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ORIGINAL REPORT

Qualitative Assessment of the Progesterone Receptor and HER2 Improves the Nottingham Prognostic Index Up to 5 Years After Breast Cancer Diagnosis

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ABSTRACT

Purpose
To investigate whether the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) can improve the Nottingham Prognostic Index (NPI) in the classification of patients with primary operable breast cancer for disease-free survival (DFS).

Patients and Methods
The analysis is based on 1,927 patients with breast cancer treated between 2000 and 2005 at the University Hospitals, Leuven. We compared performances of NPI with and without ER, PR and/or HER2. Validation was done on two external data sets containing 862 and 2,805 patients from Oslo (Norway) and Auckland (New Zealand), respectively.

Results
In the Leuven cohort, median follow-up was 66 months, and 13.7% of patients experienced a breast cancer–related event. Positive staining for ER, PR, and HER2 was detected, respectively, in 86.9%, 75.5%, and 11.9% of patients. Based on multivariate Cox regression modeling, the improved NPI (iNPI) was derived as NPI − PR positivity + HER2 positivity. Validation results showed a risk group reclassification of 20% to 30% of patients when using iNPI with its optimal risk boundaries versus NPI, in a majority of patients to more appropriate risk groups. An additional 10% of patients were classified into the extreme risk groups, where clinical actions are less ambiguous. Survival curves of reclassified patients resembled more closely those for patients in the same iNPI group than those for patients in the same NPI group.

Conclusion
The addition of PR and HER2 to NPI increases its 5-year prognostic accuracy. The iNPI can be considered as a clinically useful tool for stratification of patients with breast cancer receiving standard of care.

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INTRODUCTION

In the Western World, breast cancer is by far the most common form of cancer, as well as the second leading cause of (cancer) death in women between the ages of 40 and 50.[1,2] The Nottingham Prognostic Index (NPI)[3-5] is among several commonly used clinicopathologic scoring systems that have been developed on the basis of prognostic factors. It allows clinicians to estimate not only the clinical behavior of the tumor but also the magnitude of benefit and the need for adjuvant therapy. The NPI identifies a group of patients with an excellent prognosis who do not require adjuvant systemic therapy, after local surgery and radiotherapy, and secondly a group with a poor prognosis for whom chemotherapy would be most appropriate. Although the NPI was initially designed for relapse in patients with breast cancer who did not receive systemic adjuvant therapies, it also has prognostic value in patients receiving currently recommended adjuvant therapies.[6]

Correct classification among these groups is of major importance since unnecessary adjuvant chemotherapy can also be harmful. The large diversity in clinical outcome among patients with equal NPI predictions calls for a refinement of currently available classification systems.

Molecular classification of breast cancer based on genes for cell proliferation expressed in the tumor seems a more powerful prognostic tool for

disease-free survival (DFS) and overall survival (OS) than the currently used clinicopathologic factors. However, gene profiling of breast cancers for early relapse has mostly been compared with the same clinicopathologic features as included in NPI resulting in 30% discordance in risk group classification between NPI and prognostic gene profiling.[7] These prognostic genes have not been compared with steroid receptors and human epidermal growth factor receptor 2 (HER2) known to have a prognostic potential.[7-9] Slamon et al[10] did show a higher risk of breast cancer recurrence in tumors overexpressing HER2. The prognostic value of estrogen receptor (ER) and progesterone receptor (PR) has also been explored.[11-15] Collett et al[14] showed an important effect of taking ER and PR into account in a model including mean nuclear area, number of positive lymph nodes, and tumor diameter. Within the high-risk group, ER- and PR-positive tumors had similar survival characteristics as intermediate-risk patients. These and other studies indicate a possible improvement of the categorization of patients by incorporating the ER, PR, and HER2 into prognostic models. This study investigates the improvement of NPI for 5-year DFS of operable breast cancers by incorporating ER, PR, and HER2.

PATIENTS AND METHODS

Data

A total of 2,061 patients with operable breast cancer receiving primary surgery in the University Hospitals Leuven between January 2000 and June 2005 were available, of whom were 1,927 complete cases (93%). Missing values were mainly caused by the missing HER2 value in patients operated in the early 2000s (Table 1). Fifteen ER-negative/PR-positive tumors were excluded, due to controversy as to whether or not these tumors are false negative for ER or false positive for PR.[16] Patients received treatment according to standard of care (trastuzumab was not given at that time). Tumor size, grade,[17] and lymph node status were defined as previously published.[18] DFS was defined as the time between surgery and the first breast cancer event, including local and contralateral recurrence, and distant metastasis. Follow-up was provided until June 2009. The survival time of patients without relapse was censored at last follow-up. For bilateral cases (n = 56), the tumor with the highest NPI value was retained. The NPI was calculated during the postoperative pathologic examination. The NPI score is $0.2 \times$ size (cm) + grade + nodal status (1, 2, or 3, respectively, in case of 0, 1-3, or ≥ 4 positive lymph nodes). A patient with an NPI score lower than 3.4, between 3.4 and 5.4, or higher than 5.4, is considered to be at low, intermediate, or high risk, respectively. Due to a change in the monoclonal antibodies for immunohistochemical (IHC) detection of steroid receptors during the study period, ER and PR were considered positive for any nuclear staining.[18] For HER2, either strong expression by IHC (score 3+[19]) or *HER2* gene amplification by fluorescence in situ hybridization (FISH) was considered HER2+.

We used two external data sets to validate the performance of adding receptor information to the NPI. A first data set contains information on 862 consecutive patients from the Breast Cancer Micrometastasis group in Oslo (Norway) diagnosed between 1995 and 1998; 676 patients had complete information (78%). The second data set contains 2,805 patients from Auckland Breast Cancer Registry (New Zealand) diagnosed between January 2000 and December 2005. Complete information was available in 1,192 patients (42%). In all data sets, HER2 is most often missing (4.0% in Leuven, 8.5% in Oslo, 57.5% in Auckland). In Leuven, low-grade tumors more often had HER2 missing. In Auckland, HER2 is more missing in low-grade tumors and in older patients, but the decision whether to test HER2 also depended on the laboratory. This may explain the large amount of missing values in this cohort. In Oslo, the missingness did not depend on grade or age.

Statistical Analysis

Statistical analyses were conducted with SAS version 9.1.3 (SAS Institute, Cary, NC). DFS curves of risk groups were visualized using the Kaplan-Meier method.[20] Events were considered to occur at the first observation of a new tumor.

The improved NPI (iNPI) was built using Cox proportional hazard regression.[21] We started from a model containing only the NPI, and investigated which of the three receptors could be added as an independent prognostic factor. The decision whether or not to include a covariate was made on the basis of the Bayesian information criterion,[22] hazard ratios, and likelihood ratio *P* values. We derived the iNPI from the parameter estimates of the final model, and derived two thresholds to classify patients into three different risk groups. The optimal pair of thresholds was defined as the pair with the highest concordance index (c-index) obtained with the 0.632+ bootstrap method[23] on 1,000 bootstrap samples. The c-index is a measure indicating how well the assigned risk corresponds to the observed order of events.[24] Log-rank tests were used to compare DFS curves for the three risk groups.

The performance of NPI and iNPI were evaluated and compared on two levels. The first level relates to discrimination and classification accuracy. First, we calculated the c-index using the models' numerical values. Apart from the c-index, the models were evaluated using the risk groups rather than the numerical values. This approach is clinically more informative and is more

Table 1. Descriptive Statistics of the Complete Case Data Sets

	Leuven		Oslo		Auckland	
Characteristic	No.	%	No.	%	No.	%
No. of patients	2,061		862		2,805	
No. of complete cases	1,927		676		1,192	
Age						
Median	57		58		57	
IQR	48-66		50-67		48-67	
Missing	—		3		—	
Size						
Median	2.0		1.7		1.8	
IQR	1.5-3.5		1.1-2.5		1.2-2.8	
Missing	8		86		—	
No. of positive nodes	0	0-1	0	0-1	0	0-1
Missing	30		31		7	
ER						
Negative	252	13.08	120	17.75	320	26.85
Positive	1,675	86.92	545	80.62	872	73.15
Missing	6		46		21	
PR						
Negative	472	24.49	152	22.49	459	38.51
Positive	1,455	75.51	524	77.51	733	61.49
Missing	13		46		21	
HER2						
Negative	1,697	88.06	631	93.34	1,016	85.23
Positive	230	11.94	45	6.66	176	14.77
Missing	82		73		1,588	
Grade						
1	264	13.70	171	25.30	169	14.18
2	889	46.13	327	48.37	555	46.56
3	774	40.17	178	26.33	468	39.26
Missing	6		19		36	
NPI						
Low	601	31.19	297	43.93	333	27.94
Intermediate	935	48.52	283	41.86	579	48.57
High	391	20.29	96	14.20	280	23.49
Missing	38		118		43	
EvR	0.0252		0.0377		0.0423	

NOTE. In complete cases, the variable's size, No. of positive nodes, PR, HER2, and grade were available.

Abbreviations: IQR, interquartile range; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; NPI, Nottingham Prognostic Index; EvR, event rate.

sensitive to assess the usefulness of adding receptor information.[25,26] Therefore, the time-dependent receiver operating characteristic curve (tdROC),[27] which calculates the area under the ROC (AUC) at each time point for the categorized NPI and iNPI, was derived as a more important measure of discrimination. In addition, the three risk groups were summarized using event rates (EvR; ie, the number of observed events per person year).

The second level was risk stratification.[25] A prognostic model is clinically more relevant if it places more patients into the extreme risk groups in which treatment decisions are less ambiguous.[25,28] Therefore, we calculated the percentage of patients categorized into the low- and high-risk group (EXT%). A 95% CI on the difference between both models' performances was calculated with the bias corrected bootstrap method.[29]

All analyses were done on the complete cases. Afterward, the robustness of the obtained results were checked after imputing multiple missing values by assuming that these have occurred randomly conditional on the observed information. The development procedure was repeated on 100 imputed data sets.[30] The c-index, EvR, and EXT% were recalculated on 100 multiple imputation data sets for all three cohorts. No differences between these and the complete case analysis were noted. We therefore reported the results from the complete case analysis.

RESULTS

Leuven Study Population and NPI

Table 1 summarizes the descriptive statistics for the three complete case data sets. In the training set, the median age of patients in the study population was 57 years (range, 26 to 91), median NPI was 4.30 (range, 2.02 to 8.60), median tumor size was 2.0 cm (range, 0.1 to 16 cm), 37.4% of patients had positive lymph nodes. Tumors were low, intermediate, and high grade in 13.7%, 46.1%, and 40.2% of patients. According to NPI, 31.2%, 48.5%, and 20.3%, respectively, had a low, intermediate, and high risk of disease recurrence. In 86.9%, 75.5%, and 11.9% of the tumors ER, PR, and HER2 overexpression was detected, respectively. The event rate in the whole database equaled 0.025 patient years, meaning that we observed 0.025 events per patient year of follow-up (or, equivalently, 1 event per 40 patient years of follow-up). During the study period, with median follow-up of 66 months, 13.7% of patients showed a breast cancer–related event. A distant metastasis was observed in 202 patients and a local or contralateral event in 61 patients.

Incorporating ER, PR, and HER2 Into an Improved NPI

Stratification of NPI risk groups according to ER, PR, and HER2 indicated strong differences in DFS characteristics within NPI risk groups (Fig 1). Within the intermediate and high NPI risk group, DFS for ER-positive patients was significantly better than for ER-negative patients ($P < .001$ and $P = .010$ respectively). We did not make a comparison for the low-risk group due to the limited number of ER-negative patients. The same effect was observed for PR, with a significant difference in DFS according to PR in both intermediate ($P < .001$) and high ($P = .005$) risk groups. HER2 positivity increased the risk of relapse. For intermediate- and high-risk patients, DFS was significantly worse for HER2-positive than for HER2-negative patients ($P = .002$ and .003 respectively).

All three receptor variables were good univariate predictors of DFS ($P < .001$). In a multivariate analysis using Cox regression, we

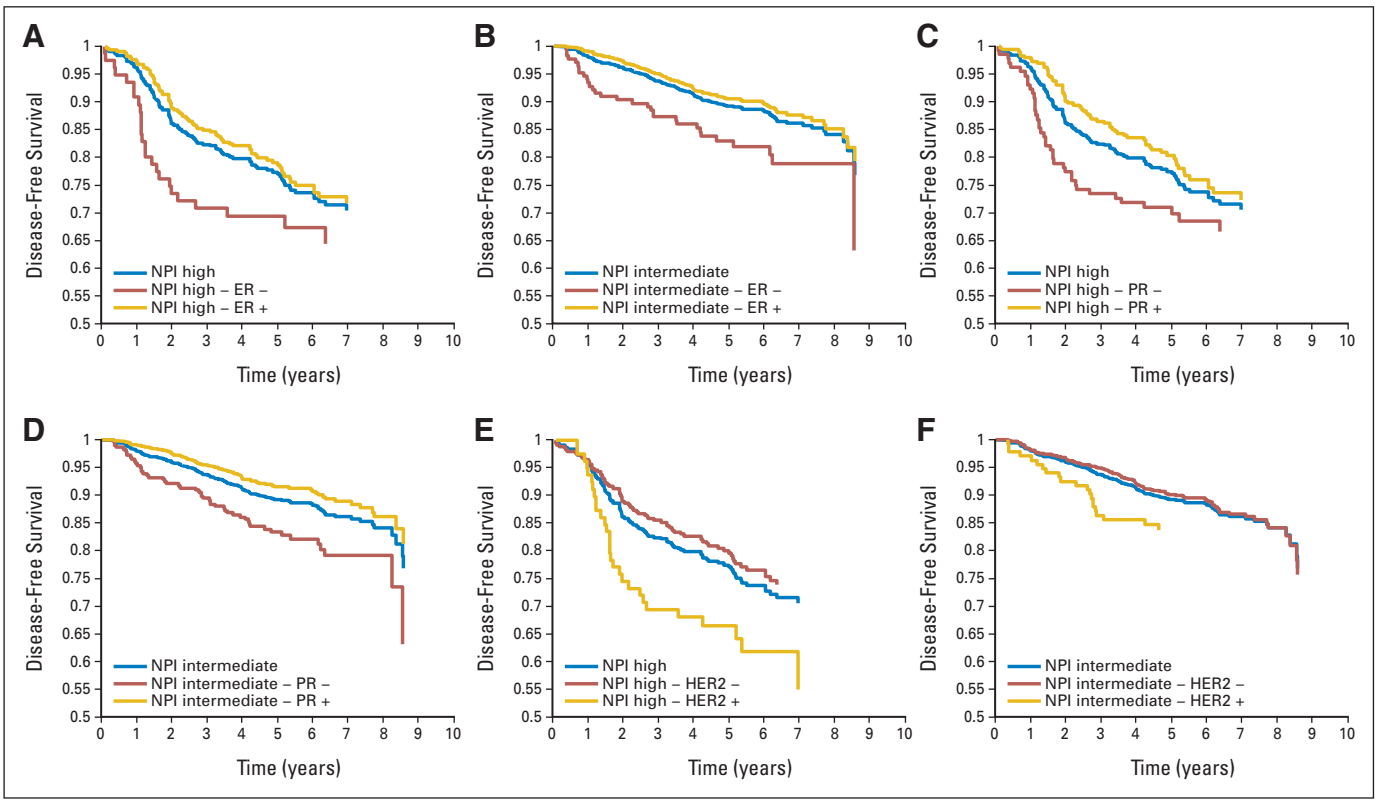

Fig 1. Survival curves within Nottingham Prognostic Index (NPI) risk groups, stratified for (A, B) estrogen receptor (ER), (C, D) progesterone receptor (PR), and (E, F) human epidermal growth factor receptor 2 (HER2). Within each NPI risk group, ER/PR positivity improved disease-free survival, while ER/PR negativity worsened survival. HER2 positivity worsened survival, while HER2 negativity improved survival.

observed that PR and HER2 gave independent prognostic information and could be added to the NPI for improved DFS predictions. We therefore selected NPI, PR, and HER2 as our final model with parameter estimates of 0.42 (SE, 0.05), −0.43 (SE, 0.13) and 0.37 (SE, 0.16), respectively. Since the parameter estimates of all three predictors were highly similar, the iNPI was calculated as the sum of the individual variables, taking the sign of the effect into account:

$$\text{iNPI} = \text{NPI} + \begin{cases} 1 \text{ if HER2 is positive} \\ -1 \text{ if PR is positive} \end{cases}$$

The optimal cutoffs, obtained with the 0.632+ bootstrap method, were 3.4 and 5.4. As a result, patients were categorized into low-, intermediate-, and high-risk groups for iNPI values below 3.4, between 3.4 and 5.4, and higher than 5.4, respectively. Since NPI and iNPI cutoffs are the same, patients can only shift between the NPI and the iNPI risk groups if they are PR+ HER2− or PR− HER2+. The PR+ HER2− patients remaining high risk according to the iNPI had an NPI score above 6.4.

Performance of NPI and iNPI on the Training and Validation Data

Tumors were PR+ and HER2+ in 77.5% and 6.7% in the Oslo cohort and in 61.5% and 14.8% in the Auckland cohort. Using the iNPI instead of the NPI reclassified 30.1%, 25.4%, and 23.5% of the patients from Leuven, Oslo, and Auckland, respectively. In all three cohorts, DFS for the low- and intermediate-risk groups according to NPI and iNPI were similar, although more patients were at low risk according to iNPI. DFS for the high-risk group was worse for iNPI than for NPI. The iNPI classified fewer patients as high risk. Figure 2, presenting Kaplan-Meier DFS curves for all groups defined by NPI-iNPI cross-classification, shows that the reclassification of most patients was in the appropriate direction. For each data set, the survival curves of reclassified patients resembled more closely those for patients in the same iNPI group than those for patients in the same NPI group. For example, in the Leuven data (Fig 2A) patient groups with an intermediate NPI risk have significantly different survival curves according to their iNPI risk ($P < .001$). On the contrary, intermediate iNPI patients have similar survival curves when stratifying according to their NPI risk ($P = .814$). This result is also observed in Oslo ($P = .037$ *v* .099; Fig 2B) and Auckland ($P = .014$ *v* .358; Fig 2C). Due to the relatively small number of patients reclassified from the low (NPI) to intermediate (iNPI) or from the high (NPI) to the intermediate (iNPI) risk groups, this test was only conducted within intermediate risk groups.

Figure 3 shows the tdROC curves and suggests that, in all three data sets, the iNPI is better than the NPI to separate relapsing from nonrelapsing patients over the whole follow-up period. Likewise, the c-index as well as the difference in EvR between high- and low-risk groups were slightly, but not significantly in the validation cohorts, higher for the iNPI than for the NPI (Table 2). Finally, EXT% was significantly higher for the iNPI, suggesting that the iNPI places an additional 10% to 15% of the patients in the low or high-risk groups compared to the NPI. Overall, discrimination tends to be slightly better for the iNPI, but this limited advantage in discrimination is accompanied with a large improvement in risk stratification.

DISCUSSION

The aim of this study was to improve the NPI for better predicting the 5-year DFS of operable breast cancers by incorporating ER, PR, and HER2. The principal finding was that the iNPI, a combination of NPI, PR, and HER2 expression, reclassified a substantial proportion of patients to another risk group for whom the DFS was significantly closer to the group they were shifted to than to the group they were shifted from. As compared with the low-risk NPI group, the low-risk iNPI group was larger and had a similar 5-year DFS. As compared with the high-risk NPI group, the high-risk iNPI group was smaller and had a worse 5-year DFS. The tdROC was higher for the iNPI than for the NPI.

The NPI divides operable patients with breast cancer into good, moderate, and poor prognostic groups with 15-year survival of 80%, 42%, and 13%, respectively.[32] Modification of the NPI by incorporating a correction for steroid receptor levels,[33] Bcl-2,[34,35] S phase function, urokinase type and plasminogen activator,[36] and Mcm-2[37] have previously been shown to provide a more accurate assessment of prognosis for most patients than the NPI alone. However, these findings still need to be reproduced in larger studies and their value relative to other markers remains to be established. Recently, the Nottingham group reported that PR is an NPI-independent predictor.[35] Hitherto, it had not been investigated on large patient cohorts whether the combination of HER2 and steroid receptors as short-term prognostic markers are NPI-independent prognostic factors.

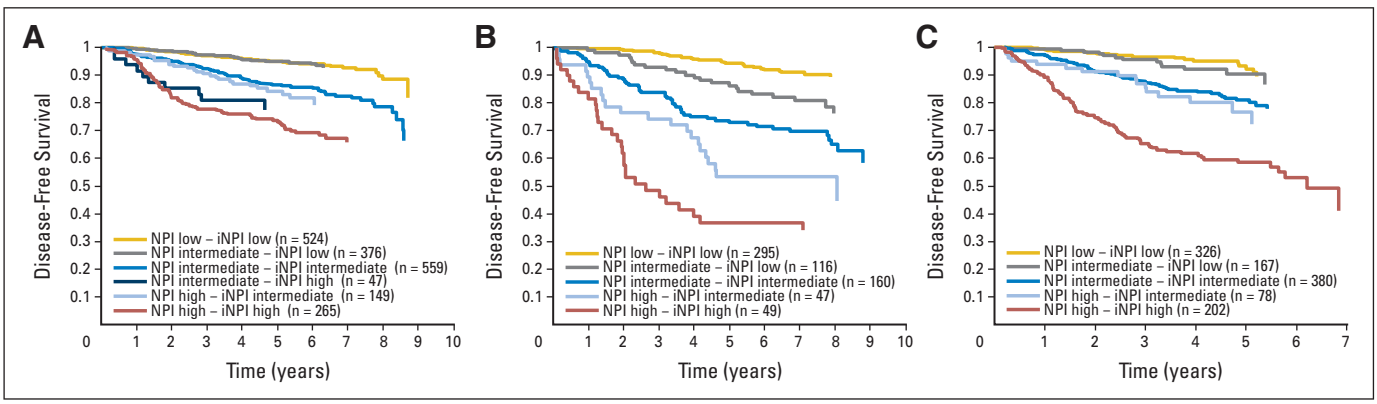

Fig 2. Survival curves according to Nottingham Prognostic Index (NPI) –improved NPI (iNPI) cross-classification. (A) Leuven cohort; (B) Oslo cohort; (C) Auckland cohort. Only groups containing more than 40 patients are shown. The three clusters show a clear separation in survival characteristics according to the iNPI group. Within the same NPI group, a large difference in survival was noted.

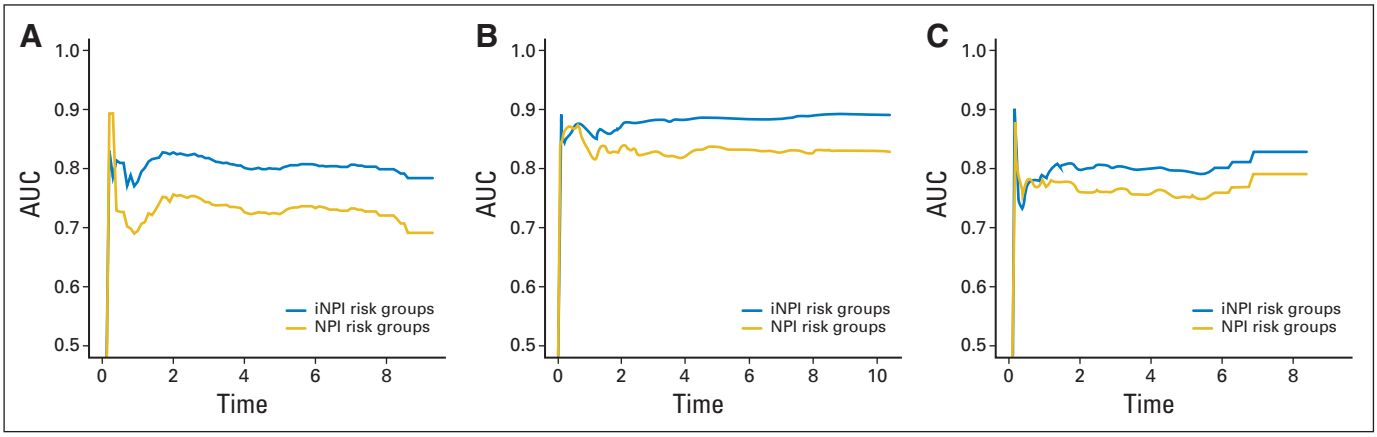

Fig 3. Time-dependent receiver operating characteristic (ROC) curves for Nottingham Prognostic Index (NPI) and improved NPI (iNPI; after categorization). (A) Leuven cohort; (B) Oslo cohort; (C) Auckland cohort. The curve for iNPI is higher than the curve for the NPI, indicating that the iNPI better separates relapsing from nonrelapsing patients. AUC, area under the (time-dependent ROC) curve.

We now report not only PR but also HER2 to be independent prognostic markers of NPI, adding on to its 5-year prognostic value. An interesting point that emerges from this work is that only two readily available markers improve prognostic outcome following breast cancer treatment. Gene expression array studies, in contrast, emphasize an approach that relies on the use of many genes to derive prognostic signatures, such as the 70-gene signature.[38] This signature seemed more powerful than traditional pathologic variables,[39] although these findings have not yet been widely validated, and some question their performance against the NPI.[40] It must be noted that the relative importance of a single prognostic marker compared with a panel of marker(s) will depend on the choice and the nature of the markers that are included in the analysis. Studies that analyze gene expression cannot be compared directly with those in which protein expression is studied and this may explain why many of the markers included in this study have not emerged as prognostic candidates in expression array studies. An obvious advantage of using immunohistochemistry is that it is relatively cheap and readily amenable to standardization in terms of methodology and interpretation, making it applicable for routine clinical use. However, immunohistochemistry is limited because an antibody may not detect all isoforms of a protein and this may be a source of contradictory reports about particular markers.[42]

Table 2. Measures of Model Performance of NPI and iNPI on the Training Data (Leuven) and Two External Validation Data Sets (Oslo and Auckland)

Measure	NPI	iNPI	95% CI for the Difference Between iNPI and NPI
Leuven			
c-index	0.6833	**0.6983**	0.0007 to 0.0282
EvR difference	0.0394	**0.0487**	0.0011 to 0.0178
EXT%	49.04	**62.90**	**0.1136 to 0.1614**
Oslo			
c-index	0.7447	**0.7549**	−0.0062 to 0.0282
EvR difference	0.1156	**0.1338**	−0.0204 to 0.0660
EXT%	58.14	**69.08**	**0.0710 to 0.1494**
Auckland			
c-index	0.7206	**0.7215**	−0.0120 to 0.0154
EvR difference	0.0865	**0.0882**	−0.0098 to 0.0174
EXT%	54.15	**64.22**	**0.0665 to 0.1178**

NOTE. For each measure, the best performing model is indicated in bold.
Abbreviations: NPI, Nottingham Prognostic Index; iNPI, improved Nottingham Prognostic Index; c-index, concordance index; EvR difference, difference in event rate in high- *v* low-risk patients; EXT%, percentage of patients classified into the most extreme risk groups.

Our data may be less relevant for a population of adjuvant trastuzumab–treated patients but this needs validation in such a group. Indeed, trastuzumab may wipe out the prognostic value of HER2. HER2 may also be of less prognostic value in anthracycline-treated patients when compared to cyclophosphamide, methotrexate, and fluorouracil–treated patients as anthracyclines are more effective if HER2 is overexpressed.[43] Type of chemotherapy was not considered and this may overestimate the prognostic value of HER2. In the University Hospitals Leuven, adjuvant CMF was given independent of HER2 status until 2003. Thereafter, we changed to anthracycline-containing regimen in almost all instances where chemotherapy was indicated based on the updated overview data of the Early Breast Cancer Trialists' Collaborative Group.

A prospective study including iNPI against a panel of potential prognostic and predictive molecular markers is needed. When different indices for breast cancer prognosis are studied, the NPI scored best with a 73% concordance rate with the 70-gene prognostic signature.[9] Whether any of the tested microarray gene expression profiling for breast cancer prognosis is better than an optimized panel of clinical, objectively measured, prognostic markers for adjuvant treatment remains an open question and is being explored in prospectively designed currently ongoing clinical trials like MINDACT (Microarray in Node-Negative Disease May Avoid Chemotherapy) and TAILOR-X (Trial Assigning Individualized Options for Treatment).

In summary, we were able to improve the prognostic assessment of patients with operable breast cancer by adding information on PR and HER2 to the NPI. Validation results indicate that 20% to 30% of patients' classification according to NPI and iNPI were discordant. Survival curves of reclassified patients resembled more closely those for patients in corresponding iNPI groups than those for patients in corresponding NPI groups. This reclassification resulted in an additional 10% of patients in the extreme risk groups, where clinical actions are less ambiguous. The number of patients within the intermediate-risk group is therefore significantly reduced.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Administrative support: Patrick Neven
Provision of study materials or patients: Vernon Harvey, Paula Murray, Björn Naume, Gro Wiedswang, Robert Paridaens, Philippe Moerman, Frederic Amant, Karin Leunen, Ann Smeets, Maria Drijkoningen, Hans Wildiers, Marie-Rose Christiaens, Ignace Vergote, Patrick Neven
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REFERENCES

1. Ferlay J, Autier P, Boniol M, et al: Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 18:581-592, 2007

2. Jemal A, Siegel R, Ward E, et al: Cancer statistics 2009. CA Cancer J Clin 59:225-249, 2009

3. Galea M, Blamey R, Elsto C, et al: The Nottingham Prognostic Index in primary breast cancer. Breast Cancer Res Treat 22:207-219, 1992

4. Lee AH, Ellis IO: The Nottingham prognostic index for invasive carcinoma of the breast. Pathol Oncol Res 14:116-115, 2008

5. D'Eredita G, Giardina C, Martellotta M, et al: Prognostic factors in breast cancer: The predictive value of the Nottingham Prognostic Index in patients with a long-term follow-up that were treated in a single institution. Eur J Cancer 37:591-596, 2001

6. Blamey RW, Ellis IO, Pinder SE, et al: Survival of invasive breast cancer according to the Nottingham Prognostic Index in cases diagnosed in 1990-1999. Eur J Cancer 43:1548-1555, 2007

7. Bueno-de-Mesquita J, van Harten W, Retel V, et al: Use of 70-gene signature to predict prognosis of patients with node-negative breast cancer: A prospective community-based feasibility study (RASTER). Lancet Oncol 8:1079-1087, 2007

8. Liu R, Wang X, Chen GY, et al: The prognostic role of a gene signature from tumorigenic breast-cancer cells. N Engl J Med 356:217-226, 2007

9. Neven P, Van Belle V, Brouckaert O, et al: Are gene signatures better than traditional clinical factors? Lancet Oncol 9:197-198, 2008

10. Slamon DJ, Clark GM, Wong SG, et al: Human breast cancer: Correlation of relapse and survival with amplification of the HER2/neu oncogene. Science 235:177-182, 1987

11. Ross J, Fletcher J: The HER2/neu oncogene in breast cancer: Prognostic factor, predictive factor and target for therapy. Oncologist 3:237-252, 1998

12. Pichon M, Broet P, Magdelenat H, et al: Prognostic value of steroid receptors after long-term follow-up of 2257 operable breast cancers. Br J Cancer 73:1545-1551, 1996

13. Cui X, Schiff R, Arpino G, et al: Biology of progesterone receptor loss in breast cancer and its implications for endocrine therapy. J Clin Oncol 23:7721-7735, 2005

14. Collett K, Skjaerven R, Maehle B: The prognostic contribution of estrogen and progesterone receptor status to a modified version of the Nottingham Prognostic Index. Breast Cancer Res Treat 48:1-9, 1998

15. Dunnwald LK, Rossing MA, Li CI: Hormone receptor status, tumor characteristics, and prognosis: A prospective cohort of breast cancer patients. Breast Cancer Res 9:R6, 2007

16. De Maeyer L, Van Limbergen E, De Nys K, et al: Does estrogen receptor negative/progesterone receptor positive breast carcinoma exist? J Clin Oncol 26:335-336, 2008

17. Elston C, Ellis I: Pathological prognostic factors in breast cancer: The value of histological grade in breast cancer: Experience from a large study with long-term follow-up. Histopathology 19:403-410, 1991

18. Brouckaert O, Pintens S, Van Belle V, et al: Short-term outcome of primary operated early breast cancer by hormone and HER2 receptors. Breast Cancer Res Treat 115:349-358, 2009

19. Wolff AC, Hammond ME, Schwartz JN, et al: American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 25:118-145, 2007

20. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

21. Cox DR: Regression models and life-tables (with discussion). Journal of the Royal Statistical Society 34:197-220, 1972

22. Schwarz G: Estimating the dimension of a model. Annals of Statistics 6:461-464, 1978

23. Efron B, Tibshirani RJ: Improvements on cross-validation: The 632+ bootstrap method. J Am Stat Asso 92:548-560, 1997

24. Harrell F, Klee K, Califf R, et al: Regression modeling strategies for improved prognostic prediction. Stat Med 95:634-635, 1984

25. Janes H, Pepe M, Gu W: Assessing the value of risk predictions by using risk stratification tables. Ann Intern Med 149:751-760, 2008

26. Pencina M, D' Agostino R Sr, D' Agostino R Jr, et al: Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. Stat Med 27:157-172, 2008

27. Heagerty P, Lumley T, Pepe M: Time-dependent roc curves for censored survival data and a diagnostic marker. Biometrics 56:337-344, 2000

28. Graf E, Schmoor C, Sauerbrei W, et al: Assessment and comparison of prognostic classification schemes for survival data, Stat Med 18:2529-2545, 1999

29. Efron B, Tibshirani R: Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. Statistical Science 1:54-75, 1986

30. Siddique J, Harel O: MIDAS: A SAS macro for multiple imputation using distance-aided selection of donors. Journal of Statistical Software, American Statistical Association 29:1-18, 2009

31. Reference deleted

32. Rampaul RS, Pinder SE, Elston CW, et al: Prognostic and predictive factors in primary breast cancer and their role in patient management: The Nottingham Breast Team. Eur J Surg Oncol 27:229-238, 2001

33. Hawkins RA, Tesdale AL, Prescott RJ, et al: Outcome after extended follow-up in a prospective study of operable breast cancer: Key factors and a prognostic index. Br J Cancer 87:8-14, 2002

34. Charpin C, Garcia S, Bonnier P, et al: Bcl-2 automated quantitative immunocytochemical assays in breast carcinomas: Correlation with 10-year follow-up. J Clin Oncol 16:2025-2031, 1998

35. Callagy GM, Pharoah PD, Pinder SE, et al: Bcl-2 is a prognostic marker in breast cancer independently of the Nottingham Prognostic Index. Clin Cancer Res 12:2468-2475, 2006

36. Malmstrom P, Bendahl PO, Boiesen P, et al: S-phase fraction and urokinase plasminogen activator are better markers for distant recurrences than Nottingham Prognostic Index and histologic grade in a prospective study of premenopausal lymph node-negative breast cancer. J Clin Oncol 19:2010-2019, 2001

37. Gonzalez MA, Pinder SE, Callagy G, et al: Minichromosome maintenance protein 2 is a strong independent prognostic marker in breast cancer. J Clin Oncol 21:4306-4313, 2003

38. van't Veer LJ, Dai H, van de Vijver MJ, et al: Gene expression profiling predicts clinical outcome of breast cancer. Nature 415:530-536, 2002

39. van de Vijver MJ, He YD, van't Veer LJ, et al: A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 347:1999-2009, 2002

40. Eden P, Ritz C, Rose C, et al: "Good Old" clinical markers have similar power in breast cancer prognosis as microarray gene expression profilers. Eur J Cancer 40:1837-1841, 2004

41. Reference deleted

42. Keyomarsi K, Tucker SL, Buchholz TA, et al: Cyclin E and survival in patients with breast cancer. N Engl J Med 347:1566-1575, 2002

43. Pritchard KI, Shepherd L, O'Malley FP, et al: HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med 354:2103-2111, 2006

