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Bioinformatics Analysis of Expression and Alterations of BARD1 in Breast Cancer

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Abstract

Background: Breast cancer is one of the most common malignant tumor type in women worldwide. BARD1 could impact function of BRCA1 as its interaction partner. In the current study, we aimed to investigate the prognostic role of BARD1 expression as well as its alterations in breast cancer using different online tools. **Methods:** We performed a bioinformatics analysis for BARD1 in patients with breast cancer using several online databases, including Oncomine, bc-GenExMiner, PrognoScan, Search Tool for the Retrieval of Interacting Genes, Cytoscape, and cBioPortal. **Results:** We found that BARD1 was highly expressed in basal-like, HER2-E, and luminal B compared with normal-like subtype. Forest plot showed that BARD1 overexpression was correlated with worse distant metastasis-free survival (hazard ratio: 2.72, 95% confidence interval: 1.02-2.21; $P = .0448$), disease-specific survival (hazard ratio: 2.65, 95% confidence interval: 1.37-5.12; $P = .0037$), and disease-free survival (hazard ratio: 1.98, 95% confidence interval: 1.22-3.24; $P = .0062$) but positively correlated with overall survival (hazard ratio: 0.66, 95% confidence interval: 0.50-0.85; $P = .0017$). Multivariate analysis indicated that BARD1 expression was significantly associated with distant metastasis-free survival (hazard ratio: 4.60, 95% confidence interval: 1.22-17.28; $P = .0239$) whereas marginally significant for disease-free survival (hazard ratio: 1.00, 95% confidence interval: 1.00-1.01, $P = .0630$) and disease-specific survival (hazard ratio: 1.96, 95% confidence interval: 0.97-3.96; $P = .0602$). Meanwhile, alterations in BARD1 interaction network were associated with worse overall survival instead of BARD1 alteration alone. **Conclusions:** Bioinformatics analysis revealed that BARD1 may be a predictive biomarker for prognosis of breast cancer. However, future research is required to validate our findings.

Keywords

breast cancer, biomarker, bioinformatics, prognosis, BARD1

Abbreviations

CI, confidence interval; DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; ER, estrogen receptor; GO, Gene Ontology; HR, hazard ratio; OS, overall survival; PR, progesterone receptor; STRING, Search Tool for the Retrieval of Interacting Genes

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Introduction

Breast cancer is one of the most common malignant tumor type in women worldwide. Although numerous potential biomarkers have been identified through various approaches, few have been utilized in practical use. Therefore, identification of new biomarkers is still urgently needed in breast cancer research. BARD1 (BRCA1-associated RING domain), a protein interact with BRCA1, which mutations have been detected in different cancers including breast cancer, ovarian cancer, and endometrial cancers,[1] stabilizes BRCA1 protein by forming a heterodimeric RING finger complex through its N-terminal regions and impacts function of BRCA1 including homologous recombination repair.

It has been reported that BARD1 is a promising candidate biomarker for different cancers. For instance, the truncated or deletion-bearing protein isoforms of BARD1 is overexpressed in gynecological cancer cells and correlated with poor prognosis.[2] Full-length BARD1 protein could improve risk stratification in patients with colon cancer, while BARD1 splice variants are associated with a poor prognosis.[3] As for the study of BARD1 genomic alterations, Gorringe *et al*[4] reported that its variants are not associated with familial breast cancer risk in Australian cohort. The study by Vahteristo *et al* suggests that the contribution of the BARD1 germline variants to breast cancer predisposition is very limited and that neither Cys557Ser nor Val507Met has an effect on familial breast cancer susceptibility.[5] Jakubowska *et al*[6] reported that there was no clear association between BARD1 Cys557Ser allele and breast cancer in Poland. Moreover, it does not appear to modify the risk of breast cancers among carriers of predisposing mutations. While Stacey *et al*[7] suggest that BARD1 Cys557Ser is an ancient variant that confers susceptibility to breast cancer.

Taken together, BARD1 variants have been studied widely in breast cancer. However, the prognostic significance of BARD1 gene expression in breast cancer required further investigation. Therefore, in the current study, we used several online tools to carry out a systematic analysis in order to evaluate the distinct prognostic value of BARD1 in breast cancer.

Materials and Methods

Oncomine Database Analysis

Oncomine database (http://www.oncomine.org), a web-based microarray database, was used to analyze the transcription level of BARD1 in different cancer types.[8,9] It is an integrated platform for data mining, including 18 000 cancer gene expression experiments in the release of Oncomine 3.0. BARD1 gene expression in clinical cancer tissue was queried and compared that with normal tissue using Student *t* test. The parameters included fold-change ≥ 2, *P* value $\leq$1e-4, and gene rank $\geq$top 10%.

Bioinformatics Analysis Using bc-GenExMiner v4.2

The Breast Cancer Gene-Expression Miner v4.2 (bc-GenExMiner v4.2),[10,11] a mining tool of 36 published annotated genomics data (total of 5696 patients), was used to conduct BARD1 expression analysis between patients at different age groups and PAM50 cancer subtypes. Relevance of BARD1 and prognosis were analyzed through univariate Cox analysis and Kaplan-Meier curve analysis. Gene correlation analysis was assessed using the correlation module. Then, Gene Ontology (GO) term results were obtained through the above gene correlation exhaustive analysis.

PrognoScan

The PrognoScan (http://www.prognoscan.org/) is a comprehensive online platform for evaluating potential biomarkers through a large number of publicly available cancer gene expression data sets.[12] It was used to validate the prognostic role of BARD1 expression in breast cancer, with *P* value, hazard ratio (HR), and 95% confidence intervals (CIs) automatically calculated. And the obtained survival results were displayed by forest plot.

Identifying the Protein Components of BARD1

The Search Tool for the Retrieval of Interacting Genes (STRING) (http://string-db.org), a database of known and predicted protein interacting, was used to determine interacting proteins using BARD1 as the query.[13] The corresponding protein–protein interaction network of BARD1 was constructed with a confidence score >0.9. We have then further imported those proteins into Cytoscape 3.4.0 to perform network analysis. NetworkAnalyzer was utilized by selecting Tools → Network Analysis → Generate Style from Statistics. Degree was mapped to the size of the nodes, that is, low degree mapped to small size. Regarding the size of the edges, coexpression was selected with low values to small sizes. As for the color of nodes or edges, low values were mapped to bright colors. By default, the brightest color is orange and the darkest color is blue. And hubs are the nodes with higher degree, that is, nodes with more connections.

cBioPortal

OncoPrint is a feature of cBioPortal (http://www.cbioportal.org/),[14,15] which is an open access resource for cancer genomic, and was used to query for genetic alterations of all the interaction partners of BARD1 extracted from STRING network. And all the 14 breast cancer studies in cBioPortal were utilized for this analysis. The percentages of alterations in these genes among breast cancer varied from 0.8% to 9% for individual genes; the *NBN* gene was amplified predominantly in the breast cancer compared to the other genes. Meanwhile, we have also investigated the prognostic value of BARD1 alterations in breast cancer. Furthermore, all the genes extracted from BARD1 interaction network were used as a query for assessing the relationship between their alterations and overall survival (OS) of breast cancer.

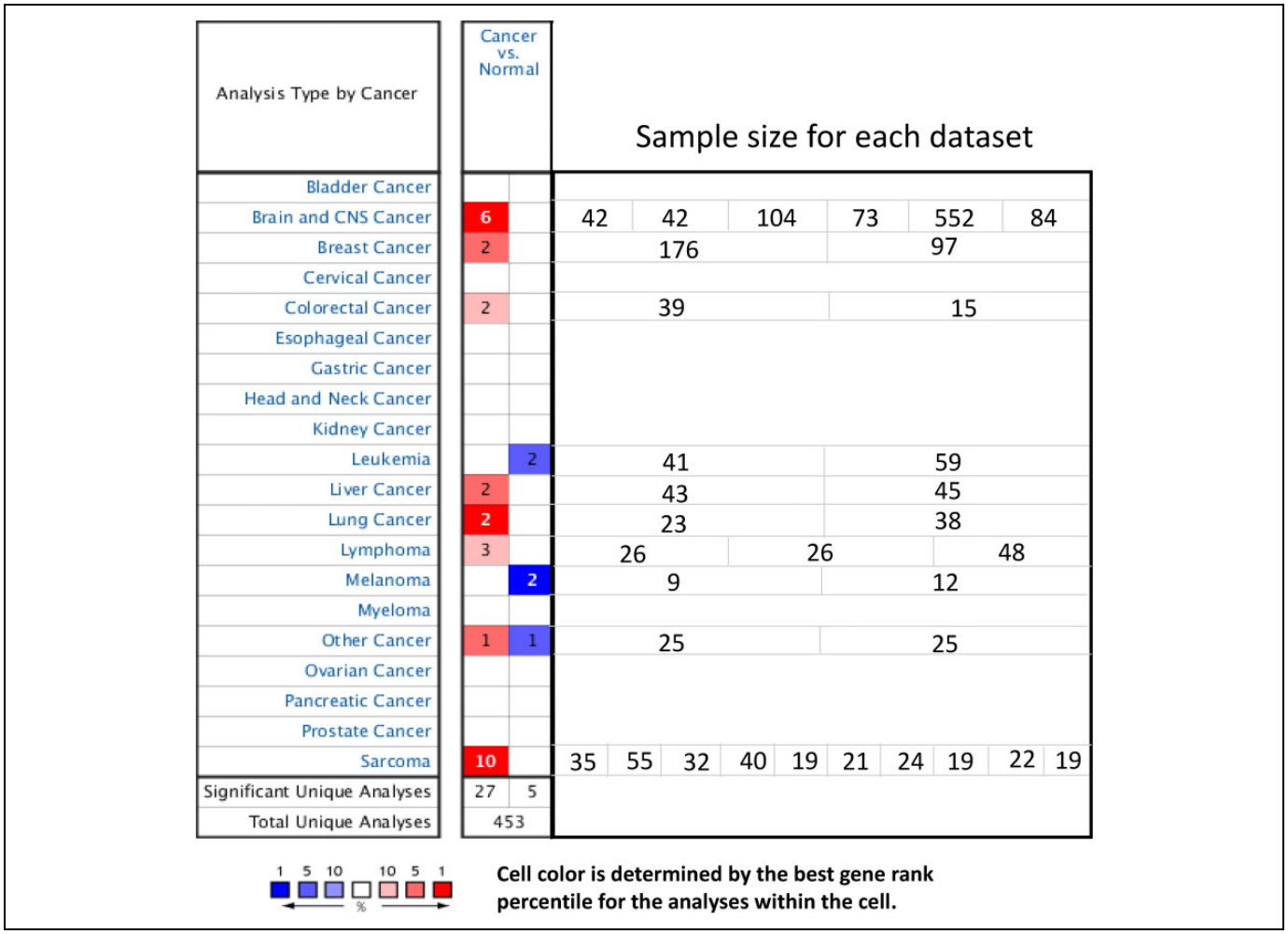

Figure 1. Expression of *BARD1* gene in different type of cancers using the Oncomine database. The threshold of fold-change ≥2, *P* value ≤1e-4, and gene rank ≥top 10%. Red and blue stand for the numbers of data sets with statistically significantly ($P < .05$) increased and decreased levels of *BARD1* gene, respectively.

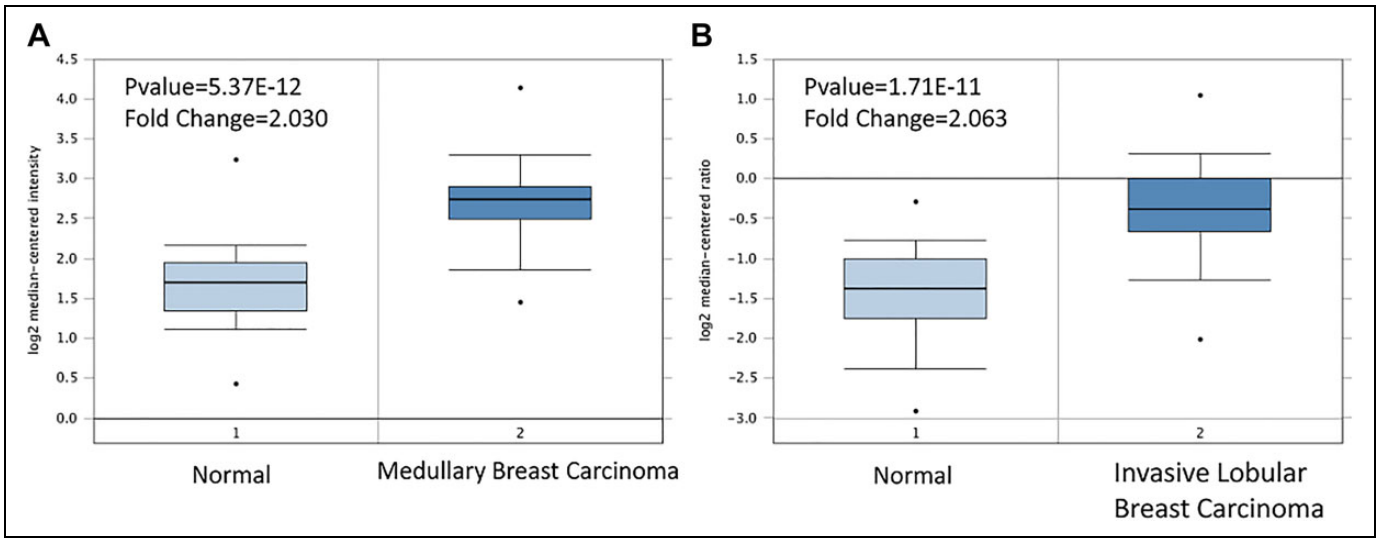

Figure 2. Comparison of BARD1 expression in normal and breast cancer tissue: (A) Medullary breast carcinoma and (B) invasive lobular breast carcinoma.

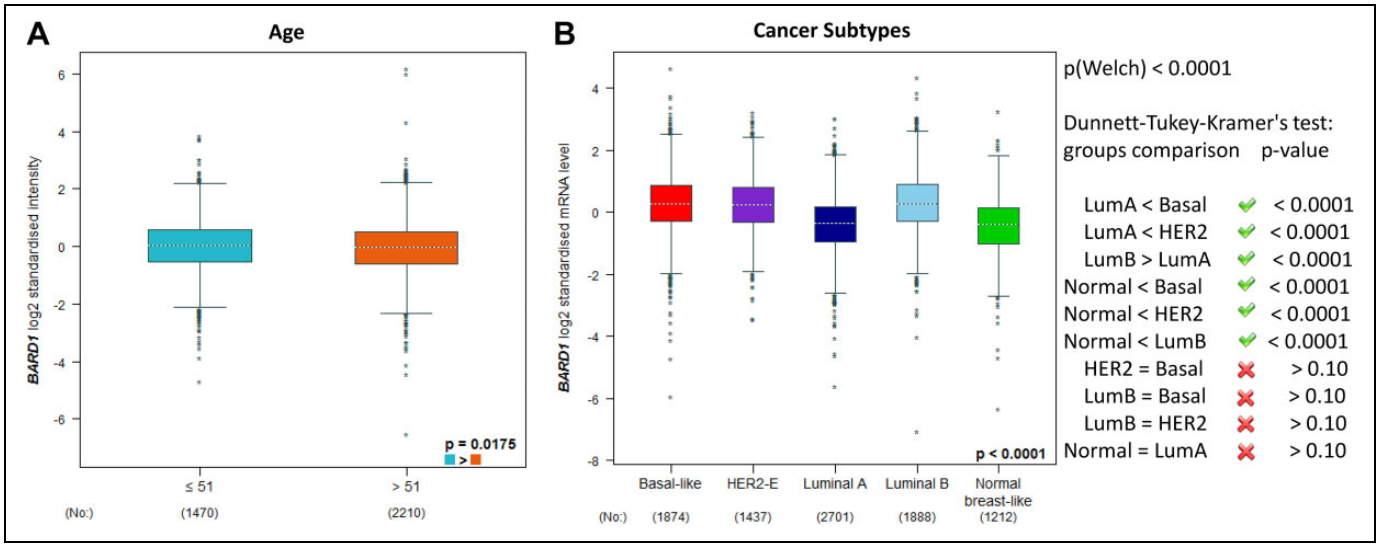

Figure 3. Box plot of BARD1 expression among different groups of patients using the bc-GenExMiner software. (A), Box plot of BARD1 expression according to age. (B), Box plot of BARD1 expression according to PAM50 cancer subtypes.

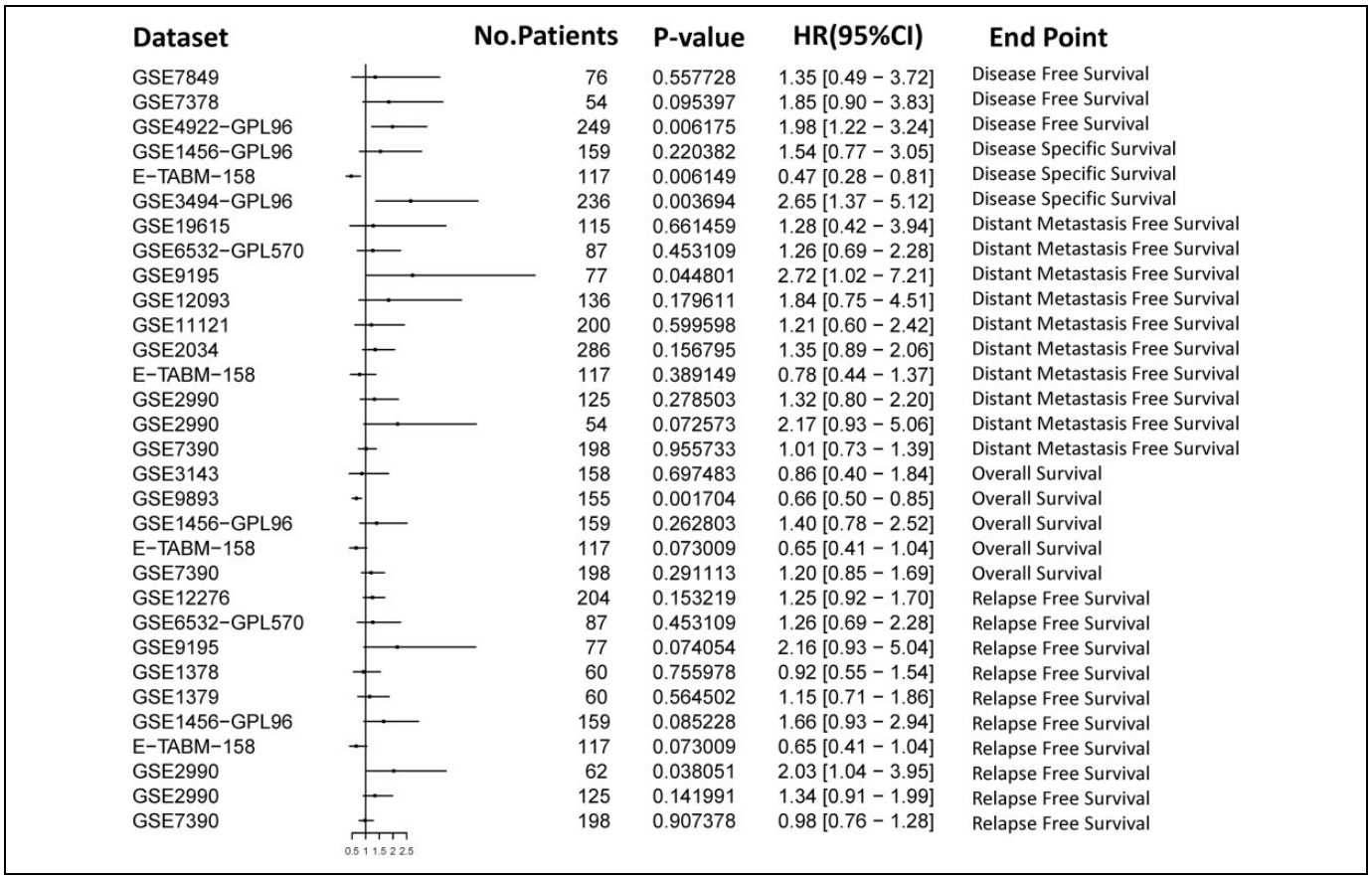

Figure 4. Forest plot displaying univariate Cox analysis of BARD1 expression.

Results

Expression of BARD1 *Gene in Different Cancer Types*

We measured the gene expression of *BARD1* in different cancers and normal tissues using the Oncomine online database. It has been revealed that BARD1 (red) was overexpressed in brain and central nervous system cancer, breast cancer, colorectal cancer, liver cancer, lung cancer, lymphoma, and sarcoma cancers, whereas decreased level of BARD1 (blue) was found in leukemia and melanoma (Figure 1). Oncomine analysis also

Table 1. Univariate and Multivariate Cox Regression of Risk Factors Associated With Survival.

	Univariate Analysis			Multivariate Analysis		
Variables	HR	95% CI	*P* Value	HR	95% CI	*P* Value
GSE9195		Distance metastasis-free survival				
Age	1.02	0.95-1.09	.6690	1.06	0.97-1.15	.2141
PR	0.43	0.12-1.53	.1910	0.49	0.11-2.09	.3320
Node	**4.76**	**1.01-22.44**	**.0484**	3.39	0.66-17.50	.1444
Size	**1.88**	**1.22-2.89**	**.0042**	1.54	0.92-2.56	.0972
BARD1	**2.72**	**1.02-7.21**	**.0448**	**4.60**	**1.22-17.28**	**.0239**
GSE4922		Disease-free survival				
Age	1.00	0.98-1.01	.7220	1.01	0.99-1.02	.5220
ER	0.83	0.47-1.46	.5180	1.22	0.67-2.23	.5146
Grade	**1.77**	**1.31-2.41**	**.0002**	**1.59**	**1.12-2.25**	**.0093**
Size	**1.02**	**1.01-1.03**	**.0014**	1.01	1.00-1.02	.0926
BARD1	**1.98**	**1.22-3.24**	**.0062**	1.00	1.00-1.01	.0630
GSE3494		Disease-specific survival				
Age	1.00	0.98-1.02	.7780	1.00	0.98-1.02	.7153
ER	0.92	0.44-1.91	.8200	1.33	0.57-3.10	.5132
Grade	**1.88**	**1.27-2.78**	**.0015**	1.24	0.78-1.97	.3606
Size	**1.05**	**1.03-1.07**	**<.0001**	**1.04**	**1.01-1.06**	**.0019**
PR	0.69	0.38-1.26	.2280	0.93	0.44-1.95	.8426
Node	**2.55**	**1.66-3.91**	**<.0001**	**2.00**	**1.22-3.28**	**.0062**
BARD1	**2.65**	**1.37-5.12**	**.0037**	1.96	0.97-3.96	.0602

Abbreviations: CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.
Note. The features significantly associated with survival were represented in bold types.

revealed that BARD1 was significantly highly expressed in invasive ductal and medullary breast carcinoma with respect to normal tissue (Figure 2).

BARD1 Expression Among Different Groups of Patients Based on Clinical Parameters

BARD1 expression among different groups of patients based on several clinical parameters was evaluated using the bc-GenExMiner v4.2. For age criteria, BARD1 was overexpressed in patients aged ≤51 years than those aged >51 years (Figure 3A). Meanwhile, BARD1 expression was also compared among different PAM50 cancer subtypes, including basal-like, HER2-E, luminal A, luminal B, and normal-like. As shown in Figure 3B, patients with luminal A breast cancer tended to express less *BARD1* gene compared with basal-like, HER2-E, and luminal B patients, whereas BARD1 was highly expressed in basal-like, HER2-E, and luminal B compared with normal-like subtype.

Prognostic Value of BARD1 Expression in Breast Cancer

The prognostic value of *BARD1* gene has been investigated using the PrognoScan database. There are 31 breast cancer data sets in all, which were divided into 4 survival groups, including 13 disease-free survival (DFS), also defined as relapse-free survival; 3 disease-specific survival (DSS); 10 distant metastasis-free survival (DMFS); and 5 overall survival (OS). Forest plot showed that BARD1 expression was negatively correlated with

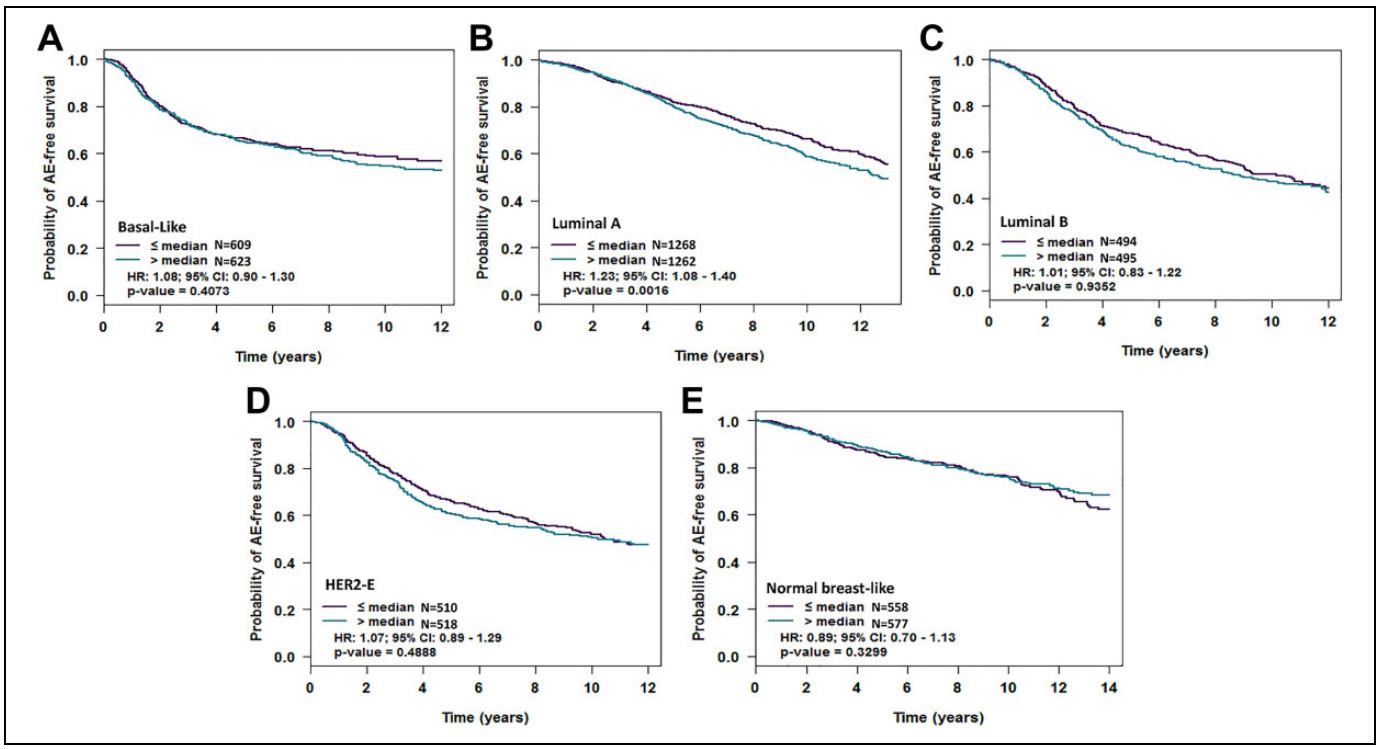

Figure 5. Survival curve evaluating the prognostic value of BARD1 using bc-GenExMiner database. Analysis is shown for (A) basal-like, (B) luminal A, (C) luminal B, (D) HER2-E, and (E) normal breast-like.

Table 2. Best Positive/Negative Correlated Genes With BARD1.

Gene Symbol	Pearson Correlation Coefficient	*P* Value	Number of Patients
Positive correlation			
NPM1P14	0.6010	<.0001	139
PKP4-AS1	0.5254	<.0001	171
LINC01845	0.4786	<.0001	171
LOC642846	0.4693	<.0001	252
PLGLA	0.4673	<.0001	171
CBWD5	0.4636	<.0001	230
GTF2H2C	0.4368	<.0001	252
DTL	0.4361	<.0001	4766
OR10J6P	0.4264	<.0001	139
OR52J3	0.4255	<.0001	190
LOC100130256	0.4247	<.0001	171
MSGN1	0.4146	<.0001	139
CCT4P2	0.4111	<.0001	139
FANCI	0.4098	<.0001	4146
ZNF658B	0.4070	<.0001	186
TPX2	0.4038	<.0001	4999
UBE2T	0.4024	<.0001	3013
Negative correlation			
JMJD7	−0.4463	.0010	51
LINC01662	−0.4230	<.0001	139
CFL1P1	−0.4157	.0024	51

DMFS (HR: 2.72, 95% CI: 1.02-2.21; $P = .0448$), DSS (HR: 2.65, 95% CI: 1.37-5.12; $P = .0037$), and DFS (HR: 1.98, 95% CI: 1.22-3.24; $P = .0062$) but positively correlated with OS (HR: 0.66, 95% CI: 0.50-0.85; $P = .0017$; Figure 4). Meanwhile, the top 3 data sets with smallest *P* value in each survival group (DMFS, DSS, and DFS) were selected to perform univariate and multivariate Cox regression. The prognostic significance of BARD1 expression level as well as clinicopathological factors in breast cancer, including patient age, lymph node status, tumor size, tumor grade, estrogen receptor, and progesterone receptor, were evaluated by Cox regression model (Table 1). As shown in Table 1, multivariate analysis indicated that BARD1 expression was significantly associated with DMFS (HR: 4.60, 95% CI: 1.22-17.28, $P = .0239$) whereas marginally significant for DFS (HR: 1.00, 95% CI: 1.00-1.01, $P = .0630$) and DSS (HR: 1.96, 95% CI: 0.97-3.96, $P = .0602$). Due to the incomplete data downloaded from PrognoScan, we couldn't perform multivariate analysis to investigate the effect of BARD1 expression as well as other covariates on OS. Meanwhile, we have stratified the analysis according to cancer subtypes including basal, HER2-E, luminal A, luminal B, and normal-like (Figure 5). Within these 5 subtypes, luminal A patients with higher BARD1 expression had a poor prognosis.

Table 3. GO Enrichment of Correlated Genes With BARD1.

Significant Terms	Description	*P* Value	Associated Genes
Biological process			
GO:0085020	Protein K6-linked ubiquitination	6.68e-06	*BARD1*, *UBE2T*
GO:0006513	Protein monoubiquitination	1.18e-04	*DTL*, *UBE2T*
GO:0006974	Cellular response to DNA damage stimulus	1.94e-04	*BARD1*, *DTL*, *UBE2T*
GO:0036297	Interstrand cross-link repair	2.55e-04	*FANCI*, *UBE2T*
GO:0031441	Negative regulation of mRNA 3′-end processing	5.19e-04	*BARD1*
GO:0045732	Positive regulation of protein catabolic process	5.67e-04	*BARD1*, *DTL*
GO:0006260	DNA replication	1.88e-03	*BARD1*, *DTL*
GO:0044314	Protein K27-linked ubiquitination	2.59e-03	*UBE2T*
GO:0035519	Protein K29-linked ubiquitination	3.11e-03	*UBE2T*
GO:0046826	Negative regulation of protein export from nucleus	3.11e-03	*BARD1*
GO:0007379	Segment specification	3.63e-03	*MSGN1*
GO:0072425	Signal transduction involved in G2 DNA damage checkpoint	5.69e-03	*DTL*
GO:0042325	Regulation of phosphorylation	7.24e-03	*BARD1*
GO:0000729	DNA double-strand break processing	7.75e-03	*BARD1*
GO:0060236	Regulation of mitotic spindle organization	8.78e-03	*TPX2*
Cellular component			
GO:0031436	BRCA1-BARD1 complex	1.20e-03	*BARD1*
GO:0031465	Cul4B-RING E3 ubiquitin ligase complex	2.99e-03	*DTL*
GO:0070531	BRCA1-A complex	4.19e-03	*BARD1*
GO:0000439	Transcription factor TFIIH core complex	4.79e-03	*GTF2H2C*
GO:0043203	Axon hillock	4.79e-03	*TPX2*
GO:0031464	Cul4A-RING E3 ubiquitin ligase complex	6.58e-03	*DTL*
GO:0005675	Transcription factor TFIIH holo complex	7.17e-03	*GTF2H2C*
Molecular function			
GO:0004842	Ubiquitin-protein transferase activity	8.32e-04	*BARD1*, *DTL*, *UBE2T*
GO:0061676	Importin-α family protein binding	3.47e-03	*TPX2*

Abbreviations: GO, Gene Ontology; mRNA, messenger RNA.

Correlated Genes With BARD1

Using bc-GenExMiner v4.2, we conducted gene correlation exhaustive analysis to obtain the best positive/negative correlated genes with BARD1 in breast cancer (Table 2). After that, the GO terms of the correlated genes with BARD1 were obtained via GO analysis (Table 3). Fifteen GO terms were found in biological process. Seven GO terms were found in cellular component. And two GO terms were found in molecular function.

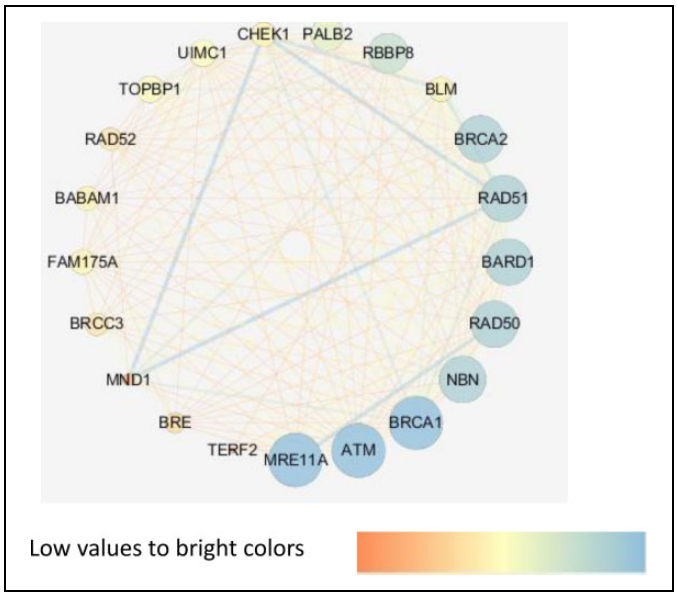

Figure 6. The protein–protein interaction network of BARD1 established by Search Tool for the Retrieval of Interacting Genes and visualized by Cytoscape software.

Interaction Networks of BARD1

The STRING website was used to find the interacting proteins of BARD1, which were then imported into Cytoscape software to perform network analysis. As shown in Figure 6, 20 predicted functional partners of BARD1 were shown in the network at protein level. In total, 21 nodes and 169 interactions were demonstrated in the current network. The average node degree is 16.1 and average local clustering coefficient is 0.899. BRAD1 is one of the hub proteins with high connectivity (large node size). Meanwhile, MRE11A, ATM, RAD50, RAD51, NBN, BRCA2, and BRCA1 are also hub proteins of this interaction network. Enrichment analysis against GO in this network suggested that for biological processes, GO:0006302 (double-strand break repair) was the most significantly enriched GO term. As for molecular function, GO:0003697 (single-stranded DNA binding) was shown to be the most relevant term associated with the interaction partners of BRAD1. While for cellular components, GO:0070531 (BRCA1-A complex) was the most enriched term.

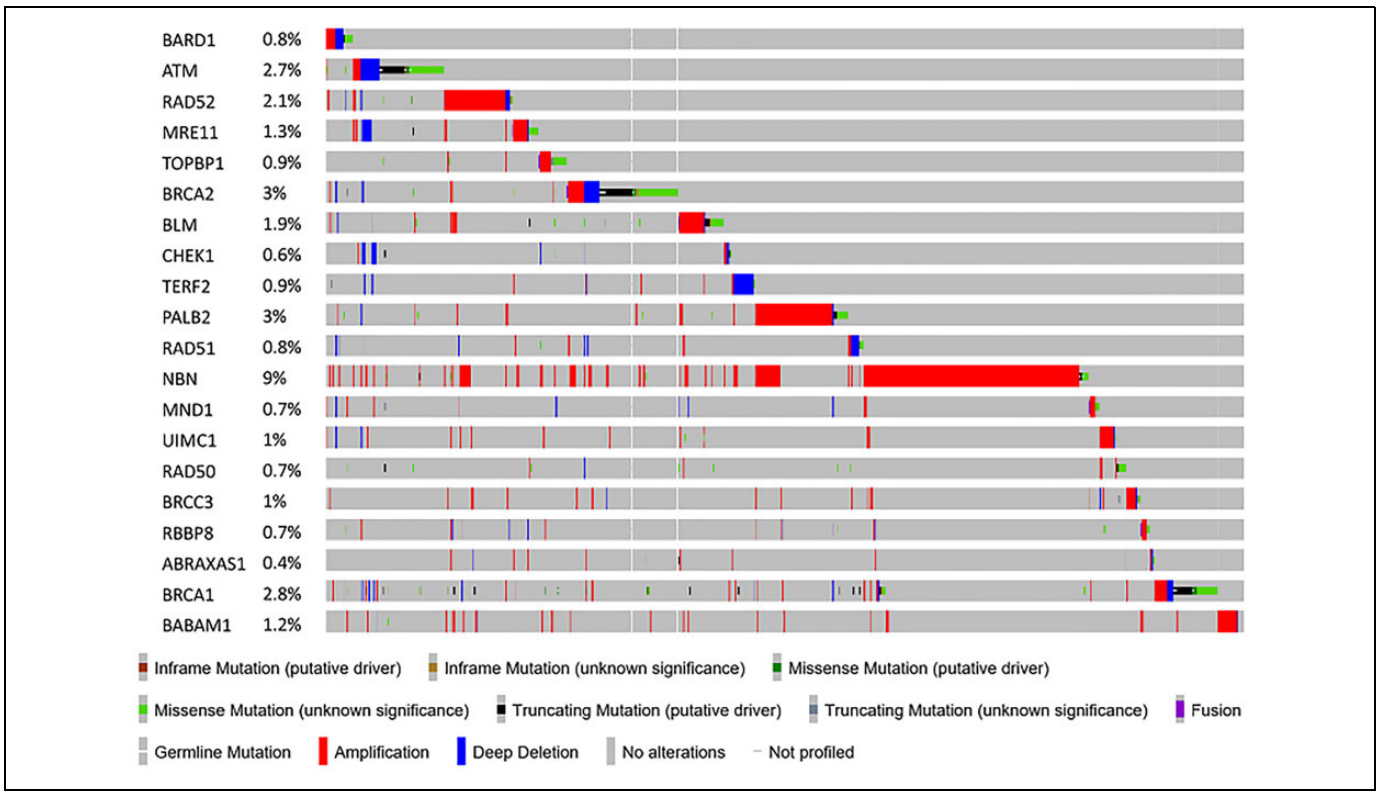

Figure 7. Genetic alteration frequency of each individual gene in BARD1 interaction network.

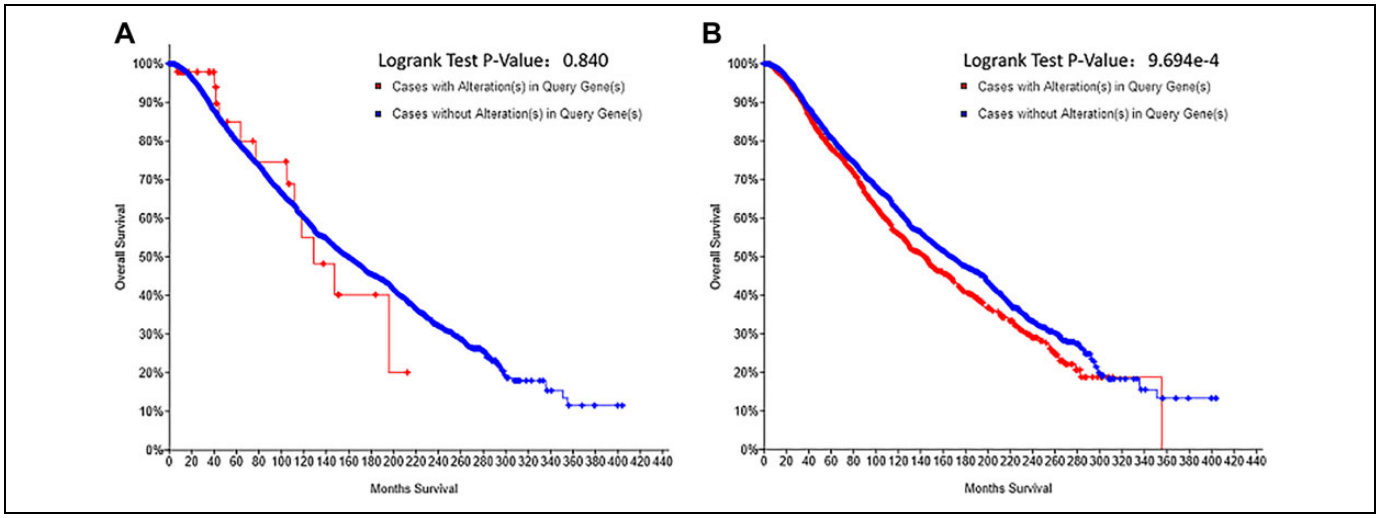

Figure 8. Kaplan-Meier plot of estimated overall survival. (A), Mutation status of BARD1. (B), Mutation status of BARD1 interaction network.

cBioPortal Analysis

Furthermore, we used the Oncoprint feature of cBioPortal (http://www.cbioportal.org) to investigate the genetic alterations of each individual gene in BARD1 predicted network. As shown in Figure 7, the percentages of alterations in these genes among 14 breast cancer data sets varied from 0.8% to 9% for individual genes. The majority of the genes were not frequently amplified, whereas the *NBN* gene was the predominantly amplified gene. In addition, we have evaluated whether the alterations in BARD1 associated with OS using cBioPortal. And it showed that BARD1 alteration alone had no impact on OS for patients with breast cancer. We also found that alterations in BARD1 interaction network were associated with poorer OS (Figure 8).

Discussion

BARD1 was first identified through its interaction with BRCA1, which mutations are responsible for 90% of the inherited breast cancer cases.[16] It has been reported that BRCA1 expression could influence the response of patients with breast cancer to chemotherapy treatment,[17,18] and decreased expression of BRCA1 has also been reported to accelerate invasiveness of sporadic or inherited breast cancer.[19] As the interaction partner of BRCA1, BRAD1 could stabilize BRCA1 protein through its N-terminal regions and thus could impact the function of BRCA1.

In this study, we performed a bioinformatics analysis to investigate the prognostic role of BARD1 expression as well as its alteration in patient with breast cancer. In Oncomine analysis, BARD1 was significantly highly expressed in invasive ductal and medullary breast carcinoma with respect to normal tissue, suggested by 2 studies, respectively. We have then further evaluated BARD1 expression among different PAM50 breast cancer subtypes using bc-GenExMiner v4.2. It confirmed that BARD1 was overexpressed in basal-like, luminal B, and HER2-E subtypes compared with normal-like subtype. However, the difference between luminal A and normal-like was not clear according to bc-GenExMiner. The confusion may be partly due to the fact that luminal A cancers are low grade, slow growing, and have the best prognosis. And luminal A breast cancer cells are similar to normal breast tissue cells.

We further investigated the prognostic role of BRAD1 expression in breast cancer. Six studies were statistically significant with *P* value less than .05, as shown in forest plot. It suggested that high expression of BARD1 was tending to correlated with poor DFS and DMFS of breast cancer. As for the DSS, the results were not consistent with HR of 0.47 and 2.65, respectively. And there was only one study that showed significant result for OS with HR 0.66. The reasons for this obvious heterogeneity displayed by forest plot may be the inclusion of follow-up time, different definition of end point, data extraction processes, and other factors. However, it needs to be further verified. Taken together, patients with high expression of BARD1 are more likely to have worse prognosis.

To discover more information about the mechanisms of interaction and how BARD1 involves in breast cancer by impacting other genes, we used STRING to visualize the protein interaction network of BARD1. And then, Oncoprint feature of the cBioPortal was used to determine the genetic alteration frequency of each gene in the above interaction network. Interestingly, the majority of genes in the BARD1 interaction network were not frequently amplified. This finding suggested that BARD1 could not impact breast cancer survival through its own alteration but through the alterations in all the genes extracted from BARD1 interaction network.

Conclusions

In conclusion, BARD1 might be a promising predictive biomarker for prognosis of breast cancer. And alterations in BARD1 interaction network were associated with worse OS.

However, in-depth experiments are needed to investigate the molecular mechanism of these results.

Authors' Note

This study was not required to obtain an approval as the study was based on deidentified retrospective patient data published at public domains.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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