160 (16)	338 (33)	369 (36)	1,017	
Unknown	0	1	1	1	3	
Adjuvant systemic treatment						
None	104 (11)	144 (15)	369 (38)	349 (36)	966	
Chemotherapy only	125 (16)	157 (20)	257 (33)	249 (32)	788	**<0.001**
Endocrine therapy only	3 (3)	6 (6)	26 (26)	66 (65)	101	
Both	22 (10)	46 (21)	64 (29)	86 (39)	218	
Unknown	0	0	0	0	0	

ER= estrogen receptor; Her2= Her2neu receptor

This table is based on the patients included in the PREDICT analyses (N= 2,073). It is based on updated adjuvant systemic treatment data. In the new data patients were mainly reallocated to having received systemic treatment instead of not having done so, and having received chemotherapy instead of only endocrine therapy.

If row percentage does not add up to 100%, this is due to the rounding at the first decimal.

*P-values for Chi-square tests (not including unknown).

Appendix Table 3 Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and PREDICT estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

		10-year all-cause mortality					*10-year breast cancer-specific mortality*			
	N (%)	Observed	Predicted	Predicted minus Observed (95-C.I.)	P	N (%)	Observed	Predicted	Predicted minus Observed (95-C.I.)	P
Overall	2073 (100)	27.2	28.3	-1.1 (-3.2 to 0.9)	0.28	1076 (100)	22.6	25.8	3.2 (0.8 to 5.6)	**0.007**
Age (years)										
≤ 35	254 (12)	26.6	33.2	-6.6 (-12.5 to -0.1)	**0.04**	132 (12)	33.0	30.7	-2.3 (-10.6 to 5.2)	0.52
36-40	353 (17)	25.3	30.2	-4.9 (-10.0 to 0.0)	0.06	183 (17)	31.1	27.9	-3.2 (-9.5 to 4.0)	0.35
41-45	716 (35)	27.5	27.5	0.0 (-3.2 to 3.3)	0.99	379 (35)	19.8	25.7	5.9 (1.8 to 10.0)	**0.003**
46-50	750 (36)	27.7	26.4	1.3 (-1.8 to 4.3)	0.39	382 (36)	17.5	23.1	5.6 (1.6 to 9.2)	**0.01**
Her2-status										
Negative	898 (43)	29.9	27.7	2.2 (-0.6 to 5.0)	0.15	628 (58)	18.3	24.5	6.2 (3.3 to 9.1)	**0.001**
Positive	211 (10)	38.9	39.6	-0.7 (-8.2 to 6.1)	0.85	169 (16)	34.3	36.8	2.5 (-4.9 to 9.4)	0.49
Unknown	964 (47)	21.9	26.3	-4.4 (-7.3 to -1.4)	**0.01**	279 (26)	25.1	22.0	-3.1 (-8.2 to 1.8)	0.22
ER-status										
Positive	1450 (70)	23.5	24.5	-1.0 (-3.2 to 1.1)	0.38	785 (73)	18.2	21.9	3.7 (1.0 to 6.4)	**0.01**
Negative	623 (30)	35.9	37.2	-1.3 (-5.2 to 2.3)	0.52	291 (27)	34.4	36.1	1.7 (-3.5 to 7.5)	0.54
Triple negative										
Not triple negative	971 (47)	28.7	28.2	0.5 (-2.1 to 3.3)	0.72	727 (68)	20.9	25.1	4.2 (1.0 to 6.9)	**0.01**
Triple negative	207 (10)	37.6	36.9	0.7 (-6.7 to 7.2)	0.84	136 (13)	33.1	34.9	1.8 (-6.7 to 9.1)	0.64
Unknown	895 (43)	23.1	26.4	-3.3 (-6.5 to -0.5)	**0.03**	213 (20)	21.6	22.0	0.4 (-5.4 to 5.9)	0.89

Table is based on updated adjuvant systemic treatment data.
ER= estrogen receptor; Her2= Her2neu receptor
[a] = PREDICT is unable to provide estimates if ER-status is unknown. Hence, all patients with an unknown ER-status, were excluded from the analyses.
- = Due to the small number of cases, we were unable to calculate this value.
* P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.

Appendix Table 3 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and PREDICT estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

				10-year all-cause mortality					*10-year breast cancer-specific mortality*	
Tumor Grade										
Grade 1	261 (13)	9.1	10.1	-1.0 (-5.0 to 3.0)	0.63	176 (16)	6.3	6.9	0.6 (-3.3 to 3.8)	0.72
Grade 2	518 (25)	19.5	21.6	-2.1 (-6.0 to 1.4)	0.25	342 (32)	17.5	18.5	1.0 (-2.9 to 4.7)	0.63
Grade 3	729 (35)	44.0	41.4	2.6 (-1.1 to 6.2)	0.16	442 (41)	35.3	39.9	4.6 (-0.1 to 9.0)	**0.05**
	N (%)	**Observed**	**Predicted**	**Predicted minus Observed (95-C.I.)**	**P**	**N (%)**	**Observed**	**Predicted**	**Predicted minus Observed (95-C.I.)**	**P**
Unknown	565 (27)	20.8	25.9	-5.1 (-8.6 to -1.2)	**0.01**	116 (11)	13.8	21.6	7.8 (1.1 to 13.9)	**0.02**
Stage										
Stage 1	690 (33)	11.0	14.0	-3.0 (-5.7 to -0.2)	**0.04**	365 (34)	12.9	12.3	-0.6 (-4.3 to 2.6)	0.77
Stage 2	1256 (61)	32.8	32.8	0.0 (-3.1 to 1.9)	0.62	638 (59)	25.4	30.2	4.8 (1.6 to 8.0)	**0.01**
Stage 3	127 (6)	64.9	61.2	3.7 (-4.6 to 12.7)	0.42	73 (7)	46.6	54.5	7.9 (-4.0 to 19.5)	0.17
Tumor size										
0.1-1.0 cm	254 (12)	8.7	12.8	-4.1 (-8.8 to 0.5)	**0.09**	155 (14)	11.0	9.8	-1.2 (-6.8 to 3.4)	0.64
1.1-2.0 cm	796 (38)	14.9	19.7	-4.8 (-7.9 to -1.9)	**0.001**	358 (33)	19.0	17.5	-1.5 (-5.8 to 2.3)	0.47
2.1-3.0 cm	469 (23)	31.0	31.7	-0.7 (-5.4 to 3.2)	0.74	261 (24)	24.1	29.4	5.3 (0.0 to 10.7)	**0.06**
3.1-5.0 cm	428 (21)	44.5	40.7	3.8 (-0.8 to 8.4)	0.11	224 (21)	29.0	36.4	7.4 (1.0 to 13.8)	0.27
>5 cm	126 (6)	68.0	58.6	9.4 (0.3 to 18.0)	**0.04**	78 (7)	38.5	52.6	14.1 (3.2 to 25.5)	**0.02**
Positive nodes										
0	1003 (48)	14.1	17.0	-2.9 (-5.4 to -0.5)	**0.02**	544 (51)	15.4	15.2	-0.2 (-3.5 to 2.9)	0.85

Table is based on updated adjuvant systemic treatment data.
ER= estrogen receptor; Her2= Her2neu receptor
[a] = PREDICT is unable to provide estimates if ER-status is unknown. Hence, all patients with an unknown ER-status, were excluded from the analyses.
- = Due to the small number of cases, we were unable to calculate this value.
[*] P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.

Appendix Table 3 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and PREDICT estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

				10-year all-cause mortality					*10-year breast cancer-specific mortality*	
1-3	689 (33)	28.3	29.6	-1.3 (-4.9 to 1.8)	0.44	380 (35)	23.9	29.5	5.6 (0.6 to 9.6)	**0.02**
4-9	273 (13)	53.6	49.7	3.9 (-2.0 to 9.8)	0.20	112 (10)	38.4	48.5	10.1 (1.2 to 19.3)	**0.03**
>9	108 (5)	75.1	70.9	4.2 (-4.1 to 12.8)	0.36	40 (4)	62.5	69.8	7.3 (-7.5 to 23.3)	0.32
Morphology										
IDC	1569 (76)	27.8	29.5	-1.7 (-3.8 to 0.6)	0.15	812 (75)	24.3	27.5	3.2 (0.2 to 6.1)	**0.03**
ILC	204 (10)	21.3	25.1	-3.8 (-9.8 to 2.3)	0.23	105 (10)	21.0	20.0	-1.0 (-9.3 to 6.7)	0.81
IL/DC	109 (5)	32.4	29.5	2.9 (-6.7 to 11.2)	0.50	52 (5)	15.4	24.4	9.0 (-1.7 to 17.7)	**0.09**
Tubular carcinoma	64 (3)	13.8	10.0	3.8 (-3.0 to 8.4)	0.22	25 (2)	0.0	5.6	-	-
Mucinous carcinoma	23 (1)	31.0	24.2	6.8 (-11.1 to 19.4)	0.39	14 (1)	14.3	20.0	5.7 (-15.7 to 14.4)	0.57
Medular	46 (2)	44.6	28.8	15.8 (4.4 to 24.5)	**0.02**	25 (2)	16.0	27.4	11.4 (-4.4 to 22.6)	0.14
Comedo carcinoma	23 (1)	26.5	32.8	-6.3 (-27.2 to 12.8)	0.55	14 (1)	21.4	26.9	5.5 (-17.8 to 20.7)	0.60
Other	35 (2)	16.0	22.3	-6.3 (-23.4 to 8.8)	0.42	29 (3)	24.1	19.0	-5.1 (-21.5 to 9.6)	0.52
Angiolymphatic invasion										
No angiolymphatic invasion	502 (24)	26.5	24.9	1.6 (5.3 to -2.3)	0.40	336 (31)	17.0	20.2	3.2 (-1.0 to 7.1)	0.12
Angiolymphatic invasion in up to 3 vessels	278 (13)	25.9	28.6	-2.7 (-8.1 to 2.7)	0.36	68 (6)	22.1	28.6	6.5 (-4.3 to 15.8)	0.21
Extensive angiolymphatic invasion	140 (7)	36.2	40.6	-4.4 (-13.1 to 4.4)	0.32	36 (3)	47.2	47.3	0.1 (-17.6 to 16.5)	0.99
Unknown	1153 (56)	26.7	28.2	-1.5 (-4.3 to 1.0)	0.26	636 (59)	24.2	27.2	3.0 (-0.1 to 6.2)	**0.07**
Type of surgery										
Breast conserving surgery	1053 (51)	19.0	21.8	-2.8 (-5.5 to -0.3)	**0.04**	575 (53)	20.0	19.8	-0.2 (-3.5 to 3.3)	0.93

Table is based on updated adjuvant systemic treatment data.
ER= estrogen receptor; Her2= Her2neu receptor
[a] = PREDICT is unable to provide estimates if ER-status is unknown. Hence, all patients with an unknown ER-status, were excluded from the analyses.
- = Due to the small number of cases, we were unable to calculate this value.
* P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.

Appendix Table 3 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and PREDICT estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

				10-year all-cause mortality					*10-year breast cancer-specific mortality*	
Mastectomy	1017 (49)	35.6	35.0	0.6 (-2.5 to 3.6)	0.70	500 (46)	25.6	32.7	7.1 (2.7 to 10.7)	**0.001**
Unknown	3 (0.1)	7.7	20.5	-	-	1 (0)	0.0	11.3	-	-
Radiotherapy										
No	450 (22)	22.2	24.3	-2.1 (-6.2 to 2.0)	0.30	225 (21)	20.9	23.1	2.2 (-3.4 to 7.7)	0.43
Yes	1623 (78)	28.5	29.4	-0.9 (-3.1 to 1.4)	0.45	851 (79)	23.0	26.5	3.5 (0.6 to 6.3)	**0.03**
Systemic treatment										
None	966 (47)	18.4	19.8	-1.4 (-3.9 to 3.9)	0.28	496 (46)	13.3	16.9	3.6 (0.4 to 6.7)	**0.03**
Chemotherapy only	788 (38)	35.5	36.8	-1.3 (-4.6 to 2.1)	0.46	377 (35)	35.0	36.1	1.1 (-3.7 to 5.7)	0.63
Endocrine therapy only	101 (5)	38.1	32.4	5.7 (-2.8 to 14.0)	0.20	62 (6)	14.5	25.9	11.4 (1.4 to 19.4)	**0.02**
Endocrine therapy and chemotherapy	218 (11)	30.0	32.9	-2.9 (-9.1 to 3.2)	0.40	141 (13)	25.5	29.2	3.7 (-3.6 to 10.8)	0.32

Table is based on updated adjuvant systemic treatment data.
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[a] = PREDICT is unable to provide estimates if ER-status is unknown. Hence, all patients with an unknown ER-status, were excluded from the analyses.
- = Due to the small number of cases, we were unable to calculate this value.
* P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.

Appendix Table 4 Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and Adjuvant! estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

		10-year all-cause mortality					*10-year breast cancer-specific mortality*			
	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P
All patients	2,710 (100)	26.7	28.7 (0.9)	-2.0 (-3.7 to -0.3)	**0.023**	1,535 (100)	24.3	23.0 (1.1)	1.3 (-0.7 to 3.4)	0.232
Age (years)										
≤ 35	328 (12.1)	34.4	39.3 (2.6)	-4.9 (-10.2 to 0.3)	0.066	189 (12.3)	33.1	33.5 (3.5)	-0.4 (-7.5 to 6.2)	0.908
36-40	447 (16.5)	28.0	34.0 (2.3)	-6.0 (-10.7 to -1.7)	**0.009**	255 (16.6)	26.2	30.4 (2.8)	-4.2 (-10 to 1.2)	0.136
41-45	936 (34.5)	25.1	27.0 (1.4)	-1.9 (-4.5 to 0.9)	0.182	538 (35.0)	22.9	21.5 (1.8)	1.4 (-2.1 to 4.9)	0.459
46-50	999 (36.9)	25.1	24.4 (1.4)	0.7 (-2.2 to 3.2)	0.638	553 (36.0)	21.8	17.3 (1.7)	4.5 (1.2 to 7.6)	**0.009**
Her2-status										
Negative	911 (33.6)	25.4	25.5 (1.4)	-0.1 (-2.7 to 2.8)	0.964	633 (41.2)	22.5	17.6 (1.5)	4.9 (1.8 to 7.8)	**0.002**
Positive	214 (7.9)	40.5	40.7 (3.4)	-0.2 (-7.2 to 6.7)	0.963	170 (11.1)	37.5	34.7 (3.7)	2.8 (-4.4 to 10.5)	0.447
Unknown	1,585 (58.5)	25.6	29.0 (1.1)	-3.4 (-5.6 to -1.2)	**0.004**	732 (47.7)	22.8	24.9 (1.6)	-2.1 (-5.3 to 0.9)	0.179
ER-status										
Positive	1,450 (53.5)	23.4	25.5 (1.1)	-2.1 (-4.5 to 0.0)	0.062	785 (51.1)	21.1	17.7 (1.4)	3.4 (0.6 to 6.0)	**0.017**
Negative	623 (23.0)	35.4	38.5 (2.0)	-3.1 (-7.1 to 0.5)	0.106	291 (19.0)	33.7	33.4 (2.8)	0.3 (-4.8 to 6.0)	0.915
Unknown	637 (23.5)	25.7	26.4 (1.8)	-0.7 (-4.1 to 2.6)	0.717	459 (29.9)	23.8	25.5 (2.0)	-1.7 (-5.7 to 2.2)	0.422
Triple negative										
Not triple negative	972 (35.9)	26.6	27.7 (1.5)	-1.1 (-4.0 to 1.8)	0.466	727 (47.4)	23.8	20.4 (1.5)	3.4 (0.5 to 6.3)	**0.029**
Triple negative	207 (7.6)	33.6	36.2 (3.3)	-2.6 (-8.9 to 3.5)	0.456	136 (8.9)	31.7	32.1 (3.9)	-0.4 (-8.6 to 7.8)	0.918

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Appendix Table 4 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and Adjuvant! estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

		10-year all-cause mortality					*10-year breast cancer-specific mortality*			
	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P
Unknown	1,639 (60.5)	25.8	28.3 (1.2)	-2.5 (-4.8 to -0.2)	0.034	672 (43.8)	23.3	24.0 (1.7)	-0.7 (-4.0 to 2.5)	0.653
Tumor Grade										
Grade 1	328 (12.1)	10.8	11.9 (1.8)	-1.1 (-4.6 to 2.3)	0.540	229 (14.9)	8.1	7.1 (1.7)	1.0 (-2.8 to 4.3)	0.555
Grade 2	644 (23.8)	21.9	23.1 (1.7)	-1.2 (-4.6 to 1.8)	0.465	459 (29.9)	19.2	17.7 (1.8)	1.5 (-2.0 to 5.0)	0.412
Grade 3	915 (33.8)	35.8	37.6 (1.7)	-1.8 (-5.0 to 1.5)	0.286	607 (39.5)	34.1	33.4 (2.0)	0.7 (-3.4 to 4.6)	0.746
Unknown	823 (30.4)	26.6	29.9 (1.6)	-3.3 (-6.3 to -0.1)	**0.040**	240 (15.6)	24.8	22.0 (2.7)	2.8 (-2.6 to 8.0)	0.307
Stage										
Stage 1	925 (34.1)	11.6	15.4 (1.2)	-3.8 (-6.1 to -1.4)	**0.005**	534 (34.8)	9.8	12.1 (1.4)	-2.3 (-4.8 to 0.3)	0.093
Stage 2	1,615 (59.6)	32.4	33.6 (1.2)	-1.2 (-3.3 to 1.3)	0.315	892 (58.1)	29.8	26.7 (1.5)	3.1 (0.0 to 5.8)	**0.042**
Stage 3	170 (6.3)	54.9	55.3 (3.9)	-0.4 (-8.1 to 7.1)	0.915	109 (7.1)	50.7	46.3 (4.7)	4.4 (-5.2 to 13.9)	0.337
Tumor size										
0.1-1.0 cm	363 (13.4)	10.2	14.9 (1.9)	-4.7 (-8.4 to -0.9)	**0.015**	221 (14.4)	7.0	11.0 (2.2)	-4.0 (-8.5 to -0.1)	0.061
1.1-2.0 cm	1,036 (38.2)	17.9	22.8 (1.3)	-4.9 (-7.5 to -2.4)	**0.002**	540 (35.2)	15.3	17.4 (1.6)	-2.1 (-5.3 to 1.2)	0.193
2.1-3.0 cm	582 (21.5)	33.2	33.2 (1.9)	0.0 (-3.9 to 3.7)	0.987	347 (22.6)	30.6	25.9 (2.4)	4.7 (0.2 to 9.5)	0.053
3.1-5.0 cm	560 (20.7)	38.3	37.9 (2.0)	0.4 (-3.4 to 4.3)	0.823	314 (20.5)	35.0	31.8 (2.7)	3.2 (-2.3 to 8.2)	0.238
>5 cm	169 (6.2)	55.3	49.1 (4.0)	6.2 (-2.1 to 13.7)	0.121	113 (7.4)	52.4	40.0 (4.8)	12.4 (2.9 to 21.5)	**0.014**
Positive nodes										

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Appendix Table 4 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and Adjuvant! estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

		10-year all-cause mortality					*10-year breast cancer-specific mortality*			
	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P
0	1,348 (49.7)	16.0	19.4 (1.1)	-3.4 (-5.6 to -1.3)	**0.002**	544 (26.2)	15.6	15.1 (1.5)	0.5 (-2.4 to 3.4)	0.748
1-3	869 (32.1)	28.7	30.8 (1.6)	-2.1 (-5.3 to 0.9)	0.171	380 (18.3)	31.9	22.7 (2.1)	9.2 (4.8 to 13.3)	**0.001**
4-9	347 (12.8)	46.4	45.5 (2.7)	0.9 (-4.6 to 6.3)	0.740	112 (5.4)	55.1	37.8 (4.7)	17.3 (7.7 to 25.6)	**0.001**
>9	146 (5.4)	67.0	61.6 (4.1)	5.4 (-3.4 to 13.3)	0.189	40 (1.9)	77.5	62.5 (7.8)	15.0 (0.1 to 30.3)	0.066
Morphology										
IDC	2,038 (75.2)	28.9	30.7 (1.0)	-1.8 (-3.9 to 0.2)	0.081	812 (39.2)	29.7	23.6 (1.5)	6.1 (3.2 to 9.0)	**0.003**
ILC	272 (10)	25.0	26.5 (2.6)	-1.5 (-6.7 to 3.4)	0.584	105 (5.1)	22.1	19.4 (4.0)	2.7 (-5.2 to 10.4)	0.477
IL/DC	129 (4.8)	25.8	25.6 (3.8)	0.2 (-7.2 to 7.5)	0.960	52 (2.5)	26.9	15.4 (5.0)	11.5 (1.4 to 21.1)	**0.048**
Tubular carcinoma	78 (2.9)	10.3	6.4 (2.8)	3.9 (-2.1 to 8.9)	0.196	25 (1.2)	5.7	-	-	-
Mucinous carcinoma	31 (1.1)	19.9	16.1 (6.6)	3.8 (-10.1 to 15.4)	0.581	14 (0.7)	20.0	14.3 (9.3)	5.7 (-20.0 to 14.4)	0.566
Medular	58 (2.1)	27.4	12.1 (4.3)	15.3 (6.6 to 23.3)	**0.016**	25 (1.2)	27.8	16.0 (7.4)	11.8 (-5.5 to 23.6)	0.125
Comedo carcinoma	40 (1.5)	26.7	37.5 (7.5)	-10.8 (-25.7 to 3.4)	0.161	14 (0.7)	26.9	21.4 (10.8)	5.5 (-19.7 to 20.7)	0.624
Other	49 (1.8)	21.5	26.5 (6.3)	-5.0 (-17.4 to 7.5)	0.444	29 (1.4)	19.3	24.1 (8.1)	-4.8 (-22.4 to 10.6)	0.541
Unknown	15 (0.6)	24.9	13.3	-	-	0	-	-	-	-
Angiolymphatic invasion										
No angiolymphatic invasion	557 (20.6)	22.4	23.0 (1.8)	-0.6 (-4.4 to 2.5)	0.747	336 (16.2)	20.6	16.0 (2.0)	4.6 (0.6 to 8.7)	**0.030**
Angiolymphatic invasion in up to 3 vessels	355 (13.1)	26.7	28.7 (2.5)	-2.0 (-7.0 to 2.6)	0.404	68 (3.3)	29.0	22.1 (4.9)	6.9 (-3.4 to 16.5)	0.165

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Appendix Table 4 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and Adjuvant! estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

		10-year all-cause mortality					*10-year breast cancer-specific mortality*			
	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P
Extensive angiolymphatic invasion	159 (5.9)	36.0	45.3 (3.9)	-9.3 (-16.9 to -1.5)	**0.013**	36 (1.7)	48.7	45.7 (8.7)	3.0 (-13.8 to 19.4)	0.729
Unknown	1,639 (60.5)	27.3	29.0 (1.1)	-1.7 (-3.9 to 0.5)	0.127	636 (30.7)	30.2	23.7 (1.7)	6.5 (3.3 to 9.8)	**0.001**
Type of surgery										
Breast conserving surgery	1,365 (50.4)	20.6	23.7 (1.1)	-3.1 (-5.3 to -0.8)	**0.008**	575 (27.7)	20.7	19.6 (1.6)	1.1 (-2.2 to 4.3)	0.503
Mastectomy	1,340 (49.4)	33.0	33.9 (1.3)	-0.9 (-3.5 to 1.8)	0.494	500 (24.1)	35.9	24.7 (2.0)	11.2 (7.1 to 14.9)	**0.001**
Unknown	5 (0.2)	18.6	20.0	-	-	1 (0.1)	-	-	-	-
Radiotherapy										
No	614 (22.7)	23.0	25.2 (1.7)	-2.2 (-5.6 to 1.2)	0.188	225 (10.9)	24.0	19.8 (2.6)	4.2 (-1.3 to 9.0)	0.120
Yes	2,096 (77.3)	27.8	29.7 (1.0)	-1.9 (-3.9 to 0.0)	0.059	851 (41.1)	28.8	22.5 (1.5)	6.3 (3.6 to 9.4)	**0.001**
Systemic treatment										
None	1,395 (51.5)	20.3	20.7 (1.1)	-0.4 (-2.4 to 1.7)	0.693	591 (28.5)	21.7	14.6 (1.5)	7.1 (4.3 to 9.9)	**0.001**
Chemotherapy only	935 (34.5)	33.5	39.5 (1.6)	-6.0 (-9.2 to -3.0)	**0.001**	317 (15.3)	35.7	35.6 (2.7)	0.1 (-5.6 to 5.2)	0.965
Endocrine therapy only	210 (7.7)	33.6	27.1 (3.0)	6.5 (0.6 to 12.5)	**0.036**	149 (7.2)	35.0	19.6 (3.2)	15.4 (8.8 to 21.5)	**0.001**
Endocrine therapy and chemotherapy	170 (6.3)	33.4	37.1 (3.7)	-3.7 (-11.3 to 3.6)	0.310	19 (0.9)	27.2	42.1 (11.7)	-14.9 (-39.5 to 6.1)	0.239

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