Promoter methylation of \textit{BRCA1} in triple-negative breast cancer predicts sensitivity to adjuvant chemotherapy

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\textbf{Background:} \textit{BRCA1} function is inactivated through \textit{BRCA1} promoter methylation in a substantial number of triple-negative breast cancers. We investigated the impact of \textit{BRCA1}-methylation status on the efficacy of adjuvant chemotherapy in patients with triple-negative breast cancer or with non-triple-negative breast cancer.

\textbf{Methods:} \textit{BRCA1} promoter methylation was assessed in 1163 unsel ected breast cancer patients. Methylation was evaluated using a methylation-specific PCR (MSP) assay.

\textbf{Results:} In the subgroup of 167 triple-negative breast cancer patients who received adjuvant chemotherapy, patients with \textit{BRCA1}-methylated tumors had a superior 10-year disease-free survival (DFS) (78\% versus 55\%, \(P = 0.008\)) and 10-year disease-specific survival (DSS) (85\% versus 69\%, \(P = 0.024\)) than those with \textit{BRCA1}-unmethylated tumors, and \textit{BRCA1} methylation was an independent favorable predictor of DFS and DSS in a multivariate analysis in this subgroup [DFS: hazard ratio (HR) = 0.45; 95\% confidence interval (CI) 0.24–0.84; \(P = 0.019\); DSS: HR = 0.43; 95\% CI = 0.19–0.95; \(P = 0.044\)]. In contrast, in 675 non-triple-negative breast cancer patients who received adjuvant chemotherapy, \textit{BRCA1} methylation was an unfavorable predictor of DFS and DSS in univariate analysis (DFS: HR = 1.56; 95\% CI 1.16–2.12; \(P = 0.003\); DSS: HR = 1.53; 95\% CI = 1.05–2.21; \(P = 0.026\)).

\textbf{Conclusions:} Triple-negative breast cancer patients with \textit{BRCA1}-methylated tumors are sensitive to adjuvant chemotherapy and have a favorable survival compared with patients with \textit{BRCA1}-unmethylated triple-negative tumors.

\textbf{Key words:} \textit{BRCA1} methylation, chemotherapy, triple-negative breast cancer

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**Introduction**

Triple-negative breast cancer is defined by the lack expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) amplification [1, 2]. This subgroup of breast cancer accounts for ~10%–17% of all breast cancers and is regarded as important because of the aggressive clinical behavior, poor prognosis, and lack of targeted therapy [1, 3, 4]. To date, chemotherapy has been the mainstay of systemic treatment of triple-negative breast cancer. Several studies showed that triple-negative breast cancer is more sensitive to adjuvant or neoadjuvant chemotherapy than other subtypes of breast cancers [5, 6]; however, only a minority of triple-negative breast cancer patients are extremely sensitive to chemotherapy [8]. In China, ~1.1% of all breast cancers are due to BRCA1 mutations [11]. BRCA1 can also be silenced in sporadic (non-hereditary) breast cancer through methylation of the promoter [12]. Approximately 13%–40% of sporadic breast cancers demonstrate BRCA1 promoter methylation [13, 14]. We and others have shown that BRCA1 methylation is associated with a relatively poor clinical outcome [15, 16]. In the present study, we investigated the association between BRCA1 methylation and the triple-negative phenotype and we asked whether, among triple-negative breast cancer patients, BRCA1 methylation predicted the response to adjuvant chemotherapy.

**Methods**

**Patients**

A total of 1611 consecutive patients with operable primary breast cancer were treated at Peking University Cancer Hospital from December 1994 to December 2002. Paraffin blocks of tumor tissue were available for 1312 patients. Among these, DNA was of insufficient quality to carry out the methylation assays described below for 149 patients and these were excluded. Thus, 1163 patients with operable primary breast cancer were analyzed in this study. The patient ages at diagnosis ranged from 25 to 87 years, with a median age of diagnosis of 50 years. Tumor stage was classified according to the tumor node metastasis (TNM) classification of the Union Internationale Contre Le Cancer. The tumor size was defined as the maximum tumor diameter measured on the tumor specimens at the time of operation.

Treatment-related information was obtained by review of medical records. Patients received radical or modified radical mastectomy (during that period, few cases were treated with breast-conserving surgery). The axillary lymph nodes were routinely dissected and lymph node metastasis was determined based on the histological examination. The majority of patients received adjuvant chemotherapy alone or a combination of chemotherapy and endocrine therapy (Table 1). Follow-up data were available for all patients, with a median follow-up time of 9 years (range 0.4–15.1 years). During the follow-up period, 323 patients developed a distant metastasis or a local recurrence and 215 patients died of breast cancer. This study was approved by the Research and Ethical Committee of Peking University Cancer Hospital.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N (%)</th>
<th>BRCA1</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>597 (51)</td>
<td>438 (50)</td>
<td>159 (54)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>566 (49)</td>
<td>431 (50)</td>
<td>135 (46)</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>665 (58)</td>
<td>491 (57)</td>
<td>171 (56)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>489 (42)</td>
<td>367 (43)</td>
<td>122 (44)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>471 (41)</td>
<td>340 (39)</td>
<td>131 (45)</td>
</tr>
<tr>
<td>Negative</td>
<td>690 (59)</td>
<td>529 (61)</td>
<td>161 (55)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9</td>
<td>8</td>
<td>1</td>
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<tr>
<td>ER status</td>
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<tr>
<td>Positive</td>
<td>711 (64)</td>
<td>535 (65)</td>
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<tr>
<td>Unknown</td>
<td>48</td>
<td>39</td>
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<td>PR status</td>
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<tr>
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<td>571 (52)</td>
<td>438 (53)</td>
<td>133 (47)</td>
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<tr>
<td>Negative</td>
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<td>385 (47)</td>
<td>149 (53)</td>
</tr>
<tr>
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<td>HER2 status</td>
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<td>Positive</td>
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<td>156 (19)</td>
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<tr>
<td>I</td>
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<td>II</td>
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<td>551 (72)</td>
<td>190 (70)</td>
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<tr>
<td>III</td>
<td>139 (13)</td>
<td>97 (13)</td>
<td>42 (16)</td>
</tr>
<tr>
<td>Unknown</td>
<td>38</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>Triple-negative breast cancer</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Non-triple-negative</td>
<td>206 (19)</td>
<td>142 (17)</td>
<td>64 (23)</td>
</tr>
<tr>
<td>Unknown</td>
<td>893 (81)</td>
<td>675 (83)</td>
<td>218 (77)</td>
</tr>
<tr>
<td>Adjuvant treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>406 (36)</td>
<td>299 (35)</td>
<td>107 (38)</td>
</tr>
<tr>
<td>C + TAM</td>
<td>483 (43)</td>
<td>364 (43)</td>
<td>119 (43)</td>
</tr>
<tr>
<td>TAM</td>
<td>181 (16)</td>
<td>140 (17)</td>
<td>41 (15)</td>
</tr>
<tr>
<td>No therapy</td>
<td>53 (5)</td>
<td>42 (5)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>40</td>
<td>24</td>
<td>16</td>
</tr>
</tbody>
</table>

*Not including 50 patients with lobular carcinomas and 38 patients with ductal carcinomas in situ.

M, methylation; U, unmethylation; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; C, chemotherapy; TAM, tamoxifen.

**DNA extraction and bisulfite modification**

DNA was extracted from paraffin-embedded breast cancer tissues by using a phenol–chloroform assay. Briefly, three to four sections, 10 μm thick, were cut from each sample, after xylene deparaffinization and absolute ethanol washing, the sections were digested by proteinase K (0.1 mg/ml) in 200 μl of DNA extraction buffer at 56°C overnight, following the phenol–chloroform extraction.

Tumor DNA (1–2 μg) and controls were treated with sodium bisulfite and purified by the Wizards DNA Clean-Up System kit (Promega, Madison, WI, USA). Bisulfite modification converts unmethylated cytosines to uracils and leaves methylated cytosines unchanged. Bisulfite conversion was confirmed by PCR amplification of bisulfite-modified DNA using primers specific for BRCA1 (Table 2). PCR products were sequenced on an automatic sequencer. Three to four sections, 10 μm thick, with three to four sections, 10 μm thick, were digested by proteinase K (0.1 mg/ml) in 200 μl of DNA extraction buffer at 56°C overnight, following the phenol–chloroform extraction.

**Table 1. Association of the methylation status of BRCA1 with clinicopathological characteristics in the entire study population of 1163 patients**
considered ampli
Grove, IL) according to the manufacturer
2+ were further evaluated by FISH using a Vysis kit (Vysis, Inc., Downers
considered negative, whereas 3+ was considered positive; tumors with score
tumor cells was scored as 2+ or 3+, respectively. A score of 0 and 1+ was
scored as 1+; a moderate or strong complete staining observed in
faint/barely perceptible staining detected in
staining or staining observed in <30% of tumor cells was given a score 0;
HER2 staining was graded according to a standard scoring method: no
specimens containing at least 10 fmol/mg proteins were considered ER or
MA) were used as the labeled ligands for ER and PR analyses, respectively.
antibody (clone CB-11, Zymed, S. Francisco, CA; dilution 1:100) [20].
methylation (antisense) [13]. Approximately 60 ng of the
bisulfite-modified DNA was used as a template for MSP. The PCR
conditions were as follows: initial denaturation at 95°C for 15 min to
activate HotStar Taq DNA polymerase (Qiagen, Germany) followed by
amplification at 95°C for 30 s, 58°C for 30 s, and 72°C for 45 s for 35
cycles, and a final extension at 72°C for 10 min. Ten microliters of PCR
products were directly loaded onto a 2.5% agarose gel, stained with
ethidium bromide and visualized under UV illumination. The
unmethylated and methylated PCR products were 86 and 75 bp,
respectively. In order to avoid the false positives and negatives, each set of
PCR contains positive, negative and blank controls. Peripheral blood
lymphocytes DNA treated in vitro with SsI bacterial methylated was used
as a positive control; DNA from normal lymphocytes was used as a
negative control; no DNA template was used as a blank control. To verify
the PCR results, nine representative MSP products of BRCA1 were cloned
with TA clone and sequenced on the ABI Prism 3730 DNA Analyzer
(Foster City, CA). The BRCA1 methylation and unmethylation were
confirmed by the clone sequencing analysis.

ER, PR, and HER2 status

ER and PR expression in the breast tumors were measured by using a
dextran-coated charcoal assay as previously described [19]. [3H]-estradiol
(Amersham, UK) and [3H]-R5020 (Dupont New England Nuclear, Boston,
MA) were used as the labeled ligands for ER and PR analyses, respectively.
Specimens containing at least 10 fmol/mg proteins were considered ER or
PR positive.

HER2 expression in the tumor tissues was determined by an
immunohistochemistry assay as described previously using a HER2-specific
antibody (clone CB-11, Zymed, S. Francisco, CA; dilution 1:100) [20].
HER2 staining was graded according to a standard scoring method: no
staining or staining observed in <30% of tumor cells was given a score 0;
faint/barely perceptible staining detected in ≥30% of tumor cells was
scored as 1+; a moderate or strong complete staining observed in ≥30% of
tumor cells was scored as 2+ or 3+, respectively. A score of 0 and 1+ was
considered negative, whereas 3+ was considered positive; tumors with score
2+ were further evaluated by FISH using a Vysis kit (Vysis, Inc., Downers
Grove, IL) according to the manufacturer’s instructions. HER2 was
considered amplified when the ratio of HER2/CEP17 signals was ≥2.2.

statistical analysis

The associations between the BRCA1 methylation status,
clinicopathological characteristics, and adjuvant treatment were determined
using Pearson’s χ²-test. Disease-free survival (DFS) was defined as the time
from the date of diagnosis to first recurrence (local or distant) or death
from breast cancer without a recorded relapse. Disease-specific survival
(DSS) was defined as the time from the date of diagnosis to death where
breast cancer was the primary or underlying cause of death. Patients who
were alive at the last follow-up were censored at the last follow-up date, and
patients who died of causes other than breast cancer were censored at the
time of death. Survival curves were derived from Kaplan–Meier estimates
and the curves were compared by log-rank tests. A multivariable Cox
regression model was applied to determine whether a factor was an
independent predictor of survival in multivariate analysis. All statistical
tests were two-sided, and the P values <0.05 were considered as statistically
significant. The statistical analyses were carried out using SPSS 16.0
software (SPSS, Chicago, IL).

results

patient characteristics

BRCA1-methylation status and clinical information were
available for 1163 patients. The clinicopathological
characteristics of the 1163 patients are presented in Table 1.
Approximately 25% of the tumors exhibited BRCA1
methylation (supplementary Figure S1A, available at Annals
of Oncology online). The sequencing assay was to verify the
BRCA1-methylated or non-methylated PCR products in the representative samples. When the case exhibited a BRCA1 promoter methylation in the tumor, the sequencing analysis showed that all cytosines in the Cpg sites in this case remained as cytosines and those cytosines not in the Cpg sites were converted to thymidines, indicating that all Cpg sites were indeed methylated (supplementary Figure S1B, available at Annals of Oncology online); whereas the case did not exhibit a BRCA1 promoter methylation in the tumor (non-methylation), the sequencing analysis showed that all cytosines in the Cpg sites in this case were converted to thymidines (supplementary Figure S1C, available at Annals of Oncology online). Data on ER, PR, and HER2 were complete for 1099 patients, of these, 206 (19%) were triple-negative (Table 1). Of the 206 triple-negative breast cancer patients, 31% were BRCA1-methylated tumors, compared with 24% of non-triple-negative breast cancer (P = 0.049) (Table 1).

associations between the BRCA1 methylation or triple-negative breast cancer and survival

We estimated the 10-year DFS and 10-year DSS of the 1163 women in the cohort. In a univariate analysis, BRCA1 methylation was associated with poor survival. The 10-year DFS rate was significantly lower in patients with BRCA1-methylated tumors than those with BRCA1-unmethylated tumors [10-year DFS: 67% versus 72%; hazard ratio (HR) = 1.34; 95% confidence interval (CI) 1.06–1.71; P = 0.015] (Figure 1A); the 10-year DSS rate was also lower in patients with BRCA1-methylated tumors than those with BRCA1-unmethylated tumors (10-year DSS: 78% versus 81%, HR = 1.29; 95% CI 0.96–1.73; P = 0.090) although this did not reach a significant difference (Figure 1B).

The 10-year DFS was significantly lower in patients with triple-negative breast cancer than those with non-triple-negative breast cancer (10-year DFS: 62% versus 73%; HR = 1.51; 95% CI 1.16–1.96; P = 0.002). The 10-year DSS was lower in patients with triple-negative breast cancer than those with other cancers (10-year DSS: 76% versus 81%; HR = 1.27; 95% CI 0.91–1.76; P = 0.160) although this did not reach a significant difference.

association between the BRCA1 methylation and survival in non-triple-negative breast cancer

In the group of 893 patients with non-triple-negative breast cancer, patients with BRCA1-methylated tumors had significantly worse DFS and DSS than did patients with unmethylated tumors (10-year DFS: 66% versus 75%; HR = 1.62; 95% CI 1.23–2.13; P = 0.001; 10-year DSS: 77% versus 82%; HR = 1.59; 95% CI 1.14–2.21; P = 0.006) (Figure 2A and B). When the analysis was restricted to the 675 non-triple-negative breast cancer patients who received patients, according to the BRCA1 methylation status; (C) DFS and (D) DSS in 675 non-triple-negative breast cancer patients who received adjuvant chemotherapy or chemotherapy plus tamoxifen (TAM), according to the BRCA1 methylation status.

Figure 2. Kaplan–Meier estimate of (A) disease-free survival (DFS) and (B) disease-specific survival (DSS) in 893 non-triple-negative breast cancer
adjuvant chemotherapy, patients with methylated tumors experienced worse DFS and DSS than did patients with unmethylated tumors (10-year DFS: 63% versus 72%; HR = 1.56; 95% CI 1.16–2.12; P = 0.003; 10-year DSS: 76% versus 81%; HR = 1.53; 95% CI 1.05–2.21; P = 0.026) (Figure 2C and D). In the subgroup of 218 non-triple-negative breast cancer patients who did not receive chemotherapy (majority of patients in this subgroup received endocrine therapy), patients with BRCA1-methylated tumors had a worse DFS or DSS than did patients with unmethylated tumors (10-year DFS: 74% versus 86%, P = 0.046; 10-year DSS, 79% versus 88%, P = 0.089) (Figure 3A and B). Indicating that in non-triple-negative breast cancer patients, the BRCA1-methylated status is associated with poor survival regardless of chemotherapy.

The associations between the BRCA1-methylation status and survival were also analyzed in HR (hormone receptor, ER and/
A, anthracyclines; A→T, anthracyclines followed by paclitaxel.

Table 2. Multivariate analyses of disease-free survival (DFS) and disease-specific survival (DSS) in 167 triple-negative breast cancer patients who received adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>DFS HR (95% CI)</th>
<th>P value</th>
<th>DSS HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 (methylated versus unmethylated)</td>
<td>0.45 (0.24–0.84)</td>
<td>0.019</td>
<td>0.43 (0.19–0.95)</td>
<td>0.044</td>
</tr>
<tr>
<td>Tumor size (&gt;2 versus ≤2 cm)</td>
<td>1.82 (1.03–3.19)</td>
<td>0.038</td>
<td>2.09 (1.04–4.21)</td>
<td>0.040</td>
</tr>
<tr>
<td>Lymph node (positive versus negative)</td>
<td>2.37 (1.34–4.22)</td>
<td>0.003</td>
<td>3.35 (1.58–7.08)</td>
<td>0.002</td>
</tr>
<tr>
<td>Histologic grade (III versus I or II)</td>
<td>1.08 (0.49–2.17)</td>
<td>0.977</td>
<td>1.19 (0.45–2.64)</td>
<td>0.844</td>
</tr>
<tr>
<td>Age (≤50 versus &gt;50 years)</td>
<td>1.49 (0.86–2.56)</td>
<td>0.151</td>
<td>2.08 (1.03–4.19)</td>
<td>0.040</td>
</tr>
<tr>
<td>Chemotherapy regimens</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>(A or A→T versus CMF)</td>
<td>1.21 (0.70–2.33)</td>
<td>0.420</td>
<td>0.94 (0.45–1.96)</td>
<td>0.862</td>
</tr>
<tr>
<td>(Other regimens versus CMF)</td>
<td>1.10 (0.47–2.59)</td>
<td>0.821</td>
<td>0.91 (0.34–2.48)</td>
<td>0.859</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; CI, confidence interval; CMF, cyclophosphamide + methotrexate + 5-fluorouracil; A, anthracyclines; A→T, anthracyclines followed by paclitaxel.

association between the BRCA1 methylation and survival in triple-negative breast cancer

Among the 206 patients with triple-negative breast cancer, 31% of the tumors were BRCA1 methylated and 69% were BRCA1 unmethylated. The majority (167/206, 81%) of patients in this group received adjuvant chemotherapy. The mean tumor size, lymph node status, age, tumor grade, and adjuvant chemotherapy regimens were not significantly different between the BRCA1-methylated tumors and BRCA1-unmethylated tumors in the 167 triple-negative breast cancer patients who received adjuvant chemotherapy. Patients with BRCA1-methylated tumors experienced a significantly better DFS and DSS than did patients with BRCA1-unmethylated tumors (10-year DFS: 78% versus 55%; HR = 0.44; 95% CI 0.23–0.83; P = 0.009; 10-year DSS: 85% versus 69%; HR = 0.40; 95% CI 0.18–0.90; P = 0.024) (Figure 4A and B). Multivariable analysis revealed that the BRCA1-methylation status was an independent favorable factor of DFS and DSS after adjustment for age (≤50 versus >50 years), tumor size (>2 versus ≤2 cm), lymph nodes status (positive versus negative), tumor grade (III versus I/II), and adjuvant chemotherapy regimens in the subgroup of 167 patients (DFS: HR = 0.45; 95% CI 0.24–0.98; P = 0.019; DSS: HR = 0.43; 95% CI 0.19–0.95; P = 0.044, respectively) (Table 2). In contrast, in the 39 triple-negative breast cancer patients who did not receive chemotherapy, the BRCA1-methylation status was not associated with DFS (10-year DFS: 39% versus 68%; HR = 1.65; 95% CI 0.54–5.04; P = 0.378) (Figure 4C) and DSS (10-year DSS: 80% versus 84%; HR = 1.23; 95% CI 0.23–6.71; P = 0.812) (Figure 4D).

discussion

For ~25% of the breast cancer patients in this study, we were able to demonstrate that the BRCA1 promoter was methylated within the tumor. Overall, patients with BRCA1-methylated tumors experienced a worse DFS than patients with BRCA1-unmethylated tumors (HR = 1.34; 95% CI 1.06–1.71; P = 0.015), but this association was not present in the triple-negative subgroup.

In the 167 triple-negative breast cancer patients who received adjuvant chemotherapy, BRCA1 methylation was associated with a favorable survival, patients with BRCA1-methylated tumors had a better DFS and DSS than did patients with unmethylated tumors in univariate and multivariable analyses in this subgroup of 167 triple-negative breast cancer patients. On the other hand, in a small subgroup of triple-negative breast cancer patients (39 of 206, 19%) who did not receive chemotherapy, BRCA1 methylation was not associated with survival. Also, among 675 non-triple-negative breast cancer patients who received chemotherapy, BRCA1 methylation was associated with worse DFS and DSS. Taken together, BRCA1 methylation associated with improved survival was only restricted to triple-negative breast cancer patients who received chemotherapy. Therefore, it is suggested that BRCA1-methylated triple-negative breast cancers are more sensitive to chemotherapy than BRCA1-unmethylated triple-negative breast cancer and deserve a larger benefit from chemotherapy. Similarly, Silver et al. [21] recently found triple-negative breast cancer patients with BRCA1 methylation are more sensitive to neoadjuvant cisplatin treatment than those without BRCA1 methylation. In contrast, Lips et al. [22] found that the BRCA1-methylation status is not associated with pathological response in triple-negative breast cancer patients who were treated with neoadjuvant chemotherapy. However, the sample size in the two studies is relatively small.
The BRCA1 protein plays a crucial role in the repair of DNA double-stranded breaks through the homologous recombination pathway [23, 24]. BRCA1-mutated cells are defective in the homologous recombination pathway and thereby sensitive to DNA damage agents [25, 26]. Recent studies showed that breast cancer patients with BRCA1 mutation are more likely to respond to neoadjuvant chemotherapy [27, 28]. Triple-negative breast cancer shares some fundamental molecular features with BRCA1-related breast cancer, such as high-tumor grade [4, 29, 30], frequent p53 mutation [31–33], and defect in the maintenance of normal chromosome X inactivation [34]. BRCA1 function can be inactivated through BRCA1 promoter methylation, therefore, BRCA1 methylated triple-negative breast cancers may exhibit similar characteristics to BRCA1-mutated breast cancers.

No targeted therapy for triple-negative breast cancer is currently available [35]. Phase I to II trials [36, 37] showed that advanced or metastatic breast cancer patients who carried a germline BRCA1 or BRCA2 mutation are highly responsive to olaparib treatment, one of poly (ADP-ribose) polymerase (PARP) inhibitors. A recent randomized trial [38] compared the efficacy of chemotherapy with or without iniparib, one of a PARP inhibitor, in patients with metastatic triple-negative breast cancer. The addition of iniparib to chemotherapy improved the clinical response and survival when compared with chemotherapy alone, this study suggested that a PARP inhibitor may extend to metastatic triple-negative breast cancer patients responded to PARP inhibitors. O’Shaughnessy et al. [39] recently reported that iniparib failed to significantly improve overall survival and progression-free survival in a phase III trial on triple-negative metastatic breast cancer. In vitro studies found that BRCA1-methylated breast cancer cells conferred a highly sensitivity to PARP inhibitors as did the BRCA1-mutated breast cancer cells [40, 41]. Our current study suggested that triple-negative breast cancer patients with BRCA1-methylated tumors were sensitive to chemotherapy therefore, it is of interest to speculate that this subset of triple-negative breast cancer patients will be sensitive to PARP inhibitors.

In conclusion, we show that an approximately one-third of triple-negative breast cancers exhibit BRCA1 methylation; BRCA1-methylated triple-negative breast cancer patients have a superior survival than BRCA1-unmethylated triple-negative breast cancer patients when these patients receive adjuvant chemotherapy, and this superior survival is attributable to heightened sensitivity to chemotherapy. Independent studies are warranted to confirm our findings; in addition, the subgroup of BRCA1-methylated triple-negative breast cancer patients may be potential candidates for treatment with PARP inhibitors and this will be the topic of future studies.

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disclosure

The authors have declared no conflicts of interest.

references

The Patient’s Anastrozole Compliance to Therapy (PACT) Program: a randomized, in-practice study on the impact of a standardized information program on persistence and compliance to adjuvant endocrine therapy in postmenopausal women with early breast cancer†

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Background: Compliance and persistence are often overlooked in adjuvant breast cancer treatment.

Patients and methods: PACT was a prospective, multicenter, randomized, open, parallel-group study assessing whether educational materials (EMs) enhanced compliance with aromatase inhibitor (AI) therapy in postmenopausal

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