

Cross-Stratification and Differential Risk by Breast Cancer Index and Recurrence Score in Women with Hormone Receptor-Positive Lymph Node-Negative Early-Stage Breast Cancer

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Abstract

Purpose: Previous results from the TransATAC study demonstrated that both the Breast Cancer Index (BCI) and the OncotypeDX Recurrence Score (RS) added significant prognostic information to clinicopathologic factors over a 10-year period. Here, we examined cross-stratification between BCI and RS to directly compare their prognostic accuracy at the individual patient level.

Experimental Design: A total of 665 patients with hormone receptor-positive (HR⁺) and lymph node-negative disease were included in this retrospective analysis. BCI and RS risk groups were determined using predefined clinical cut-off points. Kaplan-Meier estimates of 10-year risk of distant recurrence (DR) and log-rank tests were used to examine cross-stratification between BCI and RS.

Results: As previously reported, both RS and BCI were significantly prognostic in years 0 to 10. BCI provided significant additional prognostic information to the Clinical Treatment Score

(CTS) plus RS ($\Delta\text{LR-}\chi^2 = 11.09$; $P < 0.001$), whereas no additional prognostic information was provided by RS to CTS plus BCI ($\Delta\text{LR-}\chi^2 = 2.22$; $P = 0.1$). Restratification by BCI of the low and intermediate RS risk groups led to subgroups with significantly different DR rates ($P < 0.001$ and $P = 0.003$, respectively). In contrast, restratified subgroups created by RS of BCI risk groups did not differ significantly.

Conclusions: In this retrospective analysis, BCI demonstrated increased prognostic accuracy versus RS. Notably, BCI identified subsets of RS low and RS intermediate risk patients with significant and clinically relevant rates of DR. These results indicate that additional subsets of women with HR⁺, lymph node-negative breast cancer identified by BCI may be suitable candidates for adjuvant chemotherapy or extended endocrine therapy. *Clin Cancer Res*; 22(20); 1–6. ©2016 AACR.

See related commentary by Brufsky and Davidson, p. 4963

Introduction

Breast cancer is the most common cancer and the second leading cause of cancer-related death in women worldwide (1). As a result of significant advancements in the molecular characterization of breast cancer etiology, clinical management has evolved to include a comprehensive assessment of the underlying biology of the patient's tumor alongside the clinicopathologic paradigm to determine treatment strategies (2, 3). The ongoing challenge in breast cancer is the effective treatment of a heterogeneous disease associated with a wide spectrum of morphologic and molecular subtypes with variable outcomes (3).

Genomic tools and expression-based multigene signatures have increased prognostic information for early-stage breast

cancer patients beyond traditional clinicopathologic factors (4–6). The 21-gene-based Recurrence Score (OncotypeDX; RS) is a well-established multigene assay, which was developed to assess the risk of distant recurrence (DR) in women with hormone receptor-positive (HR⁺), node-negative breast cancer treated with tamoxifen (7). The RS classifies women into low (RS < 18), intermediate (RS, 18–30), and high (RS > 30) risk groups for DR. The RS has been validated and evaluated in a number of clinical trials, and results confirm the prognostic value of RS beyond that of clinical parameters for DR in the first 5 years after diagnosis (7–9). The Breast Cancer Index (BCI) is a second-generation gene expression signature developed from the combination of two biomarkers: the HOXB13:IL17BR expression ratio (H/I) and the molecular grade index (MGI; ref. 10). H/I is a biomarker that is associated with tumor responsiveness to endocrine therapy in breast cancer (10, 11). MGI consists of the average expression of five cell cycle-associated genes and provides quantitative and objective molecular assessment of tumor grade and proliferative status (10, 12). The linear, but not cubic, BCI score provides an estimate for a patient's risk for DR and stratifies patients into different risk groups in the early (year 0–5), late (year 5–10), and overall (year 0–10) time periods (10, 13).

In a previous study, the linear BCI score was shown to provide more prognostic information for DR than RS (13). However, in women with discrepant scores, their values have not been evaluated to date. Here, we investigate the comparative prognostic

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Translational Relevance

This is the first study to examine the ability of the Breast Cancer Index (BCI) to reclassify distant recurrence risk groups for distant recurrence by the Oncotype Recurrence Score (RS). The study was conducted in a set of 665 postmenopausal women with lymph node–negative, hormone receptor–positive breast cancer treated with either tamoxifen or anastrozole alone. Our results show that the BCI reclassifies women with low or intermediate risk for distant recurrence by the RS into clinically relevant different risk groups with significantly different risk of distant recurrence at 10 years of follow-up. In contrast, the RS did not significantly reclassify any patients into different risk categories. Our results showed that the prognostic value of BCI may have potential clinical impact in terms of improving individualized risk stratification for patients with lymph node–negative early-stage breast cancer.

strength, agreement, and clinical significance of cross-stratification by the RS and BCI.

Materials and Methods

Study population

The translational Arimidex, Tamoxifen Alone or Combination (TransATAC) study collected formalin-fixed paraffin-embedded (FFPE) blocks from women with HR⁺ breast cancer who did not receive chemotherapy as part of their initial treatment and who were randomized to either anastrozole or tamoxifen (14). For this analysis, only women with lymph node–negative disease and data on both molecular scores have been included ($N = 665$) with a median follow-up of 10 years.

Analytic methods

Analytic methods for RS and BCI (linear model) have been described in detail previously (5, 6, 14). In brief, RNA was extracted from FFPE primary tumor specimens by Genomic Health and gene expression analysis for both scores was done by real-time RT-PCR blinded to patients' clinical outcomes. Risk stratification with RS and BCI was based on prespecified cut-off points for 10-year risk of DR: RS <18, low risk; 18–31, intermediate risk; >31, high risk; and BCI: <5.0825, low risk; 5.0825–6.5025, intermediate risk; >6.5025, high risk.

Statistical analyses

The primary objective of this analysis was to determine the differential risk of DR for women with discrepant RS and BCI scores. The primary endpoint for the comparison was time to DR with death before DR being treated as a censoring event. The association between the risk score/categories and DR was assessed using HRs derived from Cox proportional hazard models with associated 95% confidence intervals (CI). HRs for the continuous risk scores were computed for a difference between the 25th and 75th percentile of the continuous scores [interquartile (IQR) HR].

For multivariate analyses, each score was combined with the CTS (an algorithm combining nodal status, tumor size, grade, age, and treatment) to determine the added prognostic information in that score. Changes in likelihood ratio Chi-Square values ($\Delta\text{LR-}\chi^2$) were used to measure and compare the relative amount of information of one score compared with the

other. P values were two sided, based on normal approximation, and all CIs were at the 95% level. Analyses were performed using STATA version 13.1.

Results

A total of 665 postmenopausal women with HR⁺, lymph node–negative disease have been included in this retrospective analysis. Of these, 72 (10.8%) had a DR before 10 years of follow-up. Detailed baseline characteristics for this study group have been published previously (13). In brief, median age was 62.4 years (IQR, 46.7–88.4); most women had moderately differentiated tumors (51.7%) and tumor size ≤ 2 cm (73.1%).

Table 1 shows HRs and prognostic information provided ($\text{LR-}\chi^2$) by each score and in addition to the CTS and the other score ($\Delta\text{LR-}\chi^2$). There was a significant effect of adding BCI to CTS plus RS ($\Delta\text{LR-}\chi^2 = 11.09$, $P = 0.0009$), whereas no additional prognostic information to the CTS plus BCI was added by the RS ($\Delta\text{LR-}\chi^2 = 2.22$, $P = 0.1$). Table 2 shows the cross-stratification by RS and BCI into the respective risk groups. Overall, BCI classified fewer women into intermediate risk (25.0% vs. 26.8%) but more patients into high risk than RS (16.4% vs. 14.9%). In total, 283 (42.6%) women were classified into the low, 49 (7.4%) into the intermediate, and 55 (8.3%) into high risk groups by both BCI and RS, leading to a concordance of 58.2% between RS and BCI risk categories (Table 2). Among the 278 (41.8%) discordant cases, 24.4% of BCI low risk patients were reclassified into RS-intermediate and 3.1% into RS-high risk groups (Table 2). In contrast, BCI reclassified 21.9% and 5.2% of RS-low risk patients as BCI-intermediate and BCI-high risk, respectively (Table 2).

The comparison of prognostic accuracy of RS and BCI was further assessed by Kaplan–Meier analysis. Figures 1 and 2 show cumulative Kaplan–Meier curves for 10-year DR rates for the cross-classification between RS and BCI risk groups. BCI reclassified both RS-low and RS-intermediate patients further into risk subsets with significantly differential risk of DR ($\text{LR-}\chi^2 = 14.64$, $P < 0.001$ and $\text{LR-}\chi^2 = 11.75$, $P = 0.003$, respectively; Fig. 1A and B). Among the 388 women categorized by RS as low risk, 20 women were reclassified as being high risk by BCI and had a DR risk of 23.3% by 10 years, which incurs a 7 times higher risk of DR compared with those reclassified as the BCI-low risk group [HR = 6.77 (2.12–21.58); Fig. 1A]. Those reclassified into the intermediate risk group by BCI had a three times higher risk of DR than those in the low RS risk group [HR = 2.94 (1.16–7.46)] with a 10-year risk of DR of 12.2% (Fig. 1A). Similarly, among the 178 women classified by RS as intermediate risk, 95 women were downgraded to low risk by BCI with a 10-year DR risk of 7.1% in contrast to 34 women who were upgraded to high risk by BCI with a 10-year DR risk of 27.8% (Fig. 1B). Among women classified by RS as intermediate risk, those classified by BCI as intermediate or high risk group had a 4 to 5 times actual higher risk of DR by 10 years than those classified by BCI as low risk [HR = 3.80

Table 1. HR and LR tests for BCI and RS ($\text{LR-}\chi^2$) in the univariate analysis and for both scores when added to the CTS and other score ($\Delta\text{LR-}\chi^2$) in the multivariable analysis

	HR (95% CI)	LR- χ^2 (P)
RS	1.64 (1.39–1.94)	25.16 (<0.0001)
BCI	3.24 (2.31–4.54)	48.96 (<0.0001)
		$\Delta\text{LR-}\chi^2$ (P)
CTS + RS + BCI	2.00 (1.32–3.05)	11.09 (0.0009)
CTS + BCI + RS	1.20 (0.95–1.50)	2.22 (0.1)

Table 2. Cross-stratification of women into respective risk groups by RS and BCI

BCI	RS			Total
	Low	Intermediate	High	
Low	283	95	12	390
Intermediate	85	49	32	166
High	20	34	55	109
Total	388	178	99	665

NOTE: Gray shaded areas, reclassified into higher risk groups by BCI; blue shaded areas, reclassified into lower risk groups by BCI.

(1.40–10.27) and HR = 4.83 (1.72–13.59), respectively; Fig. 1B]. Among the 99 women categorized by RS as high risk, 12 were reclassified by BCI as low risk with a nonsignificantly lower risk of DR than those in the intermediate and higher risk groups (Fig. 1C). However, no significant reclassification of any of the BCI risk groups by the RS was observed in terms of 10-year DR risk (Fig. 2).

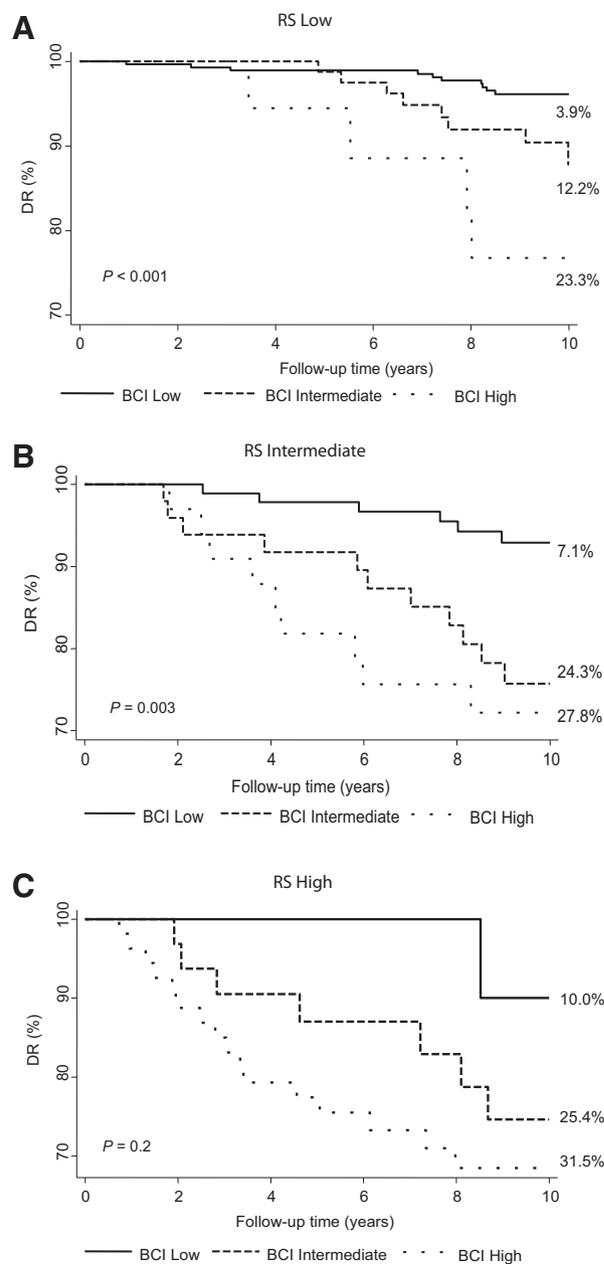
Discussion

We previously reported (13), that the linear BCI added significant prognostic information for DR beyond that of clinical parameters and the *OncotypeDx* RS in HR⁺, lymph node–negative breast cancer (13). Our results showed that BCI recategorized patients within low and intermediate RS risk groups in a statistically significant manner. In contrast, RS did not significantly reclassify any of the risk groups identified by BCI.

BCI is a gene expression–based signature that algorithmically integrates the differential expression of 5 cell cycle–related genes (MGI) and the expression ratio of H/I (10). BCI has been shown to be a significant prognostic factor in women with HR⁺, lymph node–negative disease for both early (0–5 years) and late (5–10 years) follow-up periods (10, 13). RS is based on a 21-gene signature that was developed in a tamoxifen-treated, lymph node–negative population and is in part driven by proliferation genes (7, 15). The RS has shown to be a strong prognostic marker, particularly in the early follow-up period (0–5 years; ref. 16). Although functionally similar in the ability of the two scores to profile mitogenic activity, there is no overlap in the gene characteristics between RS and BCI. The correlation between BCI and RS or CTS was weak ($\rho = 0.49$, $\rho = 0.45$, respectively), and therefore, the significant additional prognostic information shown in our analysis by BCI is not accounted for by either clinical parameters or RS. Some comparative studies have shown that multigene signatures provide comparable prognostic performance despite modest overlap (17, 18). However, these studies utilized public microarray datasets derived from tumor bank specimens, which may present selection bias with respect to the intended patient population. Here, we assessed the genomic signatures at the individual patient level data with clinical outcome from the TransATAC study.

Results of this study may have implications for clinical decision making related to early-stage breast cancer and potential disease management. For example, patients in the RS low risk group are generally considered to have a favorable prognosis with 5 years of endocrine therapy alone and are unlikely to benefit from adjuvant chemotherapy (7, 8). Recent data from the TAILORx trial have confirmed the excellent prognosis for patients with the lowest RS scores (0–10) over the first 5 years postdiagnosis (19). However, in the current study, BCI identified approximately 22% of RS low risk patients as intermediate risk and 5% as high risk. These findings suggest that a significant proportion of RS low risk

patients are at an elevated risk of late recurrence and may benefit from extended endocrine therapy. Notably, the H/I component of the BCI test has been shown to be predictive of benefit from extended endocrine therapy in the MA.17 trial (11). BCI also recategorized women who were classified by RS into the high risk into a low risk group. Although some of these women had large and poorly differentiated tumors, the low risk of DR overall is an indication that the benefit of additional endocrine or adjuvant chemotherapy is uncertain in this group. We have previously published data on cross-classification by the CTS and PAM50

**Figure 1.**

Kaplan–Meier analysis for 10-year DR rates in BCI risk groups within RS-low ($N = 388$; **A**), RS-intermediate ($N = 178$; **B**), and RS-high ($N = 99$; **C**) risk groups. DR differences were evaluated by log-rank test.

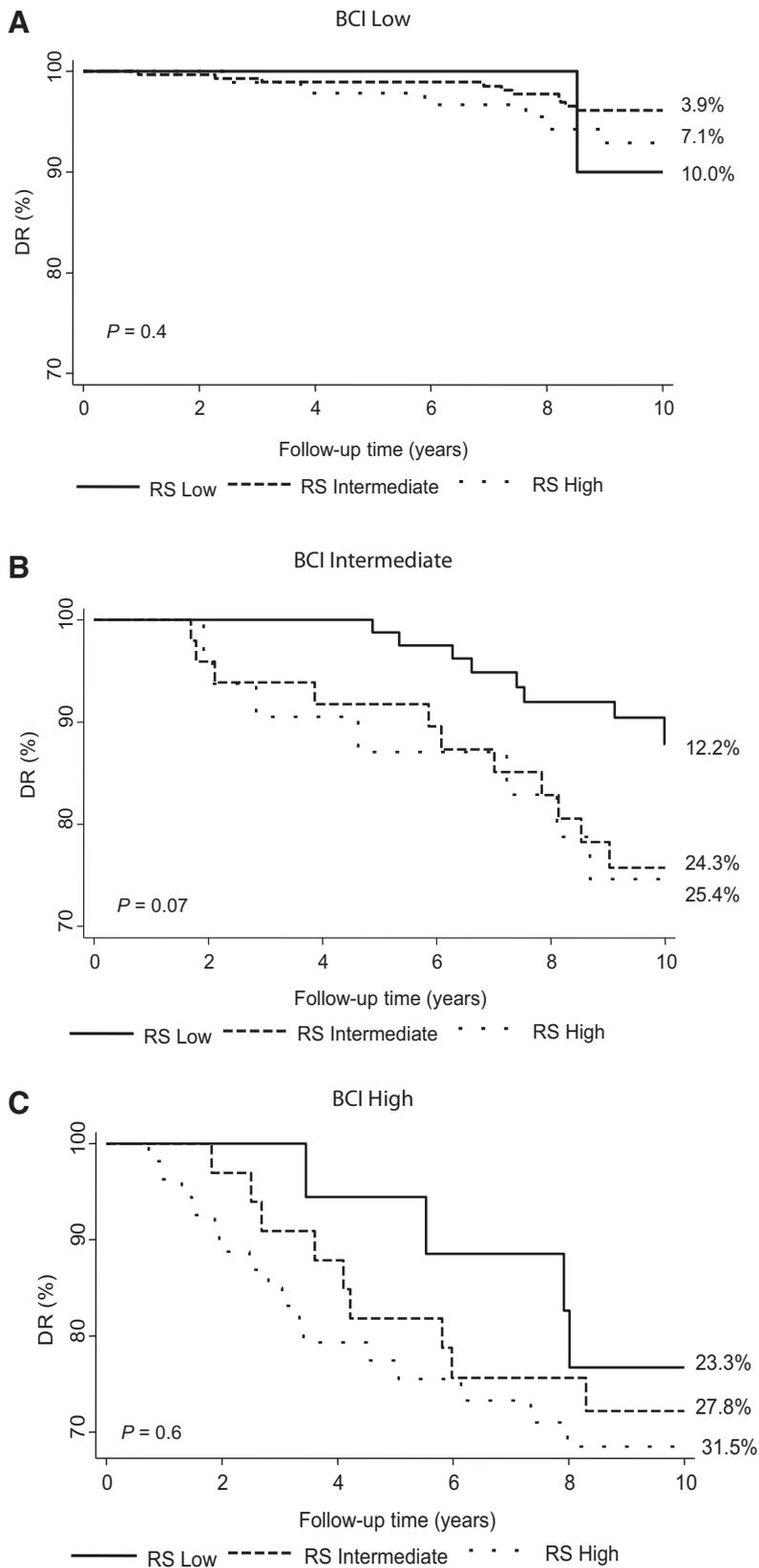


Figure 2. Kaplan–Meier analysis for 10-year DR rates in RS risk groups within BCI-low ($N = 390$; **A**), BCI-intermediate ($N = 166$; **B**), and BCI-high ($N = 109$; **C**) risk groups. DR differences were evaluated by log-rank test.

ROR in the TransATAC study (20) where the ROR categorized more women into the high risk group than the CTS alone. Both of these findings suggest the importance of nonclinical tumor characteristics, such as biology of these tumors, that need to be taken into account when assessing DR risk, specifically after 5 years of endocrine treatment (16). Finally, BCI significantly reclassified the RS intermediate risk group, a categorization that presents challenges for clinical decision making, identifying approximately half of these patients as having a low risk of recurrence and half with an elevated risk of recurrence. Of note, the subset of patients reclassified by BCI as intermediate or high risk appeared to have an elevated risk for both early and late recurrences, in contrast to those categorized to low risk groups by BCI. Although not evaluated in this study, these results suggest a potential role for both adjuvant chemotherapy and extended endocrine therapy that should be evaluated in future studies. RS cross stratification of the BCI intermediate risk group resulted in a trend toward statistical significance, with approximately half of patients downgraded to RS low risk.

Strengths of this analysis are the large sample size of women with lymph node-negative disease, with a median follow-up of 10 years. Furthermore, this patient population comes from a well-described clinical trial using both tamoxifen and anastrozole. Our study has limitations. Only a subset of the patients from the main ATAC trial were included in this analysis ($N = 665$), of whom 10.8% had a DR. Second, none of these women received chemotherapy and therefore our results may not apply to chemotherapy-treated women. Of note, patients with a high RS would receive adjuvant chemotherapy and therefore have a lower risk of DR. Finally, this analysis focused on women with lymph node-negative disease, and therefore, our results are not applicable to women with lymph node-positive disease.

In summary, this study confirmed that linear BCI provided statistically significant prognostic information in addition to traditional clinical factors and RS in women with HR⁺, lymph node-negative disease treated with adjuvant endocrine therapy. New findings from this analysis are that the BCI reclassifies quite a few women into different risk categories than RS and that these

reclassifications were associated with substantial differences in patient outcomes. Therefore, our findings on the prognostic value of BCI may have potential clinical impact with respect to improving individualized risk stratification for patients with lymph node-negative early-stage breast cancer.

Disclosure of Potential Conflicts of Interest

Y. Zhang and C.A. Schnabel have ownership interest (including patents) in bioTheranostics. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Zhang, B.E. Schroeder, C.A. Schnabel, M. Dowsett

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): I. Sestak, Y. Zhang, B.E. Schroeder, C.A. Schnabel, M. Dowsett, J. Cuzick

Writing, review, and/or revision of the manuscript: I. Sestak, Y. Zhang, B.E. Schroeder, C.A. Schnabel, M. Dowsett, J. Cuzick, D. Sgroi

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