Expression of the BRCA1 complex member BRE predicts disease-free survival in breast cancer

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Abstract Breast cancer is one of the leading causes of cancer mortality in women. Recent advances in gene expression profiling have indicated that breast cancer is a heterogeneous disease and the current prognostication using clinico-pathological features is not sufficient to fully predict therapy response and disease outcome. In this retrospective study, we show that expression levels of BRE, which encodes a member of the BRCA1 DNA damage repair complex, predicted disease-free survival (DFS) in non-familial breast cancer patients. The predictive value of BRE expression depended on whether patients received radiotherapy as a part of their primary treatment. In radiotherapy-treated patients, high BRE expression predicted a favorable DFS (hazard ratio (HR) = 0.47, 95% confidence interval (CI) = 0.28–0.78, p = 0.004), while in non-treated patients, high BRE expression predicted an adverse prognosis (HR = 2.59, 95% CI = 1.00–6.75, p = 0.05). Among radiotherapy-treated patients, the prognostic impact of BRE expression was confined to patients with smaller tumors (HR = 0.23, 95% CI = 0.068–0.75, p = 0.015) and it remained an independent factor after correction for the other prognostic factors age, tumor size, lymph node involvement, and histological grade (HR = 0.50, CI = 0.27–0.90, p = 0.021). In addition, high BRE expression predicted a favorable relapse-free survival in a publicly available dataset of 2,324 breast cancer patients (HR = 0.59, CI = 0.51–0.68, p < 0.001). These data indicate that BRE is an interesting candidate for future functional studies aimed at developing targeted therapies.

Keywords BRE · Radiotherapy · DNA damage repair · BRCA1 · Breast cancer

Introduction

Despite great improvements in diagnostic imaging techniques and treatment, breast cancer remains one of the leading causes of cancer mortality in women. Prognostication of breast cancer patients nowadays relies highly on classical clinico-pathological features, such as tumor size, histological grade, age, and lymph node metastases [1]. However, it remains a challenge to accurately predict disease outcome based on these parameters, which is necessary not to under or over treat the patients.

Over the last 20 years, there has been great interest in developing prognostic patient classification methods based on molecular screenings. Genome-wide gene expression screens have identified expression profiles that predict disease outcome and therapy response. For example, in several large patient studies, a 70-gene signature called the “MammaPrint” (Agendia, Amsterdam, the Netherlands) has been shown to outperform classical prognostication methods [2–4]. Together with other molecular classification methods [5, 6], these data indicate that the
identification of differential gene expression has great potential for improved prediction of disease outcome and subsequent treatment decisions.

DNA double strand breaks (DSBs) are one of the most cytotoxic types of DNA damage. The importance of proper repair of these breaks to maintain genomic integrity is exemplified by recurrent mutations in genes involved in DSB repair in various cancers. For example, BRCA1 mutations occur in approximately 20 % of familial breast cancer cases [7–9]. The importance of the BRCA1 multi-protein complex has been exemplified by the identification of polymorphisms and haplotypes within other BRCA1 complex members, such as RAP80 and ABRAXAS, both in BRCA1/2 mutated and non-mutated familial breast cancer patients. However, the clinical impact of these polymorphisms remains to be confirmed [10–15]. Furthermore, BRCA1 expression levels seem to predict breast cancer outcome in non-familial cases [16–19] although data are not consistent [20].

Recently, it has been shown that high expression of BRE (Brain and Reproductive organ-Expressed), another member of the BRCA1 complex [21–24], denotes a favorable prognosis in acute myeloid leukemia (AML) [25–27]. In this study, we demonstrate that BRE expression levels in breast cancer tumor tissue contained prognostic information in a cohort of 229 non-familial breast cancer patients, establishing the relevance of this DNA damage repair factor in breast cancer.

Materials and methods

Breast cancer samples

Frozen breast cancer tissue sections were available for two independent cohorts of 229 patients in total who had undergone resection of their primary tumor, as described before [28–30]. Patients underwent surgical resection of their primary tumor between November 1987 and December 1997 and were selected by the availability of RNA samples in the tumor bank of the Department of Chemical Endocrinology of the Radboud University Nijmegen Medical Centre (Nijmegen, The Netherlands). This bank contains tumor material from five different hospitals of the Comprehensive Cancer Centre East in the Netherlands. Patients had no previous diagnosis of carcinoma, no distant metastases at time of diagnosis, and no evidence of disease within 1 month after primary surgery. Patients that received neoadjuvant therapy or were diagnosed with carcinoma in situ were excluded from this study. Patients were treated with protocols established at that time. 60 % of the patients underwent mastectomy (137/229) and the remaining patients underwent lumpectomy. 74 % of the patients (169/229) received radiotherapy following surgery and 39 % (90/229) received systemic adjuvant treatment, in combination with radiotherapy or not. Adjuvant treatment consisted of endocrine treatment with tamoxifen and/or chemotherapy. Detailed patient characteristics can be found in Table 1. The median follow-up period of censored patients was 107.5 months. This study was performed according to REMARK guidelines [31].

BRE QPCR

Tissue collection, mRNA isolation, and cDNA preparation have been described before [29]. BRE expression was measured in both cohorts by QPCR using a commercially available primer/probe set (Hs01046283_m1, Life Technologies, Carlsbad, CA, USA) and normalized to expression of the housekeeping gene PBGD, as described in [26]. Normalized QPCR data were mean centered per analyzed cohort and afterward the data of the cohorts were combined to increase patient numbers for further analyses.

Statistical analyses

To statistically test the correlation of BRE expression with clinical parameters, the complete cohort was subdivided into two equally sized groups based on BRE expression. Differences in patient characteristics were tested by χ², Fisher exact, or Mann–Whitney U tests, as indicated. Disease-free survival (DFS; defined as time between surgery and diagnosis of recurrent or metastatic disease) and overall survival (OS; defined as time between surgery and death by any cause) were used as feature for disease outcome. The prognostic impact of BRE expression was visualized by Kaplan–Meier plots and statistically tested via the logrank method and univariate or multivariate Cox regression analyses. Statistical analyses were carried out by means of Graphpad (La Jolla, CA, USA) or SPSS (IBM Corporation, Armonk, NY, USA) software.

Results

BRE expression correlates with tumor size

To study the prognostic effect of BRE expression in breast cancer, BRE mRNA levels were measured in tumor tissues collected at diagnosis for a cohort of 229 breast cancer patients by QPCR. Given the association of BRE with DNA damage repair, we subdivided the patient cohort a priori in two groups based on whether they had received radiotherapy as a part of their primary treatment or not. BRE levels were gradually distributed and no difference was observed between radiotherapy-treated or non-treated
Table 1  Clinico-pathological characteristics of 229 non-familial breast cancer patients

|                                | Total cohort | Non-radiotherapy-treated | Radiotherapy-treated |
|--------------------------------|--------------|--------------------------|----------------------|
|                                | Low BRE\(^a\) (\(N = 115\)) | High BRE\(^a\) (\(N = 114\)) | \(p\)               |
|                                | Low BRE\(^a\) (\(N = 32\)) | High BRE\(^a\) (\(N = 27\)) | \(p\)               |
| Age (\(N = 229\), mean (range)) | 59.9 (31–88) | 59.2 (32–86) | 0.775\(^d\) 63.0 (33–88) | 61.5 (35–86) | 0.784\(^d\) 58.7 (31–85) | 58.3 (32–83) | 0.816\(^d\) |
| Menopausal status (\(N = 229\)) | 1.000\(^e\) |                          |                      |
| Premenopausal, no. (%)         | 29 (25.2) | 28 (24.6) | 0.923\(^e\) 6 (18.8) | 5 (18.5) | 0.923\(^e\) 23 (19.7) | 13 (16.7) | 0.806\(^e\) 0.310\(^e\) 0.806\(^e\) |
| Postmenopausal, no. (%)        | 86 (74.8) | 86 (75.4) |                       | 26 (81.3) | 22 (81.5) | 60 (72.3) | 63 (73.3) |
| Nodal category (\(N = 208\))   | 0.923\(^e\) | 0.310\(^e\) 0.806\(^e\) |                      |
| Negative, no. (%)              | 61 (58.1) | 59 (57.3) | 25 (62.5) | 18 (72.0) | 36 (47.4) | 41 (52.6) |
| 1–3 involved lymph nodes, no. (%) | 29 (27.6) | 31 (30.1) | 4 (13.8) | 7 (28.0) | 25 (32.9) | 24 (30.8) |
| ≥4 involved lymph nodes, no. (%) | 15 (14.3) | 13 (12.6) | 0 (0) | 0 (0) | 15 (19.7) | 13 (16.7) |
| Radiotherapy (\(N = 228\))     | 0.547\(^e\) | NA |                                   | 0.495\(^f\) | 0.219\(^f\) |
| Treated, no. (%)               | 83 (72.2) | 86 (76.1) | 0 (0) | 0 (0) | 83 (100) | 86 (100) |
| Non-treated, no. (%)           | 32 (27.8) | 27 (23.9) | 32 (100) | 27 (100) | 0 (0) | 0 (0) |
| Surgery (\(N = 229\))          | 0.282\(^e\) | 0.495\(^f\) 0.219\(^f\) |                      |
| Mastectomy, no. (%)            | 73 (63.5) | 64 (56.1) | 30 (93.8) | 27 (100) | 43 (51.8) | 36 (41.9) |
| Lumpectomy, no. (%)            | 42 (36.5) | 50 (43.9) | 2 (6.3) | 0 (0) | 40 (48.2) | 50 (58.1) |
| Adjuvant systemic therapy (\(N = 228\)) | 0.230\(^f\) | 0.533\(^f\) 0.269\(^f\) |                      |
| None, no. (%)                  | 70 (60.9) | 68 (60.2) | 26 (81.3) | 18 (66.7) | 44 (53.0) | 50 (58.1) |
| Endocrine therapy, no. (%)     | 30 (26.1) | 28 (24.8) | 3 (9.4) | 4 (14.8) | 27 (32.5) | 24 (27.9) |
| Chemotherapy, no. (%)          | 13 (11.3) | 9 (8.0) | 2 (6.3) | 2 (7.4) | 11 (13.3) | 7 (8.1) |
| Endocrine + Chemotherapy, no. (%) | 2 (1.7) | 8 (7.1) | 1 (3.1) | 3 (11.1) | 1 (1.2) | 5 (5.8) |
| Histology grade (\(N = 168\))  | 0.406\(^e\) | 0.151\(^f\) 0.123\(^e\) |                      |
| I, no. (%)                     | 9 (10.5) | 4 (4.9) | 1 (4.3) | 1 (5.3) | 8 (12.7) | 3 (4.8) |
| II, no. (%)                    | 36 (41.9) | 35 (42.7) | 6 (26.1) | 10 (52.6) | 30 (47.6) | 25 (39.7) |
| III, no. (%)                   | 41 (47.7) | 43 (52.4) | 16 (69.6) | 8 (42.1) | 25 (39.7) | 35 (55.6) |
| Tumor type (\(N = 193\))       | 0.744\(^e\) | 0.721\(^f\) 1.000\(^e\) |                      |
| Ductal, no. (%)                | 73 (73.0) | 70 (75.3) | 22 (71.0) | 18 (81.8) | 51 (73.9) | 52 (73.2) |
| Tubular, no. (%)               | 15 (15.0) | 15 (16.1) | 3 (9.7) | 2 (9.1) | 12 (17.4) | 13 (18.3) |
| Other (mixed/unknown), no. (%) | 12 (12.0) | 8 (8.6) | 6 (19.3) | 2 (9.1) | 6 (8.7) | 6 (8.5) |
| Tumor size (\(N = 227\))\(^c\) | 0.014\(^f\) | 0.853\(^f\) 0.005\(^e\) |                      |
| pT1, no. (%)                   | 33 (28.7) | 50 (44.6) | 11 (34.4) | 9 (33.3) | 22 (26.5) | 41 (48.2) |
| pT2, no. (%)                   | 66 (57.4) | 43 (38.4) | 19 (59.4) | 15 (55.6) | 47 (56.6) | 28 (32.9) |
| pT3/4, no. (%)                 | 16 (13.9) | 19 (17.0) | 2 (6.3) | 3 (11.1) | 14 (16.9) | 16 (18.8) |
| Estrogen receptor status (\(N = 196\)) | 0.769\(^e\) | 0.265\(^e\) 0.228\(^e\) |                      |
| Positive, no. (%)              | 61 (61.0) | 61 (63.5) | 18 (66.7) | 12 (50) | 43 (58.9) | 49 (69.0) |
| Negative, no. (%)              | 39 (39.0) | 35 (36.5) | 9 (33.3) | 12 (50) | 30 (41.1) | 22 (31.0) |
patients \( (p = 0.25) \). The dynamic range of expression was less than 50-fold \( (5.4 \text{ Ct}) \) and levels were normally distributed (based on a Kolmogorov–Smirnov test) (see Fig. 1a). This is in contrast to AML in which \( BRE \) is highly expressed in a distinctive subset of patients, while the remaining patients show little variation \[26\].

Comparisons of \( BRE \) expression with known clinico-pathological factors showed that \( BRE \) expression correlated with tumor size \( (p = 0.014) \), but not with any of the other parameters (Table 1). The correlation of \( BRE \) expression with tumor size was only observed in radiotherapy-treated patients in which high \( BRE \) expression was more often found in smaller tumors \( (p = 0.005, \text{ Table 1}) \).

**\( BRE \) expression predicts DFS in breast cancer**

Gradual differences in \( BRE \) expression (using continuous QPCR data) did not correlate with DFS or overall survival (OS) in the total cohort, as tested by univariate Cox regression analysis (DFS: Table 2, OS: data not shown). However, when the cohort was subdivided into radiotherapy-treated and non-treated patients, \( BRE \) expression (tested as continuous variable) had prognostic impact on DFS within both groups (Table 2). Remarkably, \( BRE \) expression showed opposite effects on prognosis. In the radiotherapy-treated group \( (N = 169) \), which accounted for the majority of the patients, high \( BRE \) expression correlated with a favorable DFS \( \text{(Hazard ratio (HR) } = 0.72, 95 \% \text{ confidence interval (CI) } = 0.53–0.97, p = 0.030) \), while in the non-radiotherapy-treated group \( (N = 59) \), high \( BRE \) expression correlated with a poor prognosis \( \text{(HR} = 1.79, \text{ CI} = 1.11–2.87, p = 0.016) \). Similar results were obtained when subdividing patients into two or three groups based on \( BRE \) expression, instead of using gradual QPCR data (Table 3, and data not shown).

The effect of \( BRE \) expression on DFS was visualized by Kaplan–Meier plots by subdividing the total cohort into two groups using the median of \( BRE \) expression as cut-off. Among the patients who did not receive radiotherapy, high \( BRE \) expression predicted an adverse prognosis validating the Cox regression analysis \( \text{(HR} = 2.59, \text{ CI} = 1.00–6.75, p = 0.05) \). High \( BRE \) expression predicted a favorable prognosis among the patients who received radiotherapy \( \text{(HR} = 0.47, \text{ CI} = 0.28–0.78, p = 0.004) \) (Fig. 1b). Interestingly, within the radiotherapy-treated patients, a significant correlation between \( BRE \) expression and DFS was only observed for the group of patients with smaller tumors \( \text{(HR} = 0.23, \text{ CI} = 0.068–0.75, p = 0.015) \), which contained relatively more high \( BRE \) expressing patients (Table 1; Fig. 2). No significant prognostic impact was observed in patients with larger tumors (Fig. 2). Radiotherapy was combined with adjuvant systemic treatment for a part of the cohort (see Table 1). To exclude the possibility that the effect of \( BRE \)
expression on prognosis depended on the combination of radiotherapy and adjuvant treatment, we calculated the effect of $BRE$ expression on DFS for patients treated by radiotherapy only (94 of the 169 patients that received radiotherapy). This analysis showed that also within this subcohort, high $BRE$ expression predicted favorable disease outcome (HR = 0.38, CI = 0.18–0.78, $p = 0.009$, data not shown). Within the group of patients who did not receive radiotherapy, 75% did not receive adjuvant treatment either (44 of the 59 patients). Within this group of patients, the effect of $BRE$ expression on DFS lost its significance (data not shown). This might indicate that in non-radiotherapy treated patients, the effect of $BRE$ expression on DFS is dependent on adjuvant treatment. However, as the number of patients receiving adjuvant treatment without radiotherapy was too small, we were not able to test this hypothesis.

$BRE$ expression is an independent prognostic factor in radiotherapy-treated patients

To determine whether $BRE$ expression was an independent prognostic factor for DFS in breast cancer, multivariate Cox regression analyses were performed. These analyses showed that $BRE$ expression was a prognostic factor within the group of radiotherapy-treated patients, independent of other tested prognostic factors such as age, tumor size, lymph node involvement, and histological grade (HR = 0.50, CI = 0.27–0.90, $p = 0.021$, shown in Table 3). Of note, also age, tumor size, and the number of involved lymph nodes were independent prognostic factors in this group of patients. For non-radiotherapy-treated patients, $BRE$ expression did not correlate significantly with DFS in the multivariate analysis.

$BRE$ expression predicts outcome in a large independent breast cancer cohort

To determine whether $BRE$ expression has an impact on survival in other patient cohorts, we extended our studies to a large independent, publicly available micro-array dataset of 2,324 patients (see Fig. 3, Kaplan–Meier Plotter [32] (www.kmplot.com)). We observed a favorable prognosis for patients with high $BRE$ expression (upper 50% of the patients) and an adverse survival for patients with low $BRE$ expression (lower 50%) (HR = 0.59, CI = 0.51–0.68, $p < 0.001$ after correction for multiple testing). The data of this cohort resembled the data of the first cohort of radiotherapy-treated patients (Fig. 1b). However, as no data...
were available on the number of patients who received radiotherapy within this publically available cohort, we were unable to test whether the prognostic effect of BRE expression was influenced by radiotherapy treatment.

**Discussion**

High expression of the BRCA1 complex member BRE has recently been identified in a subgroup of AML patients in whom it defines favorable prognosis [25, 26]. Here, we show that the expression of this gene also predicted disease outcome in a cohort of 229 non-familial breast cancer patients. Interestingly, the predictive value of BRE expression at diagnosis on DFS depended on whether the patient received subsequent radiotherapy treatment or not. In radiotherapy-treated patients, high BRE expression predicted a favorable disease outcome, whereas in non-radiotherapy-treated patients, it correlated with an adverse outcome (see Fig. 1; Table 3). To extend our studies, BRE expression was evaluated in a publicly available dataset of 2,324 breast cancer patients [32]. In this large cohort, high BRE expression predicted a favorable relapse-free survival, resembling the data of radiotherapy-treated patients within

### Table 2 Univariate analysis of BRE expression in correlation with DFS

|                     | Total cohort | Non-radiotherapy-treated patients | Radiotherapy-treated patients |
|---------------------|-------------|-----------------------------------|------------------------------|
|                     | p           | HR (95 % CI)                       | p                            | HR (95 % CI) |
| BRE expression (QPCR data) | 0.342      | 0.877 (0.67–1.15)                    | 0.016                        | 1.79 (1.11–2.87) |
|                     |             |                                   | 0.030                        | 0.72 (0.53–0.97) |

*HR* hazard ratio; *CI* confidence interval

### Table 3 Multivariate Cox regression analysis of BRE expression correlation with DFS

|                     | Non-radiotherapy-treated patients | Radiotherapy-treated patients |
|---------------------|-----------------------------------|------------------------------|
|                     | Univariate | Multivariatea | Univariate | Multivariatea |
|                     | p          | HR (95 % CI) | p          | HR (95 % CI) | p          | HR (95 % CI) |
| BRE (2 groupsb)     | 0.059e     | 2.51 (0.97–6.53) | 0.083e     | 2.38 (0.89–6.35) | 0.004      | 0.46 (0.27–0.79) |
|                     | (continuous) | 0.349 | 0.98 (0.89–6.35) | 0.616 | 0.99 (0.96–1.00) | 0.112 | 0.98 (0.95–1.00) |
|                     | (post- vs. premenopausal) | 0.838 | 1.07 (0.57–1.99) | 0.140 | 0.81 (0.62–1.07) |
| Tumor sizec (pT1 vs. pT2 vs. pT3/4) | 0.422 | 1.39 (0.62–3.09) | 0.465 | 1.56 (0.47–5.15) | <0.001 | 2.01 (1.42–2.84) |
| Histological grade (I vs. II vs. III vs. NDd) | 0.941 | 0.97 (0.39–2.42) | 0.895 | 1.01 (0.86–1.19) | 0.032 | 1.70 (0.86–1.05) |
| Involved lymph nodes (0 vs. 1–3 vs. ≥ 4) | 0.002 | 5.63 (1.84–17.3) | 0.034 | 3.92 (1.11–13.8) | 0.001 | 1.87 (1.30–2.68) |
| Estrogen receptor status (positive vs. negative) | 0.680 | 0.82 (0.31–2.15) | 0.362 | 0.78 (0.45–1.34) |
| Progesterone receptor status (positive vs. negative) | 0.866 | 0.92 (0.36–2.39) | 0.839 | 0.95 (0.55–1.62) |

*a* Factors included in multivariate analysis: BRE expression, age, tumor size, histological grade, and involved lymph nodes  
*b* The two groups are defined as BRE expression above or below the median expression of the total cohort, respectively  
*c* pT1: tumor size ≤ 2 cm, pT2: tumor size of 2–5 cm, pT3/4: tumor size >5 cm and/or direct extension to chest wall or skin  
*d* As data on histological grading were missing for a substantial number of patients, this group (ND not done) was included in the multivariate analyses as separate group next to histological grade I, II, or III  
*e* In non-radiotherapy-treated patients, BRE expression lost its significance when the median expression was used to divide patients based on BRE expression. When subdividing patients into three groups based on BRE expression, BRE was a significant predictor for DFS in both univariate and multivariate models  

*HR* hazard ratio; *CI* confidence interval
the cohort studied in this manuscript (Fig. 1b). The large cohort of 2,324 patients represents a collection of previously published gene expression datasets, for which integral data on clinico-pathological factors are unavailable. Therefore, we were unable to determine the impact of radiotherapy on the effect of BRE expression on disease outcome in this cohort. The identification of prognostic impact of BRE expression in two independent cohorts warrants further studies in large cohorts to validate the effects found in radiotherapy-treated and non-treated patients.

The fact that BRE expression predicted opposing effects on disease outcomes depending on radiotherapy treatment might imply that there are intrinsic differences in breast cancer patients who are treated or not treated with radiotherapy. Alternatively, there might be a direct effect of high BRE expression on radiotherapy response. The effect of BRE expression on disease outcome was not due to co-treatment with adjuvant therapy within the radiotherapy-treated group of patients as the effect of BRE expression on DFS was also present in the subgroup of radiotherapy-treated patients who did not receive adjuvant treatment. The decision for radiotherapy treatment is closely related to surgical treatment and depends on multiple factors like tumor size and the involvement of axillary lymph nodes. As the patients were consequently not randomly assigned for treatment, it was not possible to explain the opposing effect of BRE expression on the prognosis of radiotherapy-treated versus non-treated patients in this cohort. Therefore, it would be of particular interest to test BRE expression in a cohort of patients who received radiotherapy in a randomized fashion to evaluate a direct effect of BRE expression on therapy outcome.

BRE is a member of the BRCA1 complex involved in DNA double strand break repair [21–24]. This complex is recruited to DNA damaged sites via binding of the complex member Rap80 to ubiquitin chains, which are generated upon DNA damage [33–35]. Mutations in DNA damage repair factors are closely linked to familial breast cancer as 25% of these cases is characterized by mutations in factors...
involved in the DNA damage repair pathway, like BRCA1, BRCA2, PTEN, p53, CHEK2, and ATM [7–9, 36–39]. However, in non-familial breast cancer, these mutations are rare. In non-familial cases, associations between low BRCA1 expressions with poor prognosis have been identified [16–19] resembling the observations we made for BRE expression in radiotherapy-treated patients.

Depletion of BRE abrogates BRCA1 foci formation, indicating that BRE is needed for complex formation and downstream DNA repair [22–24, 40]. Several studies have described an increased radiosensitivity of cells after BRE depletion [21, 22]. Next to a role in the BRCA1 complex, BRE is also involved in death receptor-mediated apoptosis as it binds TNFα and FAS receptors, and overexpression of BRE caused resistance to apoptosis induction by various stress-related stimuli [41]. This indicates that BRE serves an anti-apoptotic role following different types of stress. It was therefore unexpected to find a positive correlation between high BRE expression and breast cancer outcome in relation to radiotherapy. High expression would enhance DNA repair and hence would render cells resistant to radiotherapy. Indeed, this reasoning seems to be true for BRCA1 as radiotherapy has been shown to be especially beneficial for patients with low BRCA1 levels, whereas there was no benefit for patients with high BRCA1 levels [42]. On the other hand, high expression of the Mre11/Rad50/Nbs1 complex, also involved in DNA damage repair, predicts a good response to radiotherapy [43], indicating that DNA repair proteins can contribute differentially to radiotherapy response. In this case, high BRE expression might attenuate the DNA damage repair pathway following radiotherapy. Potentially, high BRE expression causes a misbalance in the BRCA1 multi-protein complex formation, thereby reducing the functionality of the complex and rendering cells more sensitive to radiation-induced DNA damage. It would be of particular interest to study the subcellular localization of BRE in these tumors to determine whether responses can be attributed to the DNA damage response or death receptor signaling. The data described in this study indicate that BRE is an interesting candidate for further functional studies in breast cancer to test its effect on radiotherapy responses.

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Conflict of interest The authors declare no conflict of interest in this study.

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