Loss of BRCA1 Expression May Predict Shorter Time-to-progression in Metastatic Breast Cancer Patients Treated with Taxanes

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Abstract. *Background: Preclinical studies have indicated that BRCA1 functions differentially to modulate the chemosensitivity of cancer cells. Patients and Methods: To clarify these findings, BRCA1 expression in primary tumors was evaluated by immunohistochemistry in 50 patients with metastatic breast cancer. Results: BRCA1 expression was absent in 29 (58.0%) out of the 50 breast tumors tested. BRCA1-absent tumors were more frequently progesterone receptor-negative (p=0.019) than BRCA1-present tumors. Taxane-based chemotherapy was administered to 19 patients. Although BRCA1 expression did not relate to the clinical tumor response to taxane-based chemotherapy, time-to-progression (TTP) was significantly shorter in patients with BRCA1-absent tumors than in BRCA1-present tumors (mean±SD: 6.5±4.9 and 14.7±5.9 months, respectively; p=0.006). The Cox proportional hazard model revealed that BRCA1 absence was an independent predictor of progression (hazard ratio: 3.22; p=0.035). Conclusion: These results suggest that the absence of BRCA1 expression is an independent predictor of shorter TTP in advanced breast cancer patients treated with taxane-based chemotherapy.*

Germline mutations in *BRCA1* account for approximately 3% of all breast cancer cases (1). The *BRCA1* gene encodes a nuclear protein that responds to DNA damage by participating in the cellular pathways responsible for DNA repair, mRNA transcription, cell cycle regulation and protein ubiquitination (1). Since most chemotherapeutic agents function by damaging DNA, the role of BRCA1 as a predictive biomarker of response to these agents has been investigated (2). As no predictive response biomarker is currently available to guide the choice of cytotoxic chemotherapy for cancer, a number of patients will fail to respond to these agents without clinical benefit. Several possible biomarkers, such as *p53* mutations (3) and HER2 overexpression (4), are under investigation without conclusive results.

Preclinical studies have indicated that BRCA1 functions differentially to modulate the chemosensitivity of cancer cells. It has been suggested that BRCA1 inhibits apoptosis after treatment with DNA-damaging agents, such as alkylating agents, topoisomerase I or II inhibitors and platinum-based compounds. In contrast, BRCA1 is required for the induction of apoptosis in response to spindle poisons (5). It has been reported that the mechanism by which BRCA1 participates in the sensitivity to spindle poisons may involve the stress-activated c-jun N-terminal kinase pathway (6).

Anthracyclines and taxanes play an important role, not only in the management of metastatic breast cancer, but also in the postoperative adjuvant setting. Both agents are active as anticancer agents but are toxic. Several adverse events, such as severe myelosuppression, alopecia and peripheral neuropathy are frequently observed in patients treated with these agents. It is essential for so-called tailor-made treatments to find biomarkers that can predict sensitivity to cytotoxic chemotherapy. These findings prompted us to investigate BRCA1 expression in breast cancer tissues as a predictive biomarker for advanced breast cancer patients treated with anthracyclines or taxanes.

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Patients and Methods

Patients. Four hundred and twenty patients with primary breast cancer underwent radical surgery in the Department of Breast and Thyroid Surgery, Kawasaki Medical School between 1991 and 1999, with recurrence occurring in 72 patients by December 2002. Complete data on the treatment procedures, outcome and follow-ups were available for 50 out of the 72 patients. Taxane-based chemotherapy was administered in 19 out of the 50 patients and anthracycline-based chemotherapy in 25 out of the 50 patients. Medical records were reviewed in December 2004.

In the taxane-based chemotherapy group, 13 patients received taxane (docetaxel or paclitaxel) alone, 3 patients taxane with medroxyprogesterone acetate, 2 patients taxane with pamidronate and one taxane with trastuzumab. Patient characteristics were as follows (median and range): age, 58 years (41 – 69); disease-free survival, 21 months (1 – 73); and number of previous chemotherapy regimens, 1 (0 – 3). The main metastatic site was the viscera in 9 patients, soft tissue in 8 patients and bone in 2 patients. In the anthracycline-based chemotherapy group, 16 patients received anthracycline (pirarubicin, epirubicin or doxorubicin) alone and 9 patients received a combined chemotherapy with anthracycline, 5-Fluorouracil and/or cyclophosphamide. Medroxyprogesterone acetate was concurrently administered to 6 patients and toremifene citrate to one patient. Their characteristics were as follows (median and range): age, 54 years (31 – 67); disease-free survival, 20 months (1 – 73); and number of previous chemotherapy regimens, 1 (0 – 4). The main metastatic site was the soft tissue in 10 patients, viscera in 9 patients, and bone in 6 patients.

The clinical response to chemotherapy was classified according to the UICC criteria (7) into 4 categories: complete response (CR, disappearance of tumor and continuous effect for more than 4 weeks), partial response (PR, tumor reduction rate more than 50% and no new lesions for more than 4 weeks), no change (NC, tumor reduction rate less than 50% or tumor enlargement rate less than 25% and no new lesions for 4 weeks), and progressive disease (PD, tumor enlargement rate more than 25% or appearance of new lesions). The response was clinically assessed every month after the start of treatment or earlier if clinically indicated. Patients who showed NC for at least 6 months were included in the assessment of clinical benefit.

Immunohistochemistry (IHC). Primary tumor samples of the 50 patients were subjected to IHC for BRCA1, estrogen receptors (ER), progesterone receptors (PgR), HER2, p53 and Ki-67. The samples (formalin-fixed and paraffin-embedded blocks) were obtained from the Department of Pathology, Kawasaki Medical School. Serial 5-μm sections were prepared and one was conventionally stained with hematoxylin-eosin solution. Franking sections were dewaxed with xylene and hydrated with PBS. The IHC assay was then performed as follows: retrieving the antigen by autoclaving (121˚C, 5 min); blocking endogenous peroxidase with 0.1% sodium azide and 0.3% hydrogen peroxidase; blocking nonspecific protein binding with 10% ovalbumin; and binding with diluted primary antibody: BRCA1 (rabbit polyclonal, Ab-1, Oncogene, Boston, MA, USA), 1:100; ER (mouse monoclonal, clone 1D5, Dako Corporation, Carpinteria, CA, USA), 1:500; PgR (mouse monoclonal, clone 1A6, Novocastra-Vector Laboratories Inc., Burlingame, CA, USA), 1:100; HER2 (rabbit polyclonal, Dako Corporation), 1:50; p53 (mouse monoclonal, Dako Corporation), 1:50; Ki-67 (mouse monoclonal, Dako Corporation), 1:50 with PBS at 4˚C overnight. Control experiments were performed by substituting normal mouse or rabbit serum for the primary antibody. The reaction was visualized with a Histfine kit (Nichirei, Tokyo, Japan). The sections were counterstained with hematoxylin. One pathologist (M. K.) evaluated the IHC in a blinded manner.

The IHC results were evaluated as follows: BRCA1, nuclear immunoreaction in more than 10% of the tumor cells as positive, 1-10% as weakly positive and none as absent; ER, nuclear immunoreaction in more than 10% as positive and less than 10% as negative; PgR, nuclear immunoreaction in more than 10% as positive and less than 10% as negative; HER2, the assessment of overexpression was performed as recommended by the HercepTest scoring guidelines (8); p53, the percentages of nuclear immunoreaction-positive cells; and Ki-67, the percentages of nuclear immunoreaction-positive cells.

Statistical analysis. All values are expressed as the mean±SD. ANOVA analysis was used to compare the differences between 2 groups. A 2-sided p value less than 0.05 was considered statistically significant. Actuarial survival curves were estimated using the Kaplan-Meier method and differences were compared with the log-rank test. Multivariate analysis was made using Cox proportional hazard model. All statistical analyses were performed using StatView computer software (ATMS Co., Tokyo, Japan).

Results

Clinicopathological characteristics of BRCA1-absent breast cancer. IHC analysis revealed that no nuclear expression of BRCA1 was detected in 29 (58%) of 50 primary breast tumors tested. A positive expression of BRCA1 was observed in 12 tumors (24%) and a weakly positive expression in 9 tumors (18%). Representative findings of the BRCA1 immunoreaction are shown in Figure 1.

The clinicopathological differences between BRCA1-absent and -present tumors were investigated. BRCA1-absent tumors tended to be ER-negative compared with BRCA1-present tumors (48.3% *vs.* 23.8%, $p=0.079$). BRCA1-absent tumors had a significantly higher PgR-negative rate than BRCA1-present tumors (51.7% *vs.* 19.0%, $p=0.019$). The other parameters, including age, tumor size, lymphovascular invasion, HER2 status, Ki-67 labeling index and p53-positive rate were not significantly different between BRCA1-absent and -present tumors (Table I).

Response and outcome of patients treated with taxane-based chemotherapy. To test the hypothesis that BRCA1 expression is a predictor of response to taxanes, the response and outcome of 19 patients treated with taxane-based chemotherapy were analyzed with regard to BRCA1 expression.

No difference was observed in terms of the objective response rate and clinical benefit rate between patients with BRCA1-absent and -present tumors (30.8% *vs.* 16.7%, not

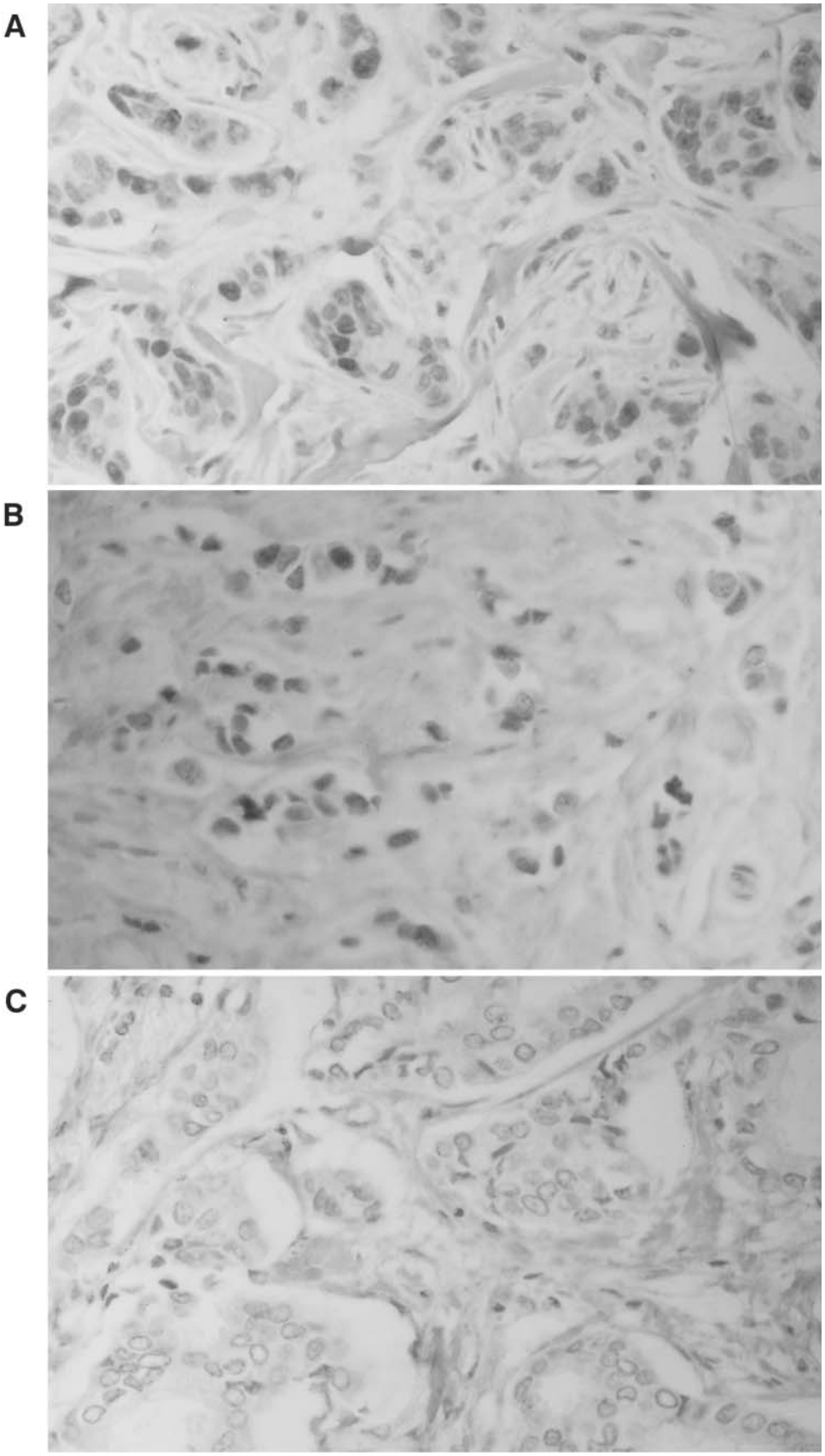

Figure 1. *Expression of BRCA1 protein in breast cancer tissues. Nuclear staining for BRCA1 is present in more than 10% of tumor cells (A, x 400), in 1 – 10% of tumor cells (B, x 400) and is absent in all tumor cells (C, x 400).*

Table I. *Clinicopathological charactersistics according to BRCA1 status.*

BRCA1	Absence (N=29)	Presence (N=21)	*p* value
Age (years)	52.3±9.2	49.4±9.4	NS[a]
Tumor size (cm)	3.2±2.6	3.4±3.1	NS
Nodal status			
Negative	4[b]	4	
Positive	25	17	NS
Lymphovascular invasion			
Negative	15	7	
Positive	12	13	NS
ER status			
Negative	14	5	
Positive	15	16	0.079
PgR status			
Negative	15	4	
Positive	14	17	0.019
HER2 status			
Negative	21	18	
Positive	8	3	NS
Ki-67 labeling index (%)	11.5±12.0	13.9±15.0	NS
p53-positive rate (%)	13.6±20.4	6.8±12.2	NS
Disease-free interval (months)	22.4±17.7	24.5±18.0	NS

[a]Not significant
[b]Number of cases
ER=estrogen receptors

Table II. *Clinical background of patients treated with taxane-based therapy.*

BRCA1 status	Absence (N=13)	Presence (N=6)	*p* value
Age (years)	52.9±8.7	58.8±9.7	NS[a]
Disease-free interval (months)	23.6±19.9	26.2±19.8	NS
Number of previous chemotherapy	1.5±1.0	1.3±0.5	NS
Dominant metastatic site			
Visceral	6[b]	3	
Bone	1	1	
Soft tissue	6	2	NS
Chemotherapy			
Docetaxel-based	11	5	
Paclitaxel-based	2	1	NS
Clinical response			
CR	1	0	
PR	3	1	
NC	6	5	
PD	3	0	NS
Clinical benefit			
Yes	9	5	
No	4	1	NS
Time-to-progression (months)	6.5±4.9	14.7±5.9	0.006

[a]Not significant
[b]Number of cases
CR=complete response
PR=partial response
NC=no change
PD=progressive disease

significant [NS]; 69.2% *vs.* 83.3%, NS; respectively). In contrast, time-to-progression (TTP) was significantly shorter in patients with BRCA1-absent tumors than those with BRCA1-present tumors (6.5±4.9 and 14.7±5.9, respectively; $p=0.006$) (Table II). The actuarial analysis of progression-free survival between patients with BRCA1-absent and -present tumors also revealed a significant difference by the log rank test ($p=0.019$) (Figure 2).

To compare the predictive power of BRCA1 expression for TTP with other possible predictors, disease-free interval, main metastatic site, ER, PgR, HER2, Ki-67 labeling index and p53-positive rate, the Cox proportional hazard model was applied to the 19 patients. This analysis revealed that BRCA1 expression was an independent predictive factor of TTP (hazard ratio: 3.22; the 95% confidence interval, 1.09 to 9.57; $p=0.035$).

Response and outcome of patients treated with anthracycline-based chemotherapy. To test the hypothesis that BRCA1 expression is a predictor of response to anthracyclines, the response and outcome of 25 patients treated with anthracycline-based chemotherapy were analyzed with regard to BRCA1 expression.

No difference was observed in terms of the objective response rate and clinical benefit rate between patients with BRCA1-absent and -present tumors. Additionally, there was no difference in TTP between them (Table III).

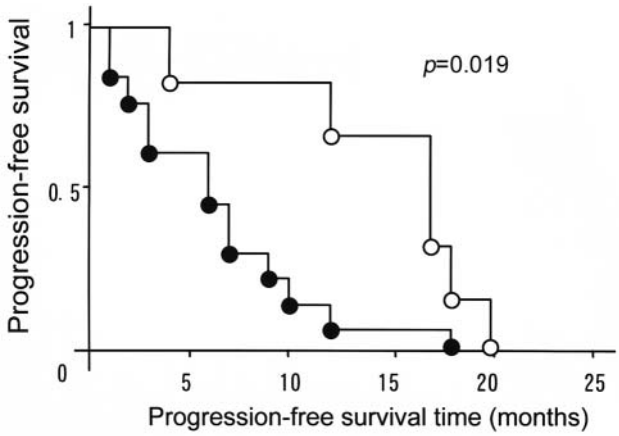

Figure 2. *Progression-free survival curves according to the absence or presence of BRCA1 expression in metastatic breast cancer patients treated with taxane-based chemotherapy. ●– –●, patients with BRCA1-absent tumors; ○– –○, patients with BRCA1-present tumors.*

To explore predictors of the response and outcome of patients treated with anthracycline-based chemotherapy, the other factors, including disease-free interval, main metastatic site ER, PgR, HER2, Ki-67 labeling index and

Table III. *Clinical background of patients treated with anthracycline-based therapy.*

BRCA1 status	Absence (N=15)	Presence (N=10)	*P* value
Age (years)	52.6±9.4	52.7±8.2	NS[a]
Disease-free interval (months)	22.1±19.2	22.0±17.4	NS
Number of previous chemotherapy	1.1±1.0	1.2±1.1	NS
Dominant metastatic site			
Visceral	6[b]	3	
Bone	3	3	
Soft tissue	6	4	NS
Chemotherapy			
Pirarubicin-based	7	7	
Epirubicin-based	5	3	
Doxorubicin-based	3	0	NS
Clinical response			
CR	1	0	
PR	1	2	
NC	5	6	
PD	8	2	NS
Clinical benefit			
Yes	6	4	
No	9	6	NS
Time-to-progression (months)	4.3±4.7	5.6±5.6	NS

[a]Not significant
[b]Number of cases
CR=complete response
PR=partial response
NC=no change
PD=progressive disease

p53-positive rate were analyzed in this population. No significant factor predicting response or outcome was extracted by either univariate or multivariate analysis.

Discussion

Taxanes, as well as anthracyclines, are key agents for the treatment of patients with breast cancer in either an adjuvant or metastatic setting. Both agents have potent antitumor activity associated with a variety of severe adverse effects. Therefore, predictive factors of response to taxanes and anthracyclines are required in clinics.

Taxanes bind to β-tubulin, sensitize microtubules, block their depolymerization, arrest cells in mitosis and induce apoptotic cell death (9). Several possible predictive factors of response to taxanes have been investigated. From a mechanistic viewpoint, these predictors can be classified into 3 categories: a) Aberration of the target molecule of taxanes, β-tubulin. Gene mutations of β-tubulin were reportedly related to the response to paclitaxel in non-small-cell lung cancer (10). It is also suggested that classIII β-tubulin overexpression is a prominent mechanism of paclitaxel resistance in ovarian cancer (11); b) Reduction in the intratumoral activity of taxanes. The expression level of multidrug resistance gene-1, an efflux pump of taxanes, was suggested to correlate with the response to paclitaxel-based chemotherapy in ovarian cancer patients (12). The mRNA expression level of CYP3A4, an enzyme which inactivates taxanes, was also suggested to relate to the response to docetaxel in breast cancer patients (13); c) Aberration of the apoptosis pathway induced by taxanes. Preclinical studies have suggested that the down-regulation of Bcl-2, an anti-apoptotic molecule, is a mechanism of paclitaxel resistance (14). The overexpression of survivin, an anti-apoptotic molecule, was suggested to correlate with paclitaxel resistance in ovarian cancer patients (15). The damage response gene, *p53*, has been investigated as a biomarker of the response to taxanes (3, 16); however, the clinical significance of these factors remains controversial.

A series of preclinical studies have suggested that BRCA1 participates in the sensitivity to spindle poisons, such as taxanes, mediated through the stress-activated JNK pathway (2, 5, 6). Recent *in vitro* studies have indicated that the induced expression of BRCA1 in breast cancer cells increased the cell sensitivity to paclitaxel by increasing apoptosis, and that the inhibition of BRCA1 expression with siRNA technology in breast cancer cells resulted in paclitaxel resistance (5, 6); however, there is only one clinical study on the relationship between BRCA1 expression and sensitivity to taxanes. It was suggested in a small study of 25 patients with advanced breast cancer that a lower expression of BRCA1 mRNA tended to be associated with increased decetaxel sensitivity (17). This finding is in disagreement with preclinical studies that indicated an increased level of BRCA1 protein resulting in increased sensitivity to taxanes (2). In contrast, in this study, the analysis of protein expression levels of BRCA1 in breast tumors revealed for the first time that increased BRCA1 expression correlated with a better outcome, a longer TTP, for metastatic breast cancer patients treated with taxane-based chemotherapy (Table II and Figure 2).

The protein expression levels of BRCA1 in breast tumors were not significantly related to the clinical tumor response to taxane-based chemotherapy in this study (Table II). As this study is retrospective, the patient population was heterogeneous. In addition, chemotherapy regimens and the evaluation protocol for tumor response were not pre-defined. These factors may render difficult the precise evaluation of the antitumor effect of chemotherapy. Prospective studies are clearly needed to investigate whether BRCA1 expression correlates with the clinical tumor response to taxane-based chemotherapy; however, it should be noted that TTP is one of the most important indicators of patient benefit from chemotherapy in the metastatic setting, and that disease progression is easier for

clinicians to evaluate than objective response. TTP might be a more suitable parameter to evaluate the efficacy of chemotherapy than the objective response rate or clinical benefit rate in retrospective clinical studies.

A series of preclinical studies revealed that reduced BRCA1 expression increases the sensitivity to DNA-damaging agents, in agreement with the role of BRCA1 in DNA damage repair (1, 2). Additionally, some clinical studies have suggested that BRCA1 mutations modify the response to DNA-damaging chemotherapy in patients with hereditary breast cancer or ovarian cancer (18, 19). These findings suggest that BRCA1 expression may also predict the response to DNA-damaging agents, such as anthracyclines, in sporadic breast cancer or ovarian cancer; however, there was no significant relationship between the expression level of BRCA1 and the clinical tumor response or outcome of breast cancer patients in this study.

Anthracyclines inhibit topoisomerase II, stabilize the topoisomerase-DNA complex and cause the arrest of DNA replication forks and double-strand breaks. They have additional modes of action, such as DNA interstrand cross-linking and the generation of oxygen-free radicals (2). Therefore, anthracyclines cannot simply be categorized as DNA-damaging agents. In addition, an alkylating agent, cyclophosphamide, and/or an anti-metabolite, 5-Fluorouracil, were concurrently administered with an anthracycline to 9 out of 25 patients in this study. These findings may lead to an insignificant correlation of BRCA1 expression with clinical tumor response.

It is interesting to note that BRCA1-abasent breast tumors tended to be ER-negative and PgR-negative in this study (Table I). It has been reported that hereditary breast cancer related to BRCA1 mutations is usually ER-negative and PgR-negative (20). BRCA1-related tumors are also reported to be HER2-negative and p53-positive (21). No relationship was found between BRCA1 and HER2 expressions but BRCA1-absent tumors tended to have a higher percentage of p53-positive tumor cells in this study (Table I). Although no analysis of BRCA1 mutations was conducted in this study, these findings suggest that BRCA1-absent sporadic breast tumors have similar phenotypes to BRCA1-mutated breast tumors. Interestingly, recent reports have suggested that hypermethylation of the BRCA1 promoter was highly correlated with decreased BRCA1 expression in ovarian cancer and that somatic BRCA1 inactivation by hypermethylation of the promoter could modify the profile of tumor progression in most non-BRCA1/BRCA2 familial breast tumors (22, 23). Hypermethylation of the BRCA1 promoter may lead to a decrease in the protein expression levels of BRCA1 and provide unique phenotypes, such as the hormone receptor-negative phenotype, in some sporadic breast cancers.

In conclusion, the results of this study suggest, for the first time, that the absence of BRCA1 expression is an independent predictor of shorter TTP in advanced breast cancer patients treated with taxane-based chemotherapy. A lower expression of BRCA1 may decrease the sensitivity of tumor cells to taxane-based chemotherapy. Prospective studies are warranted to clarify the relationship between the BRCA1 expression and sensitivity to taxane-based chemotherapy in breast cancer patients.

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