

Identification of GATA3 as a Breast Cancer Prognostic Marker by Global Gene Expression Meta-analysis

Rohit Mehra,¹ Sooryanarayana Varambally,¹ Lei Ding,¹ Ronglai Shen,^{1,3} Michael S. Sabel,^{4,5} Debashis Ghosh,³ Arul M. Chinnaiyan,^{1,2,5} and Celina G. Kleer^{1,5}

Departments of ¹Pathology, ²Urology, ³Biostatistics, and ⁴Surgery, and ⁵The Comprehensive Cancer Center, University of Michigan Medical School, Ann Arbor, Michigan

Abstract

GATA binding protein 3 (GATA3) is a transcriptional activator highly expressed by the luminal epithelial cells in the breast. Here we did a meta-analysis of the available breast cancer cDNA data sets on a cohort of 305 patients and found that GATA3 was one of the top genes with low expression in invasive carcinomas with poor clinical outcome. To validate its prognostic utility, we did a tissue microarray analysis on a cohort of 139 consecutive invasive carcinomas ($n = 417$ tissue samples) immunostained with a monoclonal antibody against GATA3. Low GATA3 expression was associated with higher histologic grade ($P < 0.001$), positive nodes ($P = 0.002$), larger tumor size ($P = 0.03$), negative estrogen receptor and progesterone receptor ($P < 0.001$ for both), and HER2-neu overexpression ($P = 0.03$). Patients whose tumors expressed low GATA3 had significantly shorter overall and disease-free survival when compared with those whose tumors had high GATA3 levels. The hazard ratio of metastasis or recurrence according to the GATA3 status was 0.31 (95% confidence interval, 0.13-0.74; $P = 0.009$). Cox multivariate analysis showed that GATA3 had independent prognostic significance above and beyond conventional variables. Our data suggest that immunohistochemical analysis of GATA3 may be the basis for a new clinically applicable test to predict tumor recurrence early in the progression of breast cancer. (Cancer Res 2005; 65(24): 11259-64)

Introduction

Adjuvant systemic therapy has contributed to the reduction in mortality observed in the Western world over the last 15 years. A major problem in clinical oncology is distinguishing those patients most likely to recur, and therefore most likely to benefit from adjuvant systemic therapy, from those with a sufficiently favorable prognosis that they might forego adjuvant systemic therapy to avoid toxicity. This highlights the need for novel molecular predictors of tumor behavior at the time of diagnosis that can be implemented in the clinic.

By applying a two-stage Bayesian mixture modeling strategy, our group was able to develop a meta-signature predictive of disease-free survival in breast cancer patients (1). GATA binding protein 3 (GATA3), a transcriptional activator, emerged as one of the top genes with low expression in the meta-signature.

Note: R. Mehra and S. Varambally contributed equally to this work. A.M. Chinnaiyan and C.G. Kleer share senior authorship.

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Requests for reprints: Celina G. Kleer, Department of Pathology, University of Michigan, 3510C MSRB1, 1150 West Medical Center Drive, Ann Arbor, MI 48109. Phone: 734-615-3448; Fax: 734-615-3441; E-mail: kleer@umich.edu.

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In breast cancer, high GATA3 mRNA levels are seen in the luminal A type, associated with estrogen receptor (ER) expression and with a favorable prognosis (2–5). Recently, Usary et al. (4) identified and characterized in detail somatic mutations of GATA3 in five ER- α -positive invasive breast cancers and in the ER-positive breast cancer cell line MCF-7 and suggested that loss of GATA3 may contribute to tumorigenesis in ER-positive breast cancers. Here, we show that GATA3 protein levels are strongly associated with the degree of differentiation of breast cancer and that low GATA3 protein expression is an independent predictor of tumor recurrence after treatment in breast cancer patients.

Materials and Methods

Meta-analysis of breast cancer microarray data sets. Four published and publicly available breast cancer data sets were obtained from the authors' websites (6–9). These included 53,377 array elements from 305 breast tumor samples. A common set of 2,555 genes was identified by Unigene Cluster IDs. For each data matrix of the 2,555 genes, data preprocessing was carried out including standard normalization procedures (A and B) for different array platforms and missing data imputation by a k -nearest neighbors algorithm (10, 11). Each gene expression profile was then median centered and divided by the SD for each gene. A mixture model based data transformation was applied to each of the data matrix of the 2,555 genes. The original expression data from each study were mapped to a common probability scale and a "meta-cohort" was generated based on such data integration. The association of each gene expression profile with patient survival outcome was assessed using a univariate Cox regression model within a leave-one-out cross-validation scheme. Genes were then ranked by the significance of the effect size estimates. An essential list of 23 genes was determined based on appearance in top-ranked gene lists for each of the 305 samples from the leave-one-out analysis; GATA3 was on this list.

Western blot analysis. Nine frozen invasive carcinomas of the breast were dissected following review of an H&E section to confirm the presence and location of the carcinoma in the block by a pathologist (C.G.K.). Protein extracts for Western blot analysis were prepared from these cancer tissues. In addition, four breast cell lines (MCF-7, MDA-MB-231, HME, and MCF-10A) were used. Standard immunoblot analysis was done using an anti-GATA3 mouse monoclonal antibody (sc-269, Santa Cruz Biotechnology, Inc., Santa Cruz, CA) at 1:250 dilution (4). α -Actin and β -tubulin were used to control for equal loading.

Immunofluorescence and confocal microscopy. The breast tissue sections were deparaffinized in xylene. Slides were deparaffinized and blocked in PBS-Tween 20 with 5% normal donkey serum for 1 hour. A mixture of rabbit anti-E-cadherin antibody (LabVision Corp., Fremont, CA) and mouse anti-GATA3 antibody (Santa Cruz Biotechnology) was added to the slides at 1:50 and 1:100 dilutions, respectively, and incubated overnight at 4°C following standard immunofluorescence methods (12).

Breast sample collection and tissue microarray development. Breast tissue samples were obtained from the Surgical Pathology files at the University of Michigan with Institutional Review Board (IRB) approval. One hundred thirty-nine consecutive invasive breast carcinomas treated at our institution between 1987 and 1991 were reviewed (C.G.K.) and used to

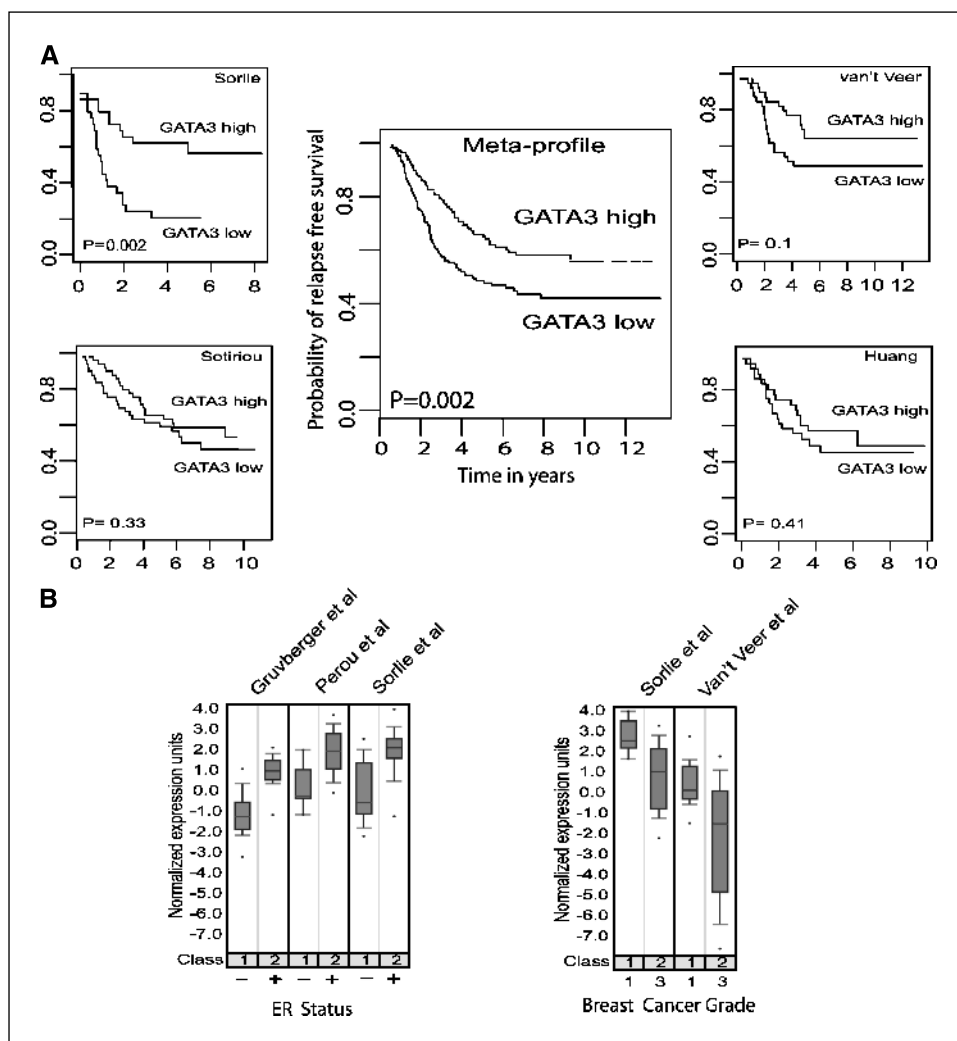


Figure 1. GATA3 transcript is associated with prognosis in breast cancer. *A*, GATA3 expression was determined in four published cDNA data sets analyzed independently and combined in a meta-analysis using a mixture modeling approach which unifies disparate gene expression data on a common probability scale and allows for a powerful tool to study the prognostic significance of single genes and gene signatures across different data sets. *B*, expression of GATA3 according to ER status and the histologic grade of the invasive carcinomas. GATA3 expression is higher in ER-positive, well-differentiated (low-grade) invasive carcinomas.

construct a TMA ($n = 417$ tissue microarray samples) using a manual arrayer as previously described (12). Each tumor was sampled in triplicate to account for tumor heterogeneity. Outcome information was obtained by chart review (M.S.S.) with IRB approval. The median duration of follow-up time was 8.9 years (range, 44 days-17 years). Clinicopathologic variables were assessed using well-established criteria (13).

Immunohistochemistry, digital image capture, and analysis. Immunohistochemistry was done on the TMA using standard biotin-avidin complex technique and a mouse monoclonal antibody against GATA3 (Santa Cruz Biotechnology) at 1:100 dilution as previously described (4). GATA3 was evaluated at least thrice for each microarray element and at least nine times for each tumor using a previously validated Web-based tool (TMA Profiler, University of Michigan, Ann Arbor, MI; ref. 14). GATA3 expression was scored blindly and independently by two surgical pathologists (C.G.K. and R.M.) as negative (score = 1), weak (2), moderate (3), and strong (4) on the basis of the intensity of staining and the percentage of tumor cells stained using a system that has been validated previously (15). The TMAs were previously stained for ER, progesterone receptor (PR), and HER-2/neu using well-described procedures (12, 15). The median value of all measurements from a patient was used for subsequent analysis. High GATA3 expression was defined as a median intensity of >2.5 and low GATA3 was defined as a median intensity of ≤ 2.5 .

Statistical analyses. Statistical analyses were done using SAS (SAS Institute, Inc., Cary, NC) software by the biostatisticians in the study (R.S. and D.G.). GATA3 expression was dichotomized into low staining (median score ≤ 2.5) and high staining (median score > 2.5). No data-based

optimization of the cut point was done. Associations between the GATA3 score and clinicopathologic features were assessed using χ^2 tests for 2×2 table analysis and Wilcoxon rank-sum test for $2 \times n$ comparisons. Overall survival time and time to breast cancer specific mortality were calculated from the date of surgery until the subjects' date of death or date of death due to breast cancer, respectively. Patients experiencing competing events were censored at the date of the competing event. Treatment failures included local recurrence and regional or distant metastases. Patients not experiencing failure events were censored on their last date of follow-up or date of death. Univariate associations were assessed using the log-rank test and the product-limit method of Kaplan and Meier. The Cox proportional hazards model was used to determine the best multivariate model of disease applied to variables including GATA3 protein expression, histologic grade, tumor size, lymph node status, angiolymphatic invasion, and ER, PR, and HER2 status. Associations with disease-free survival and overall survival were assessed for each variable. To determine the influence of multiple variables simultaneously, a multivariate Cox proportional hazards model was applied to the clinical variables and GATA3. Wald's test was used to determine statistical significance in the Cox models.

Results

Meta-analysis of breast cancer data sets identifies GATA3 as a prognostic marker. GATA3 mRNA expression was analyzed independently and by doing a meta-analysis of the four available data sets comprising a cohort of 305 patients containing data on

the expression levels of 2,555 genes. GATA3 expression was associated with survival in one of the four cDNA data sets when analyzed independently; however, a strong association was found when all the data sets were combined in the meta-analysis (log-rank $P = 0.002$; Fig. 1A). The levels of GATA3 transcript were significantly lower in invasive carcinomas that metastasized when compared with invasive carcinomas that did not metastasize. These results are in line with published data showing that the mixture modeling approach we used unifies disparate gene expression data on a common probability scale and allows for robust, interstudy-validated prognostic signatures (1). Furthermore, GATA3 levels were significantly lower in the subset of ER-negative invasive carcinomas ($P < 0.0001$) and in invasive carcinomas of high histologic grade ($P < 0.0001$; Fig. 1B).

GATA3 protein expression in breast cancer tissues. To validate the mRNA results, we did Western blots using a monoclonal antibody specific for GATA3 on nine randomly selected invasive carcinomas of the breast. We found that four had moderate to high GATA3 levels whereas five had low GATA3. As seen in Fig. 2A, in invasive carcinomas, low GATA3 protein was associated with negative ER status and high GATA3 was associated with positive ER. Furthermore, we determined the GATA3 expression of four breast cell lines with known ER status: ER-positive MCF-7 and ER-negative MDA-MB-231, HME, and MCF-10A cells. In the cell lines, GATA3 levels were also associated with the ER expression. Immunofluorescence showed crisp GATA3 expression exclusively in the nucleus of cancer cells, consistent with its function (Fig. 2B). Using TMAs, we next evaluated the expression of

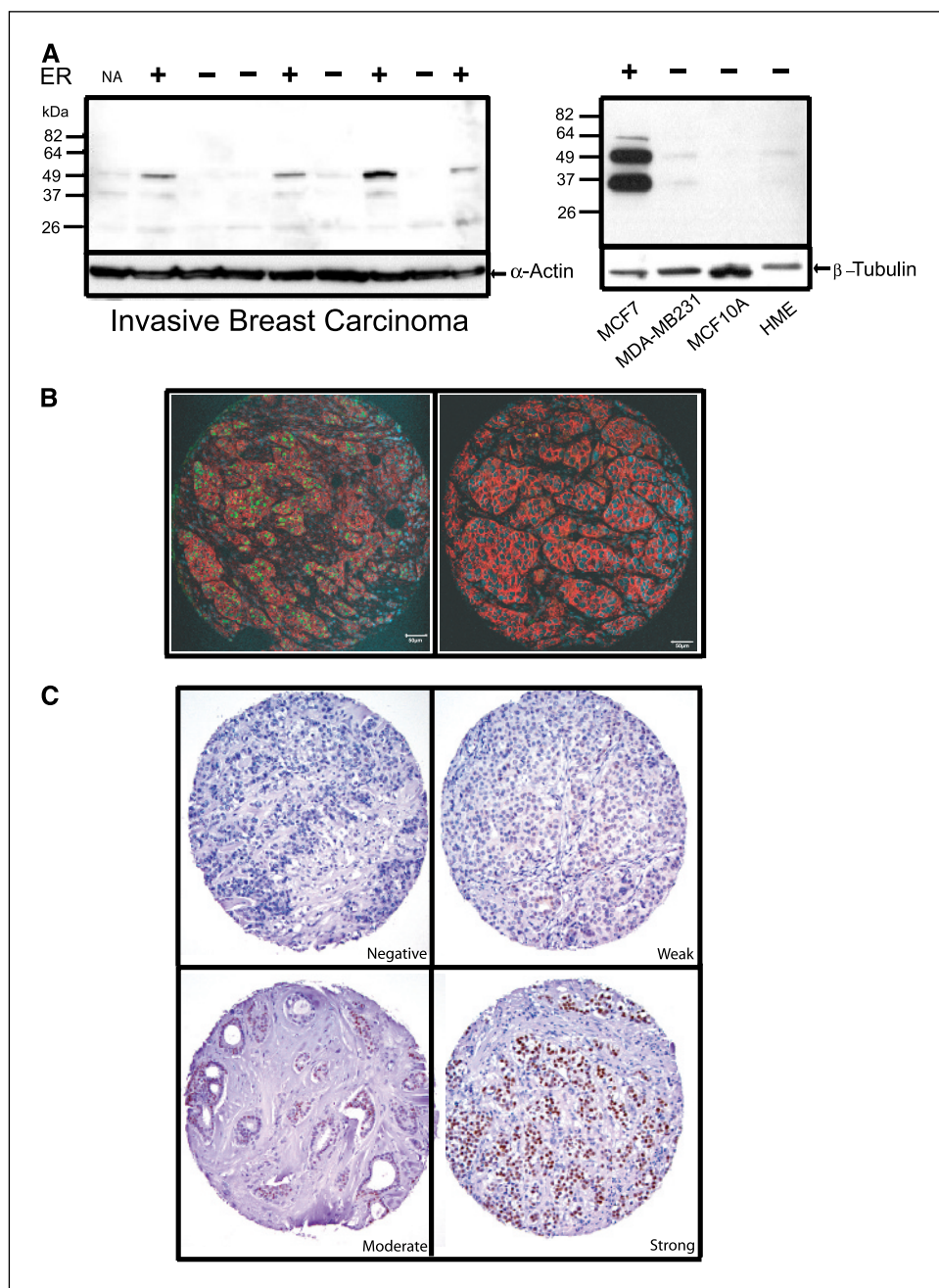


Figure 2. GATA3 protein expression in breast cancer. **A**, using a monoclonal antibody for GATA3 (sc-269), immunoblot analysis showed expression of GATA3 in nine invasive carcinomas of the breast. Two previously described bands (4, 19) at ~49 and 23 kDa are seen. GATA3 expression was associated with the ER status of the invasive carcinomas. **Right**, GATA3 expression in breast cell lines. Note the association with ER status. α -Actin and β -tubulin were used to control for equal loading. **B**, immunofluorescence and confocal microscopy revealed that GATA3 protein is localized to the nucleus of cancer cells. *Green*, GATA3; *red*, E-cadherin; *blue*, 4',6-diamidino-2-phenylindole. **Left**, invasive carcinoma positive for GATA3; **right**, invasive carcinoma negative for GATA3. **C**, GATA3 protein expression was evaluated using a high-density tissue microarray. GATA3 protein expression was readily identified in cancer cell nuclei and ranged from negative to strong in different cases of invasive breast cancer ($\times 100$).

GATA3 protein in a wide range of breast tissues (139 patients, $n = 417$ samples) to characterize its expression *in situ* by immunohistochemistry. GATA3 protein expression was observed in the nucleus (Fig. 2C) as previously reported (4).

Using our breast cancer TMA and a specific anti-GATA3 antibody, we were in the position to evaluate clinical and pathology associations of GATA3 protein levels in breast cancer. In our patient cohort ($n = 139$), 129 had complete follow-up information. Clinical and pathologic characteristics are shown in Supplementary Table S1. The median age of the patients was 58.5 years (range, 29-93 years). The 3-, 5-, and 10-year disease-specific survival rates were 74%, 68%, and 64%, respectively. Low GATA3 expression was associated with larger tumor size (Wilcoxon test, $P = 0.03$) and the presence of axillary lymph node metastasis (Kruskal-Wallis test, $P = 0.002$). Low GATA3 levels were also associated with higher histologic grade (Kruskal-Wallis test, $P < 0.001$), negative ER and PR (Wilcoxon test, $P < 0.001$ for both), and HER-2/neu overexpression (Wilcoxon test, $P = 0.03$; Supplementary Table S2). The TMA analyses confirmed the breast cancer cDNA expression data showing a significant reduction of GATA3 expression levels in patients with worse outcome.

As expected, at the univariate level, lymph node status, tumor size, and histologic tumor grade were associated with disease-specific and overall survival (Table 1). PR was inversely associated with outcome. We found a strong association between GATA3 and survival. Low GATA3 protein levels were associated with a shorter disease-free interval and a high probability of death (Fig. 3A and B). The 10-year disease-free survival for patients with invasive cancers expressing low GATA3 levels was 55% and, by contrast, for high levels of GATA3, 84% (log-rank $P = 0.005$). The hazard ratio of metastasis or recurrence according to the GATA3 status was 0.31 [95% confidence interval (95% CI), 0.13-0.74; $P = 0.009$]. Furthermore, low GATA3 expression was associated with disease-specific

survival in patients with lymph node-negative disease (log-rank $P = 0.02$; Fig. 3C).

Despite the strong association between GATA3 and ER expression in breast carcinomas, we noted that there is a group of ER-positive tumors expressing low GATA3. We hypothesized that GATA3 levels may have prognostic value in patients with ER-positive tumors. Of the 83 ER-positive invasive carcinomas in our consecutive patient cohort, 38 (45.8%) had high and 45 (54.2%) had low GATA3 expression. Patients with high GATA3 had uniformly good prognosis. However, low GATA3 characterized a subset of ER-positive invasive carcinomas with a higher rate of recurrence and/or metastasis (log-rank $P = 0.04$; Fig. 3D). The prognostic value of GATA3 was independent of hormonal treatment as it was significantly associated with outcome in ER-positive patients treated with tamoxifen and those that did not receive tamoxifen (Supplementary Fig. S1).

The best multivariable model predictive of disease-specific survival showed that low GATA3 was a strong independent predictor of outcome providing survival information above other prognostic features, with a hazard ratio of 0.12 (95% CI, 0.01-1.01; $P = 0.05$; Table 1). The risk of recurrence for GATA3 low cases was eight times higher than that of the risk for GATA3 high cases.

Discussion

We validated the expression of GATA3 independently in the four previously published available cDNA databases and characterized its expression in a cohort of consecutive invasive carcinomas, with the aim of defining its role as a novel breast cancer prognostic biomarker. At the univariate level, GATA3 protein, tumor size, the presence of axillary lymph node metastases, histologic tumor grade, and PR status were associated with survival. Multivariable Cox regression analysis showed that low GATA3 expression was an independent predictor of outcome. These findings support the potential clinical utility of incorporating GATA3 into clinical nomograms to help determine the risk of cancer progression.

The promising prognostic utility of GATA3 in breast cancer patients has been suggested by analyses of published breast tumor microarray data (4, 16, 17). We provide a validation of those results derived from individual data sets. By doing a meta-analysis, we unified disparate gene expression data on a common probability scale, thus providing a robust interstudy validation of GATA3 expression as a prognostic marker. Our results further strengthen the value of the mixture model based data transformation in the identification and cross-validation of biomarkers across cDNA data sets which are based on different experimental platforms.

We found that GATA3 expression was strongly associated with ER expression and with the histologic grade of the carcinomas, a measure of differentiation. In DNA microarray analyses, GATA3 was associated with the expression of ER and of a subset of genes important for breast luminal cell differentiation including LIV-1, RERG, and TFF3 (2-4). Our data support these observations and suggest a role for GATA3 in maintaining a differentiated state in breast cells. We found a strong association between GATA3 and ER expression at the mRNA and protein levels. Recently, Usary et al. (4) reported a strong association between GATA3 and ER in normal breast luminal epithelial cells and discovered mutations of GATA3 near the highly conserved second zinc-finger domain required for DNA binding in breast cancers and in the MCF-7 breast cancer cell line, which suggested that GATA3 is expressed in normal

Table 1.

Factor	Hazard ratio (95% CI)	<i>P</i>
(A) Univariate analysis of disease-free survival		
GATA3	0.31 (0.13-0.74)	0.009
Histologic grade	2.28 (1.28-4.05)	0.005
ER	0.55 (0.30-1.02)	0.06
PR	0.45 (0.24-0.84)	0.01
HER-2/neu	1.12 (0.50-2.53)	0.78
ALI	3.67 (1.98-6.82)	<0.0001
Lymph node (0, 1-3, 4+)	2.29 (1.52-3.46)	<0.0001
Size (>2 vs ≤2 cm)	2.84 (1.37-5.85)	0.005
(B) Multivariate Cox model of disease-free survival		
GATA3	0.12 (0.01-1.01)	0.05
Histologic grade	1.56 (0.59-4.15)	0.37
ER	1.10 (0.33-3.65)	0.88
PR	0.62 (0.18-2.08)	0.44
HER-2/neu	1.36 (0.42-4.38)	0.61
ALI	2.28 (0.94-5.54)	0.07
Lymph node (0, 1-3, 4+)	1.39 (0.44-4.37)	0.57
Size (>2 vs ≤2 cm)	1.99 (0.76-5.21)	0.16

Abbreviations: PR, progesterone receptor; ALI, angiolymphatic invasion.

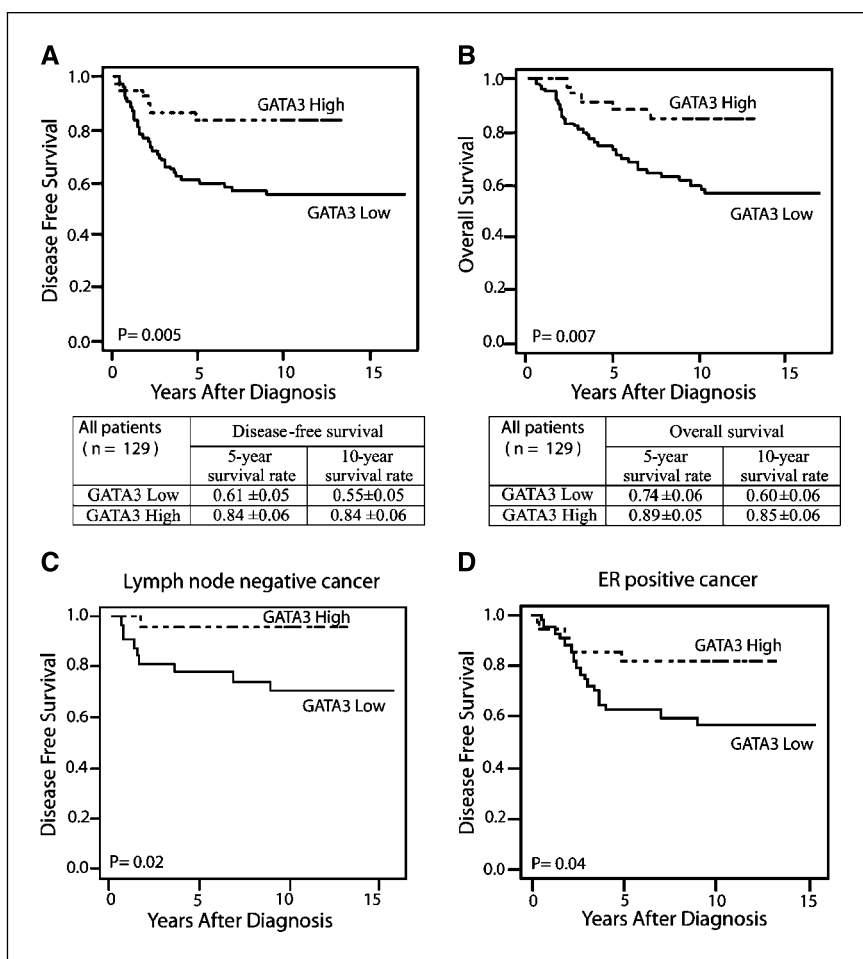


Figure 3. Low GATA3 levels are associated with aggressive breast cancer. Kaplan-Meier analysis of disease-specific (A) and overall (B) survivals according to GATA3 protein expression evaluated by immunohistochemical analysis. Patients with tumors expressing low GATA3 had worse disease-free survival and overall survival. C and D, Kaplan-Meier curves of disease-free survival according to GATA3 levels in lymph node-negative and ER-positive breast cancers.

mammary epithelium and that decreased expression due to mutation or deletion may contribute to breast cancer development.

Despite genomic coexpression of ER and GATA3 transcription factors in breast cancer, estrogens do not regulate GATA3 (3). Although the gene for ER is not induced by GATA3, it has been suggested that GATA3 variants may contribute to tumorigenesis in ER-positive tumors (4). In our study, we identified a group of ER-positive invasive carcinomas that have low GATA3 protein levels. Furthermore, GATA3 was able to uncover a group of ER-positive invasive carcinomas with worse clinical outcome who developed tumor recurrence and/or metastases independently of hormonal treatment, which may have clinical implications. Future studies will test the model developed in this study to confirm these initial observations.

Furthermore, GATA3 protein levels were able to discern which node-negative patients develop tumor recurrence or metastases from those who do not. These results suggest that detection of GATA3 protein may be useful in supplying additional power to delineate prognosis in node-negative breast cancer patients. In the future, this may pave the way to tailor the aggressiveness of therapies to molecular profiles that include GATA3.

By interrogating 29 cancer microarray data sets for evidence of differential expression of GATA3 transcript in benign and malignant tissues using Oncomine 2.0 (18), GATA3 was elevated in several carcinomas including lung ($P = 0.002$), prostate ($P = 0.003$), pancreas ($P = 0.046$), liver ($P < 0.0001$), endometrium

($P = 0.004$), adenoid cystic carcinoma of salivary gland ($P < 0.0001$), and diffuse large B-cell lymphomas ($P = 0.007$). These microarray studies suggest a role of GATA3 in several human tumor types.

In summary, we show that GATA3 is a promising novel prognostic biomarker in breast cancer. Our retrospective studies suggest that GATA3 levels may be used to identify patients with ER-positive and lymph node-negative breast cancer with a more aggressive phenotype, thereby enhancing our prognostic knowledge. Although our results are promising, they need to be validated in relationship to outcome in the context of controlled clinical trials. If confirmed, application of GATA3 immunohistochemical analysis will be technically straightforward and clinically useful.

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