# Correlation of Breast Cancer Index (BCI) Risk Classification with Tumor Grade and Ki-67 in a Large Series of Patients with Early-stage, ER+ Breast Cancer

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## INTRODUCTION

- Breast Cancer Index (BCI) is a gene expression-based assay that reports both prognostic and predictive results for patients with early-stage, ER+ breast cancer.[1-3]
- BCI Predictive is based on the HoxB13/IL17BR (H/I) ratio, an endocrine response biomarker, and has been demonstrated to predict likelihood of benefit from extended endocrine therapy.[3]
- BCI Prognostic is based on the algorithmic combination of H/I and a set of proliferation-based genes (molecular grade index, MGI), and has been shown to significantly stratify patients based on risk of overall (0-10y) and specifically late (post-5 year) recurrence.[1,2,4]
- MGI is comprised of 5 cell cycle genes (BUB1B, CENPA, NEK2, RACGAP1, and RRM2) and recapitulates tumor grade.[4]
- In this study, correlative analyses of risk stratification by BCI Prognostic and MGI vs tumor grade and Ki67 were performed to characterize their relationship to other markers of proliferation.

## MATERIALS & METHODS

- Descriptive analyses were performed using data from the BCI Clinical Correlative Database, which contains demographic information, clinical and pathologic characteristics, and test results for cases submitted for BCI testing in clinical practice.
- Tumor grade and Ki67 information was abstracted from pathology reports; data were available for 1335 and 372 patients with node-negative breast cancer, respectively.
- Ki67 categories (low, intermediate, and high) were based on 10% and 20% IHC expression cutoffs.
- BCI risk categories (low, intermediate, and high) and MGI risk categories (low and high) were based on established clinical cutpoints (5.0825 and 6.5025 for BCI, 0.0 for MGI).
- Pearson correlation was performed to compare BCI Prognostic and MGI to Ki67 as continuous variables; coefficient of determination derived from the analysis of variance (ANOVA) model was used to compare continuous BCI Prognostic and MGI to categorical tumor grade.
- Chi-square test assessed the significance of concordance between BCI Prognostic and MGI risk groups to tumor grade and Ki67 groups.
- Restratification by BCI and MGI were performed within tumor grade and Ki67 expression categories.

## RESULTS

**Table 1. Patient Characteristics**

| | |
|---|---|
| **Total Number of Cases** | N=1359 |
| **Age, mean/median** | 57y / 58y |
| **ER status (N=905)** | |
| Positive | 894 (99%) |
| Negative | 11 (1%) |
| **PR status (N=899)** | |
| Positive | 801 (89%) |
| Negative | 94 (10%) |
| Borderline | 4 (1%) |
| **Her2 status (N=858)** | |
| Negative | 774 (90%) |
| Positive | 84 (10%) |
| **Nodal status (N=1359)** | |
| Negative | 1359 (100%) |
| Positive | 0 (0%) |
| **Tumor size (N=1347)** | |
| ≤1 cm | 356 (26%) |
| >1-≤2 cm | 656 (49%) |
| >2-≤5 cm | 308 (23%) |
| >5 cm | 27 (2%) |
| **Tumor grade (N=1335)** | |
| 1 | 389 (29%) |
| 2 | 711 (53%) |
| 3 | 235 (18%) |
| **Ki67 (N=372)** | |
| Low (≤ 10%) | 137 (37%) |
| Intermediate (11-20%) | 91 (24%) |
| High (>20%) | 145 (39%) |

- Mean age at diagnosis was 57 years.
- The majority of tumors were T1 (75%) and HER2- (90%).
- 99% were ER+, and 89% were PR+.
- Both tumor grade and Ki67 were distributed across low, intermediate, and high classifications.

## RESULTS

**Table 2. BCI Prognostic Risk Classification vs Grade (N=1335)**

| | Grade 1 (N=389) | Grade 2 (N=711) | Grade 3 (N=235) |
|---|---|---|---|
| **BCI Low Risk** (N=712) | 305 | 365 | 42 |
| **BCI Intermediate Risk** (N=341) | 69 | 216 | 56 |
| **BCI High Risk** (N=282) | 15 | 130 | 137 |

**Table 3. BCI Prognostic Risk Classification vs Ki67 (N=372)**

| | Ki67 Low (N=137) | Ki67 Inter (N=91) | Ki67 High (N=145) |
|---|---|---|---|
| **BCI Low Risk** (N=196) | 109 | 47 | 40 |
| **BCI Intermediate Risk** (N=102) | 21 | 36 | 45 |
| **BCI High Risk** (N=74) | 6 | 8 | 60 |

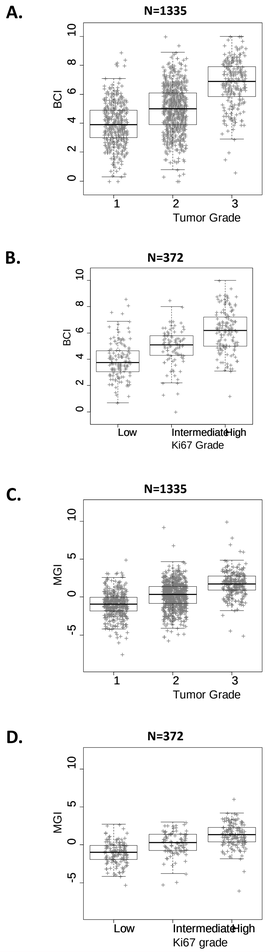
**Table 4. MGI Risk Classification vs Grade (N=1335)**

| | Grade 1 (N=389) | Grade 2 (N=711) | Grade 3 (N=235) |
|---|---|---|---|
| **MGI Low Risk** (N=624) | 294 | 295 | 35 |
| **MGI High Risk** (N=711) | 95 | 416 | 200 |

**Table 5. MGI Risk Classification vs Ki67 (N=372)**

| | Ki67 Low (N=137) | Ki67 Inter (N=91) | Ki67 High (N=145) |
|---|---|---|---|
| **MGI Low Risk** (N=165) | 104 | 40 | 21 |
| **MGI High Risk** (N=207) | 32 | 51 | 124 |

**Figure 1. Correlation of BCI/MGI vs Grade/Ki67**




## RESULTS

- BCI Prognostic and MGI (as continuous variables) correlated weakly with tumor grade (coefficient of determination = 0.26 and 0.22, respectively) and continuous Ki67 ($r^2$ = 0.35 and 0.33, respectively).
- Discordance between BCI Prognostic and both tumor grade and Ki67 were statistically significant (p<0.00001 and p<0.00001, respectively).
- BCI Prognostic classified 4% of Grade 1 tumors as high risk and 18% of Grade 3 tumors as low risk. In addition, BCI classified 51% of Grade 2 tumors as low risk and 18% as high risk (Table 2).
- BCI Prognostic classified 4% of low Ki67 patients as high risk and 28% of high Ki67 patients as low risk. In addition, BCI classified 52% of Ki67 Intermediate as low risk and 9% as high risk (Table 3).
- Discordance between MGI and both tumor grade and Ki67 were significant (p<0.00001 and p<0.00001, respectively).
- MGI classified 24% of Grade 1 tumors as high risk and 15% of Grade 3 tumors as low risk. In addition, MGI classified 41% of Grade 2 grade tumors as low risk and 59% as high risk (Table 4).
- MGI classified 24% of low Ki67 patients as high risk and 14% of high Ki67 patients as low risk. In addition, MGI classified 44% of Ki67 intermediate patients as low risk and 56% as high risk (Table 5).

## CONCLUSIONS

- Data from this large retrospective analysis indicate that BCI Prognostic and MGI are capturing distinct information related to tumor proliferative status compared with tumor grade and Ki67.
- The algorithmic combination of the mitogenic (MGI) and endocrine response (H/I) gene signatures within BCI Prognostic has been demonstrated to be a superior prognostic factor to clinicopathologic variables in previous multivariate analyses.[1]

## REFERENCES

1. Zhang Y et al. Clin Cancer Res. 2013;19:4196–205.
2. Sgroi DC et al. Lancet Oncol. Oct 2013; 14: 1067–1076.
3. Sgroi DC et al. J Natl Cancer Inst. 2013;105:1036–42.
4. Ma et al. Clin Cancer Res. 2008 May 1;14(9):2601-8.

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Highlights:

- In this study, correlative analyses of risk stratification by BCI Prognostic and Molecular Grade Index (MGI; 5 genes making up the proliferative component of BCI) vs tumor grade and Ki67 were performed to characterize their relationship to other markers of proliferation.
- Discordance between both BCI Prognostic and MGI to tumor grade and Ki67 were statistically significant.

| | Grade 1 | Grade 2 | Grade 3 | Ki67 Low | Ki67 Intermediate | Ki 67 High |
|---|---|---|---|---|---|---|
| Reclassification by BCI | 4% BCI High | 51% BCI Low<br>18% BCI High | 18% BCI Low | 4% BCI High | 52% BCI Low<br>9% BCI High | 28% BCI Low |
| Reclassification by MGI | 24% MGI High | 41% MGI Low<br>59% MGI High | 15% MGI Low | 24% MGI High | 44% MGI Low<br>56% MGI High | 14% MGI Low |

- Data from this large retrospective analysis indicate that BCI Prognostic and MGI are capturing distinct information related to tumor proliferative status compared with tumor grade and Ki67.
- The algorithmic combination of the mitogenic (MGI) and endocrine response (H/I) gene signatures within BCI Prognostic has been demonstrated to be a superior prognostic factor to clinicopathologic variables in previous multivariate analyses.

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