Bioinformatics analysis revealing prognostic significance of \textit{RRM2} gene in breast cancer

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\textbf{Background:} Ribonucleotide reductase M2 subunit (\textit{RRM2}) plays vital roles in many cellular processes such as cell proliferation, invasiveness, migration, angiogenesis, senescence, and tumorigenesis. However, the prognostic significance of \textit{RRM2} gene in breast cancer remains to be investigated. \textbf{Methods:} \textit{RRM2} expression was initially evaluated using the Oncomine database. The relevance between \textit{RRM2} level and clinical parameters as well as survival data in breast cancer was analyzed using the Kaplan–Meier Plotter, PrognoScan, and Breast Cancer Gene-Expression Miner (bc-GenExMiner) databases. \textbf{Results:} \textit{RRM2} was overexpressed in different subtypes of breast cancer patients. Estrogen receptor (ER) and progesterone receptor (PR) were negatively correlated with \textit{RRM2} expression. Conversely, the Scarff–Bloom–Richardson (SBR) grade, Nottingham prognostic index (NPI), human epidermal growth factor receptor-2 (HER-2) status, nodal status, basal-like status, and triple-negative status were positively related to \textit{RRM2} level in breast cancer samples with respect to normal tissues. Patients with increased \textit{RRM2} showed worse overall survival, relapse-free survival, distant metastasis-free survival, disease-specific survival, and disease-free survival. \textit{RRM2} also exerted positive effect on metastatic relapse event. Besides, a positive correlation between \textit{RRM2} and \textit{KIF11} genes was confirmed. \textbf{Conclusion:} Bioinformatics analysis revealed that \textit{RRM2} might be used as a predictive biomarker for prognosis of breast cancer. Further studies are needed to more precisely elucidate the value of \textit{RRM2} in evaluating breast cancer prognosis.

\textbf{Introduction}

Breast cancer is the most frequently diagnosed tumor and a leading cause of cancer-related deaths among women worldwide [1]. Early diagnosis and treatment strategies including surgery, chemotherapy, radiotherapy, endocrine agents, and biological targeting agents have reduced patient morbidity and mortality; however, the prognosis of breast cancer remains poor. While clinical, pathological, and molecular features are widely used for establishing prognostics and predicting outcomes, finding more sensitive and specific biomarkers as surrogates of these features is the current trend in breast cancer research [2].

Ribonucleotide reductase M2 subunit (\textit{RRM2}), a rate-limiting enzyme for DNA synthesis and repair, displays vital roles in many critical cellular processes such as cell proliferation, invasiveness, migration, angiogenesis, and senescence [3]. \textit{RRM2} is frequently overexpressed in various malignancies and functions like a tumor driver [4–8]. Accumulating evidence has suggested that targeting \textit{RRM2} may be a novel strategy for cancer treatment. For example, \textit{RRM2} protected glioblastoma cells from endogenous replication stress, DNA damage, and apoptosis; \textit{RRM2} inhibition sensitized glioblastoma cells to agent treatment [9]. Knockdown of \textit{RRM2} attenuated melanoma growth both \textit{in vitro} and \textit{in vivo}, which correlated with maintenance of senescence-associated cell-cycle arrest [10]. In terms of breast cancer, both genetic suppression by RNA interference approach and pharmacological inhibition by small molecular antagonist of \textit{RRM2} gene significantly reversed tamoxifen-resistant cell proliferation, reduced cell motility,
Figure 1. Expression of RRM2 gene in 20 types of malignant tumor and corresponding normal tissues using the Oncomine database

Red and blue represent the numbers of datasets with statistically significant ($P < 0.05$) increased and decreased levels of RRM2 gene, respectively. Cell color is determined by the best gene rank percentile for the analyses within the cell, and the gene rank was analyzed by percentile of target genes in the top of all genes measured by each study.

activated pro-apoptotic pathways, and decreased tumor growth [11–13]. Moreover, it was reported that RRM2 was associated with chemoresistance of breast cancer cells to adriamycin; suppression of RRM2 synthesis could enhance the chemosensitivity to toxic insult [14]. Taken together, these findings suggest that RRM2 may act not only as an oncogene, but also as a promising prognostic biomarker and potential therapeutic target in cancer.

Therefore, in the present study, we evaluated the significance of RRM2 gene expression in breast cancer by using bioinformatics analysis of the clinical parameters and survival data in several large online databases.

Materials and methods

Oncomine

The Oncomine (http://www.oncomine.org), an online database containing microarray expression data from a variety of human cancers, was used to determine the level of RRM2 in breast cancer patients and normal individuals with the threshold of fold change $\geq 2$, $P$-value $\leq 1E-4$, and gene rank $\geq$ top 10% [15]. Gene co-expressed with RRM2 was analyzed and displayed as a heat map.

Breast Cancer Gene-Expression Miner

The Breast Cancer Gene-Expression Miner v4.1 (bcGenExMiner v4.1, http://bcgenex.centregauducheau.fr/BCGEM), a mining tool of published annotated genomics data, was utilized to evaluate the association between RRM2 gene and clinical parameters, as well as the relevance with metastatic relapse event [16,17]. The correlation between RRM2 and KIF11 were generated using the correlation module.
Figure 2. Box plot comparing RRM2 expression in normal individuals and breast cancer patients derived from the Oncomine database
Analysis is shown for male breast carcinoma (A), intraductal cribriform breast adenocarcinoma (B), invasive breast carcinoma (C), invasive lobular breast carcinoma (D), invasive ductal breast carcinoma (E), ductal breast carcinoma in situ (F), invasive ductal breast carcinoma epithelia (G), and ductal breast carcinoma (H). * stands for the maximum and minimum values.

Table 1 RRM2 expression in different subtypes of breast cancer and normal tissues using the Oncomine database

| Breast cancer subtype                      | P-value* | t test | Fold change | Patient number | Reference    |
|-------------------------------------------|----------|--------|-------------|----------------|--------------|
| Male breast carcinoma                     | 1.95E-19 | 19.864 | 9.832       | 3              | TCGA          |
| Intraductal cribriform breast adenocarcinoma | 1.32E-17 | 18.111 | 8.163       | 3              | TCGA          |
| Invasive breast carcinoma                 | 1.24E-28 | 14.159 | 5.003       | 76             | TCGA          |
| Invasive lobular breast carcinoma         | 3.51E-16 | 9.962  | 4.522       | 36             | TCGA          |
| Invasive ductal breast carcinoma          | 2.51E-38 | 20.624 | 5.282       | 389            | TCGA          |
| Ductal breast carcinoma in situ epithelia | 2.05E-5  | 5.180  | 12.792      | 9              | PMID: 19187537 |
| Invasive ductal breast carcinoma epithelia | 9.52E-5  | 4.513  | 10.319      | 9              | PMID: 19187537 |
| Ductal breast carcinoma                   | 6.37E-6  | 9.800  | 39.696      | 40             | PMID: 16473279 |

*Statistical significance was determined by the Student’s t test.

PrognoScan
The PrognoScan (http://www.prognoscan.org/) is a large database with clinical annotation and a web-based tool for assessing the biological relationship between gene expression and prognostic information including overall survival, relapse-free survival, distant metastasis-free survival, disease-specific survival, and disease-free survival in breast cancer patients [18]. Cox P-values and hazard ratio (HR) with 95% confidence intervals were calculated automatically.
Table 2 Relationship between RRM2 expression and clinical parameters of breast cancer patients using the bc-GenExMiner database

| Variables                  | Patient number | RRM2 mRNA | P-value* |
|----------------------------|----------------|-----------|----------|
| Age (years)                |                |           |          |
| ≤51                        | 1317           | −         | 0.1700   |
| >51                        | 2015           | −         |          |
| ER                         |                |           | <0.0001  |
| Negative                   | 1468           | Increased |          |
| Positive                   | 3810           | −         |          |
| PR                         |                |           | <0.0001  |
| Negative                   | 946            | Increased |          |
| Positive                   | 1439           | −         |          |
| HER-2                      |                |           | <0.0001  |
| Negative                   | 1409           | −         |          |
| Positive                   | 201            | Increased |          |
| Nodal status               |                |           | 0.0175   |
| Negative                   | 2447           | −         |          |
| Positive                   | 1509           | Increased |          |
| Basal-like status          |                |           | <0.0001  |
| Non-basal-like             | 4089           | −         |          |
| Basal-like                 | 1112           | Increased |          |
| Triple-negative status     |                |           | <0.0001  |
| Non-triple-negative        | 3986           | −         |          |
| Triple-negative            | 374            | Increased |          |

*Statistical significance was determined by the Welch's test.

Table 3 RRM2 expression and survival data of breast cancer patients using the PrognoScan database

| Dataset   | Probe name   | End point                     | Patient number | Cox P-value | HR       |
|-----------|--------------|-------------------------------|----------------|-------------|----------|
| GSE12276  | 209773_s_at  | Relapse-free survival         | 204            | 0.001805    | 1.36 [1.12–1.65] |
| GSE6532-GPL570 | 209773_s_at  | Relapse-free survival         | 87             | 0.025415    | 1.39 [1.04–1.87] |
| GSE6532-GPL570 | 209773_s_at  | Distant metastasis-free survival | 87             | 0.025415    | 1.39 [1.04–1.87] |
| GSE9195    | 209773_s_at  | Relapse-free survival         | 77             | 0.029912    | 2.01 [1.07–3.78] |
| GSE9195    | 209773_s_at  | Distant metastasis-free survival | 77             | 0.027181    | 2.30 [1.10–4.82] |
| GSE11121   | 209773_s_at  | Distant metastasis-free survival | 200            | 0.001108    | 1.99 [1.32–3.02] |
| GSE2034    | 209773_s_at  | Distant metastasis-free survival | 286            | 0.001001    | 1.64 [1.22–2.20] |
| GSE1456-GPL96 | 209773_s_at  | Overall survival              | 159            | 0.000074    | 2.41 [1.56–3.73] |
| GSE1456-GPL96 | 209773_s_at  | Relapse-free survival         | 159            | 0.000026    | 2.53 [1.64–3.90] |
| GSE1456-GPL96 | 209773_s_at  | Disease-specific survival     | 159            | 0.000014    | 3.23 [1.90–5.47] |
| GSE7378    | 201890_at    | Disease-free survival         | 54             | 0.021327    | 1.99 [1.11–3.59] |
| GSE7378    | 209773_s_at  | Disease-free survival         | 54             | 0.013458    | 2.36 [1.19–4.67] |
| E-TABM-158 | 209773_s_at  | Disease-specific survival     | 117            | 0.026993    | 0.71 [0.53–0.96] |
| GSE3494-GPL96 | 209773_s_at  | Disease-specific survival     | 236            | 0.000122    | 2.07 [1.43–3.00] |
| GSE4922-GPL96 | 209773_s_at  | Disease-free survival         | 249            | 0.000007    | 1.96 [1.46–2.63] |
| GSE2990    | 209773_s_at  | Relapse-free survival         | 62             | 0.016824    | 1.73 [1.10–2.70] |
| GSE2990    | 209773_s_at  | Distant metastasis-free survival | 54             | 0.012179    | 2.04 [1.17–3.58] |
| GSE7390    | 209773_s_at  | Overall survival              | 198            | 0.012109    | 1.35 [1.07–1.70] |
| GSE7390    | 209773_s_at  | Distant metastasis-free survival | 198            | 0.049656    | 1.24 [1.00–1.54] |
Figure 3. Box plot evaluating RRM2 expression among groups of patients according to different clinical parameters using the bc-GenExMiner software

Analysis is shown for age (A), SBR (B), NPI (C), ER (D), PR (E), HER-2 (F), nodal status (G), basal-like status (H), and triple-negative status (I).

Kaplan–Meier Plotter
The Kaplan–Meier Plotter (http://kmplot.com/analysis/), a platform containing gene expression information and survival data of 5143 clinical breast cancer patients, was applied to verify the prognostic value of RRM2 gene in overall survival, relapse-free survival, and distant metastasis-free survival [19].

UCSC Xena
The heat map of RRM2 and KIF11 in the same patient cohort were constructed by data mining in TCGA Breast Cancer using the UCSC Xena browser (http://xena.ucsc.edu/).

Results

Increased expression of RRM2 gene in breast cancer patients
We first checked the expression of RRM2 gene in 20 types of malignant tumor using the Oncomine database. Increased level of RRM2 (red) was observed in gastrointestinal cancers, gynecological cancers, urogenital cancers, and breast cancer (Figure 1). Our analysis also revealed that RRM2 was significantly higher expressed in male breast carcinoma, intraductal cribriform breast adenocarcinoma, invasive breast carcinoma, invasive lobular breast carcinoma, invasive ductal breast carcinoma, ductal breast carcinoma in situ, invasive ductal breast carcinoma epithelia, and ductal breast carcinoma, compared with the corresponding normal tissues (Figure 2A–H and Table 1).

RRM2 expression and clinical parameters in breast cancer patients
By using the bc-GenExMiner online tool, we next compared RRM2 expression among groups of patients, according to different clinical parameters. Regarding age, there was no significant difference between ≤51- and >51-year
Figure 4. Survival curve and forest plot evaluating the prognostic value of RRM2

Analysis is shown for overall survival (A), relapse-free survival (B), distant metastasis-free survival (C) using the Kaplan–Meier Plotter, and forest plot of metastatic relapse event using the bc-GenExMiner database (D).

RRM2 expression and prognosis in breast cancer patients

We then investigated the prognostic value of RRM2 gene. The Kaplan–Meier curves indicated that lower level of RRM2 correlated with preferable overall survival (Figure 4A). While breast cancer patients with up-regulated RRM2 demonstrated worse relapse-free survival (Figure 4B), patients with decreased RRM2 expression presented better distant metastasis-free survival (Figure 4C). Furthermore, RRM2 exerted positive effect on metastatic relapse event, as suggested by the forest plot using the bc-GenExMiner tool (Figure 4D). The PrognoScan database showed that overexpression of RRM2 was significantly associated with inferior overall survival, relapse-free survival, distant metastasis-free survival, disease-specific survival, and disease-free survival (Table 3).

Co-expression of RRM2 gene

To further investigate the underlying regulation of RRM2 in breast cancer, data mining of the co-expression of RRM2 gene was performed using the Oncomine database. The co-expression profile of RRM2 was identified with a large cluster of 1802 genes across 61 breast carcinomas, and KIF11 is a principal correlated gene (Figure 5A). Data mining in bc-GenExMiner revealed a positive correlation between RRM2 and KIF11 (Figure 5B). By comparing the RRM2...
Figure 5. Co-expression of RRM2 gene

(A) Co-expression profile of RRM2 identified using the Oncomine database. (B) Correlation between RRM2 and KIF11 expression in breast cancer analyzed using the bc-GenExMiner software. (C) Heat map of RRM2 and KIF11 expression across PAM50 breast cancer subtypes in the TCGA database obtained from the UCSC Xena web-based tool.

and KIF11 expression heat map derived from the UCSC Xena web-based tool, it was confirmed that RRM2 expression gradually elevated with increasing KIF11 transcript level, which was determined among a 50-gene qPCR assay (PAM50) breast cancer subtypes in TCGA database (Figure 5C). These data indicated that RRM2 could be associated with the KIF11 signaling pathways in breast cancer.

Discussion

RRM2 plays vital roles in diverse cellular functions such as cell proliferation, invasiveness, migration, angiogenesis, senescence, and tumorigenesis [3]. It was reported that RRM2 was associated with resistance of breast cancer cells to chemotherapy and endocrine agents and that targeting RRM2 may be a novel strategy for cancer treatment [11–14]. However, the significance of RRM2 expression in prognosis of breast cancer remains largely unclear.

In the present work, we analyzed the expression profile of RRM2 by Oncomine database. RRM2 gene was higher expressed in male breast carcinoma, intraductal cribriform breast adenocarcinoma, invasive breast carcinoma, invasive lobular breast carcinoma, invasive ductal breast carcinoma, ductal breast carcinoma in situ, invasive ductal breast carcinoma epithelia, and ductal breast carcinoma patients, with respect to normal individuals. By using the bc-GenExMiner online tool, we found that ER and PR were negatively correlated with RRM2 expression. Conversely, SBR, NPI, HER-2 status, nodal status, basal-like status, and triple-negative status were positively related to RRM2 level in breast cancer samples with respect to normal tissues. As known to all, patients with ER or PR negative, nodal positive, HER-2 positive, basal-like positive, basal-like or triple-negative status generally display an unsatisfied therapeutic response and
worse clinical outcome. Therefore, our results suggested that lower expression of \( RRM2 \) may predict a better prognosis of breast cancer.

We further investigated the prognostic value of \( RRM2 \) in breast cancer using the Kaplan–Meier Plotter, PrognoScan, and bc-GenExMiner databases. Patients with increased \( RRM2 \) showed worse overall survival, relapse-free survival, distant metastasis-free survival, disease-specific survival, and disease-free survival. Additionally, high \( RRM2 \) expression was correlated with an increased risk of metastatic relapse event, as suggested by the forest plot. These findings collectively demonstrated that the level of \( RRM2 \) might be a useful predictive biomarker for prognosis of breast cancer. We finally analyzed the co-expression of \( RRM2 \) using the Oncomine, bc-GenExMiner, and UCSC Xena web-based tools and confirmed that \( KIF11 \) gene was positively correlated with \( RRM2 \) expression. \( KIF11 \), a molecular motor protein involved in mitosis, was critical for proliferation and self-renewal in chemoresistant breast cancer cells [20]. \( KIF11 \) knockdown inhibited tumor growth both \textit{in vitro} and \textit{in vivo}, and its expression was responsible for shorter survival time [21]. Thus, our data indicated that \( RRM2 \) might contribute to breast cancer progression and drug insensitivity associated with \( KIF11 \) expression.

In summary, the present bioinformatics analysis showed that \( RRM2 \) was overexpressed in breast cancer patients with respect to normal tissues and was associated with a worse survival. \( RRM2 \) could be used as a predictive biomarker for prognosis of breast cancer with co-expressed \( KIF11 \) gene. Further studies are needed to more precisely elucidate the value of \( RRM2 \) in evaluating breast cancer prognosis.

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**Competing interests**

The authors declare that there are no competing interests associated with the manuscript.

**Author contribution**

Conceived and designed the experiments: W.-X.C. and L.-G.Y. Analyzed the data: W.-X.C., L.-Y.X., and L.C. Contributed analysis tools: Q.Q., L.S., and Y.-L.Z. Wrote the paper: W.-X.C.

**Abbreviations**

bc-GenExMiner, Breast Cancer Gene-Expression Miner; ER, estrogen receptor; HER-2, human epidermal growth factor receptor-2; NPI, Nottingham Prognostic Index; PR, progesterone receptor; \( RRM2 \), ribonucleotide reductase M2 subunit; SBR, Scarff–Bloom–Richardson.

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