



# Predictive value of the Theros Breast Cancer Index (TBCI) for distant recurrence and overall survival (OS) in comparison to Adjuvant! Online and clinicopathologic characteristics in women with lymph node (LN)-negative, ER-positive breast cancer (BCa).

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## Abstract

**Background:** Gene expression profiles may have higher predictive power for relapse over traditional clinicopathologic prognostic factors. TBCI combines the 2-gene index HOXB13:IL17BR and a 5-gene Molecular Grade Index (MGI) and is a continuous predictor of individual risk of distant recurrence. Adjuvant! Online (AO), a web-based actuarial tool, predicts 10-year BCa recurrence and OS based on clinical patient and tumor characteristics and treatment. We sought to determine if TBCI provided additional predictive power for recurrence and OS over AO.

**Methods:** This was a single-institution, retrospective study. Tumor tissue from 262 patients with ER(+), LN(-) BCa with at least 10 year follow up was assessed by a pathologist (for verification of histologic grade and ER status) and then evaluated using the TBCI assay. AO was used to predict risk of relapse for each patient. Results were correlated to distant recurrence and overall survival. Statistical analysis to compare prognostic utility of TBCI and AO was conducted according to a pre-specified analysis plan using pre-determined models and cutoffs.

**Results:** In univariate analysis, both TBCI and AO were highly significant predictors of recurrence and death, and the association remained significant for TBCI after adjusting for other standard variables (age, tumor size, grade and treatment). In a multivariate model of TBCI and AO together, TBCI predicted recurrence with a hazard ratio (HR) of 2.46 [1.49-4.05] ( $p < 0.001$ ), and AO predicted recurrence with an HR of 1.35 [1.09-1.69] ( $p < 0.01$ ). TBCI predicted overall survival with a hazard ratio (HR) of 3.08 [1.81-5.24] ( $p < 0.0001$ ), and AO predicted overall survival with a HR of 1.31 [0.97-1.79] ( $p = 0.08$ ).

**Conclusions:** TBCI predicted BCa recurrence and OS more accurately than AO and traditional clinical and pathologic features. TBCI and AO both retained predictive significance in a multivariate analysis of recurrence, indicating that they can provide complementary information.

## Background

Recent studies of gene expression profiles suggest their higher predictive power for relapse over the traditional clinicopathologic predictors of recurrence (grade, stage, tumor size, etc) that are incorporated into the AO predictive model.

TBCI combines the 2-gene index HOXB13:IL17BR and a 5-gene Molecular Grade Index (MGI) and is a continuous predictor of individual risk of distant recurrence.

We sought to determine if TBCI provided additional predictive power for recurrence and OS over AO.

**Statistical Analysis:** Kaplan-Meier analysis with log-rank test and Cox proportional hazard regression were performed to assess the association of Breast Cancer Index (BCI) and Adjuvant! Online (AO) with both distant recurrence and overall survival. Multivariate Cox regression models were performed to assess the prognostic capacity of BCI after adjusting for known prognostic factors.

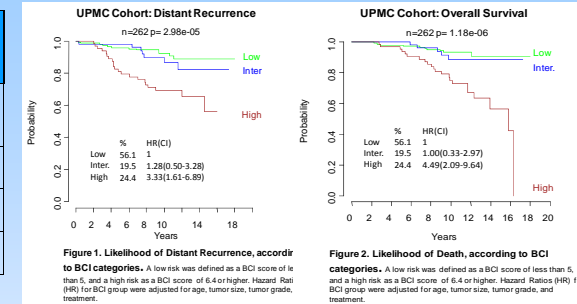
Description	Mean	All (n=262)
Age		56.2
	Range	25 - 81
	< 50	80(31%)
	>=50	182(69%)
Tumor Grade		66(25%)
	1	155(59%)
	2	41(16%)
	3	41(16%)
Tumor Size	Mean	1.67
	Range	0.1-10
	< 2 cm	187 (71%)
	>= 2 cm	75 (29%)
Treatment	Tam	173(66%)
	Tam + Chemo	89(34%)
Recurrence Follow-up (years)	Mean	10.22
	Range	0.23 - 17.99
Recurrence Event	No	222 (84.7%)
	Yes	40 (15.3%)
Overall Follow-up (years)	Mean	10.86
	Range	2.29 - 17.99
Death Event	No	225 (86%)
	Yes	37 (14%)

Univariate	P value	Hazard Ratio (95% CI)
BCI	6.3e-05	2.71 (1.66-4.1) <sup>‡</sup>
Adjuvant! Online	4.7e-04	1.46 (1.18-1.81) <sup>‡</sup>
Multivariate without BCI		
Age (>= 50 vs. < 50)	0.11	1.83 (0.87-3.85)
Tumor Size (>= 2cm vs. < 2cm)	0.44	1.30 (0.66-2.57)
Tumor Grade	0.0185	
	2 vs. 1	0.056
	3 vs. 1	0.0063
Treatment ( Tam + chemo vs. Tam)	0.022	2.28 (1.12-4.62)
Multivariate with BCI		
Age (>= 50 vs. < 50)	0.14	1.77 (0.83-3.77)
Tumor Size (>= 2cm vs. < 2cm)	0.66	1.17 (0.59-2.31)
Tumor Grade	0.037	
	2 vs. 1	0.067
	3 vs. 1	0.012
Treatment ( Tam + chemo vs. Tam)	0.048	2.08 (1.01-4.29)
BCI	6.4e-04	2.55 (1.49-4.37)
Multivariate with only BCI and Adjuvant! Online		
Adjuvant! Online	0.0069	1.35 (1.09-1.69)
BCI	4.1e-04	2.46 (1.49-4.05)

Risk Category	Percentage of Patients	Rate of Distant Recurrence at 10 Years (95% CI)
Low	56.1%	7.49(4.06-13.60)
Intermediate	19.47%	13.28(6.09-27.62)
High	24.43%	30.7(20.77-43.87)

<sup>‡</sup>The hazard ratios in tables 3 and 4 calculated for BCI and Adjuvant! Online are relative to an increment of their inter-quartile ranges, 3.482 for BCI, 5 for Adjuvant! Online, respectively.

Univariate	P value	Hazard Ratio (95% CI)
BCI	7.5e-06	3.27 (1.95-5.49) <sup>‡</sup>
Adjuvant! Online	0.0078	1.48 (1.11-1.98) <sup>‡</sup>
Multivariate without BCI		
Age (>= 50 vs. < 50)	0.012	3.11 (1.28-7.53)
Tumor Size (>= 2cm vs. < 2cm)	1.00	1.00 (0.49-2.06)
Tumor Grade	0.012	
	2 vs. 1	0.27
	3 vs. 1	0.0083
Treatment ( Tam + chemo vs. Tam)	0.16	1.70 (0.81-3.56)
Multivariate with BCI		
Age (>= 50 vs. < 50)	0.018	2.97 (1.21-7.28)
Tumor Size (>= 2cm vs. < 2cm)	0.65	0.85 (0.41-1.75)
Tumor Grade	0.026	
	2 vs. 1	0.29
	3 vs. 1	0.015
Treatment ( Tam + chemo vs. Tam)	0.20	1.64 (0.77-3.49)
BCI	3.2e-05	3.28 (1.87-5.74)
Multivariate with only BCI and Adjuvant! Online		
Adjuvant! Online	0.081	1.31 (0.97-1.79)
BCI	3.3e-05	3.08 (1.81-5.24)



## Conclusions

- Both BCI and AO were highly significant predictors of distant recurrence and death.
- In combination, BCI and AO provide complementary information in association with distant recurrence ( $p < 0.001$  for BCI,  $p < 0.01$  for AO).
- In combination, AO becomes non-significant for predicting overall survival and BCI remains highly significant ( $p < 0.0001$ ).
- BCI remains highly significant for distant recurrence ( $p < 0.001$ ) and overall survival ( $p < 0.0001$ ) after adjusting for age, tumor size, tumor grade and treatment.

