Predictive value of BRCA1 expression on the efficacy of chemotherapy based on anti-microtubule agents: a pooled analysis across different malignancies and agents

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Background: Breast cancer susceptibility gene 1 (BRCA1) expression has been suggested as a predictor in anti-neoplastic treatment with anti-microtubule agents. However, the existing evidence is conflicting. Consulting the literature, we sought to examine the true impact of BRCA1 expression on the efficacy of anti-microtubule agents.

Methods: Medline by PubMed and Embase databases were searched for eligible studies. The primary endpoints were objective response rate (ORR) and progression free survival (PFS). Additional subgroup analyses stratified for detection methods, regimen, and patient origin were also performed.

Results: A total of 13 relevant studies involving a total of 1,490 cases were enrolled. Involved agents included paclitaxel, docetaxel and vinorelbine; Malignancies included non-small cell lung cancer, gastric cancer, esophageal carcinoma, ovarian carcinoma, malignant pleural mesothelioma, breast cancer, and small cell lung cancer. Through meta-analyses, we observed a potentially greater ORR in the population with high BRCA1 expression vs. low BRCA1 expression (OR 1.63, 95% CI: 0.92 to 2.88, P=0.09) but the heterogeneity is severe (P=0.01; I$^2=61\%$). Similar results were observed in PFS (high vs. low expression, HR 0.93, 95% CI: 0.75 to 1.15, P=0.49; heterogeneity, P<0.01, I$^2=75\%$). After stratification by testing methods, a significantly higher ORR in the population with high BRCA1 expression was shown in the subgroup using mRNA as a quantitative method (OR 2.90, 95% CI: 1.92 to 4.39, P<0.01; I$^2=0\%$) whereas the difference in the subgroup using immunohistochemistry (IHC) was not significant (OR 0.60, 95% CI: 0.33 to 1.10, P=0.10; I$^2=0\%$). Stratification by regimen (platinum-based vs. non platinum-based) and patient origin (Asian vs. Caucasian) did not reduce the heterogeneity.

Conclusions: Although the predictive value of BRCA1 expression on the anti-microtubule chemotherapy remained uncertain based on overall results, our exploratory analyses suggested that detection using mRNA might be a preferred technique, however, further validation is required to substantiate our findings.

Keywords: Breast cancer susceptibility gene 1 (BRCA1); anti-microtubule agents; meta-analysis

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Introduction

Despite the development of monoclonal antibodies and small molecule pathway inhibitors, chemotherapy remains the go-to treatment for patients with cancer, including neoadjuvant chemotherapy, adjuvant chemotherapy and palliative chemotherapy. Excitingly, an improvement in the efficacy of chemotherapy has been observed in recent years. However, its sensitivity varies from one patient to another. With the advances of molecular biological techniques, we have gained a deeper understanding of the pathogenesis and proliferation of the tumor at the molecular level. Thus, focus on the molecular characteristics of the disease to guide treatment choice has increased; one example is the trending use of molecular markers to predict activity of chemotherapeutic agents.

Anti-microtubule agents act by binding to soluble and/or polymerized tubulin in the microtubules ultimately affecting microtubule function. Vinca alkaloids and taxanes are two families of anti-microtubule agents wildly used in clinics including solid tumors and hematological malignancies, such as non-small cell lung cancer, breast cancer and ovarian cancer (1). Taxanes, a class of diterpenes derived from the plants of the genus Taxus (yews), are mitotic inhibitors that stabilize and protect the microtubule polymer from disassembly, causing chromosomes to be unable to forma metaphase spindle conformation, blocking progress of mitosis, and triggering cell death (2,3). Vinca alkaloids, such as vinorelbine, restrain mitosis and apoptosis by binding to tubulin and preventing its assembly into microtubules (4).

Breast cancer susceptibility gene 1 (BRCA1), a scaffold protein, was first identified as an early-onset breast and ovarian cancer susceptibility gene (5). It has multiple roles not only in DNA damage repair but also in cell cycle regulation and apoptosis through association with other proteins (6). It has been reported that BRCA1 correlated positively with taxanes sensitivity, which functions as a sensitizer to apoptosis induced by anti-microtubule agents (7). A number of investigations have found that BRCA1 may be used as a predictive biomarker of response to anti-microtubule agents (5). Yang et al. (8) reported the potential role of BRCA1 in predicting sensitivity of NSCLC, and found that patients with high/positive BRCA1 had better ORR. However, existing evidence is conflicting. We conducted a systematic review to evaluate the associations of expression of BRCA1 and the efficacy of anti-microtubule agents on cancer patients.

Materials and methods

Literature search

Literature search was conducted using PubMed and Embase from their dates of inception to Oct 23, 2014. The search strategy employed was a combination of: BRCA1 or “Breast cancer susceptibility gene 1” or “Breast cancer 1” and chemotherapy or paclitaxel or docetaxel or vinorelbine. Language was limited to English and Chinese.

Inclusion criteria and exclusion criteria

Articles retrieved from the search were independently reviewed by two reviewers (Mingzhe Zhang & Jianrong Zhang), and any discrepancies were resolved by discussion with the third reviewer (Jianfei Shen). The following criteria was used to select publications: (I) cancer patients, regardless of tumor type, should be included; (II) only studies that detected BRCA1 expression by immunohistochemistry (IHC) or reverse transcriptase polymerase chain reaction (QPCR) were included; (III) original papers must contain enough data to calculate the objective response rate (ORR); studies that failed to meet all of the above criteria were excluded from analyses. Reviews, animal or cell line studies were also excluded.

Data collection and quality assessment

Publication characteristics including first author’s name, publication year, patients’ original country, middle/mean age of study sample, first-line chemotherapeutic agents with doses and sample type, detection method of BRCA1, sample size, and disease stage were extracted from each eligible publication. End points of interest were ORR, overall survival (OS), and progression-free survival (PFS). Each included study was scored by two independent reviewers (Shengyi Zhong and Yang Liu).

Statistical analysis

To estimate ORR, patients were divided into two groups: patients that responded to treatment (responders) and patients that did not respond to treatment (non-responders). Responders were defined as complete response (CR) or partial response (PR). Non-responders included stable disease (SD) and progressive disease (PD). Disease control ratio (DCR), was defined as CR, PR and SD. The pooled
odds ratio (OR) and its 95% confidence intervals (CIs) were calculated by the methods proposed by Mantel and Haenszel (9), or DerSimonian R and Laird N (10). Time-to-event data OS and PFS, hazard ratios (HRs) and associated 95% CI were estimated using the methods reported by Parmar (11). Heterogeneity between the studies was determined by Q-test and \( I^2 \) metric (no heterogeneity; \( I^2=0–25\% \); moderate heterogeneity; \( I^2=25–50\% \); large heterogeneity; \( I^2=50–75\% \); extreme heterogeneity) (12). The fixed-effect model was applied in the initial analysis, and if significant heterogeneity existed, the random-effect model was used. Begg’s test was used to evaluate the publication bias. \( P<0.05 \) indicated significant publication bias (13). All \( P \) values were two-tailed, REVIEW MANAGER (version 5.3 for Windows; the Cochrane Collaboration, Oxford, UK) and STATA version 11.1 (Stata Corporation, USA) were used to perform most data analyses.

Results

Eligible studies

Our search of PubMed database revealed 1,045 potentially relevant articles, 976 studies were immediately excluded upon review of their title and abstract. A total of 69 full text articles were carefully screened, 33 of which were excluded due to lack of sufficient data for extraction, another 20 articles were then excluded due to containing other therapeutic and unable to separate the results of \( BRCA1 \) and \( BRCA2 \). Finally a total of 13 studies were selected for analysis. Figure 1 summarizes the flow chart. Among these studies, the object response rate (ORR) was provided in 9 studies (5,7,14-20), the remaining 4 studies provided only OS or PFS (21-24). Characteristics of all involved studies are summarized in Table S1.

Characteristics of eligible studies

Our meta-analysis contained 13 studies involving a total of 1,490 cancer patients who had been treated with anti-microtubule agents as first- or second-line chemotherapy treatment. In all included studies, the major components of the chemotherapy regimen were anti-microtubule agents (including taxanes, paclitaxel, docetaxel and vinorelbine). Of the 13 included studies, 4 were for non-small-cell lung cancer, 3 were for breast cancer, and 2 were for ovarian cancer; the remaining four were for malignant pleural mesothelioma, esophageal squamous cell carcinoma, small cell lung cancer and gastric cancer. Of the 13 studies, 7 were from an East-Asian population (14,16-20,24), the other 6 studies were from a European population (5,7,15,21-23). Characteristics of included studies are summarized in Table S1.

\( BRCA1 \) level and the clinical outcome of chemotherapy

The ORR was reported in 9 of the included studies consisting of a total of 729 patients. By synthesis, we observed greater ORR in population with high \( BRCA1 \) expression vs. low expression (OR 1.63, 95% CI: 0.92 to 2.88, \( P=0.01 \); \( I^2=61\% \) (Figure 2). No significant difference was observed...
in PFS (high vs. low expression, HR 0.93, 95% CI: 0.75 to 1.15, P=0.49; heterogeneity, P<0.01, I²=75%) and OS (high vs. low expression, HR 0.77, 95% CI: 0.57 to 1.04, P=0.09; heterogeneity, P=0.0, I²=74%) (Figure 3). When analyzing the DCR, 4 studies consisting of 233 patients were included for comparison. No significant difference between the two groups was found (high vs. low expression, OR=0.83, 95% CI: 0.38 to 1.80, P=0.63; I²=17%, P=0.63 for heterogeneity).

Subgroup analyses

After stratification by testing methods, a significantly higher ORR in the population with high BRCA1 expression was shown in the subgroup using mRNA as a measure approach (OR 2.90, 95% CI: 1.92 to 4.39, Chi² =0.39, P<0.01) whereas the difference in the subgroup using IHC was not significant (OR 0.60, 95% CI: 0.33 to 1.10, Chi² =1.92, P=0.10). The interaction between the two subgroups was significant (Chi² =17.61, P<0.01). However, results stratified by therapeutic regimens revealed a similar tendency between subgroups (for platinum-based studies, high vs. low expression, OR 1.62, 95% CI: 1.10 to 2.39, Chi² =9.26, P=0.01; for non-platinum-based studies, high vs. low expression, OR 1.79, 95% CI: 0.41 to 7.70, Chi² =11.90, P=0.44); but there was no significant interaction between stratifications (Chi² =0.7, P=0.4). A potential association between BRCA1 and efficacy was found in the non-Asian

Figure 2 Meta-analysis on objective response rate among neoplastic patients who received anti-microtubule agents according to BRCA1 expression. CI, confidence interval; I², inconsistency statistic. BRCA1, breast cancer susceptibility gene 1.

Figure 3 Forest plots for the association between BRCA1 level and PFS and OS in patients who received anti-microtubule. (A) Hazard ratio of PFS in patients who received anti-microtubule agents with high BRCA1 expression vs. low BRCA1 expression; (B) hazard ratio of OS in patients who received anti-microtubule agents with high BRCA1 expression vs. low BRCA1 expression. PFS, progression free survival; OS, overall survival; BRCA1, breast cancer susceptibility gene 1.
population but not in the Asian population (for non-Asian population studies, high vs. low expression, OR 2.42, 95% CI: 0.95 to 6.13, \( \chi^2 = 11.23, P=0.06 \); for Asian studies, high vs. low expression, OR 1.31, 95% CI: 0.65 to 2.62, \( \chi^2 = 5.3, P=0.45 \)) but the interaction was not significant (\( \chi^2 = 1.08, P=0.3 \)). Details about the results on subgroup analysis are shown in Table 1 and Figure 4.

### Table 1: Subgroup analysis on objective response rate among cancer patients receiving anti-microtubule agents to BRCA1 expression

<table>
<thead>
<tr>
<th>Categories of included studies</th>
<th>ORR (event/total)</th>
<th>Test for subgroup differences</th>
<th>Test for effect size</th>
<th>Test for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 expression</td>
<td></td>
<td>Subgroup analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/-negative BRCA1</td>
<td>9/342</td>
<td>0.39 0.94</td>
<td>0.06 (0.33, 1.10)</td>
<td>0.1</td>
</tr>
<tr>
<td>High/positive BRCA1</td>
<td>140/380</td>
<td>1.32 0.75</td>
<td>2.96 (1.3, 1.92)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Detection methods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunohistochemical</td>
<td>4/98</td>
<td>0.39 0.94</td>
<td>0.6 (0.33, 1.10)</td>
<td>0.1</td>
</tr>
<tr>
<td>Non-immunohistochemical</td>
<td>108/270</td>
<td>1.32 0.75</td>
<td>2.96 (1.3, 1.92)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Regimens</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum-based</td>
<td>65/236</td>
<td>0.39 0.94</td>
<td>0.6 (0.33, 1.10)</td>
<td>0.1</td>
</tr>
<tr>
<td>Non platinum-based</td>
<td>36/97</td>
<td>1.32 0.75</td>
<td>2.96 (1.3, 1.92)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patient origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>55/187</td>
<td>0.39 0.94</td>
<td>0.6 (0.33, 1.10)</td>
<td>0.1</td>
</tr>
<tr>
<td>Non-Asia area</td>
<td>35/155</td>
<td>1.32 0.75</td>
<td>2.96 (1.3, 1.92)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Figure 4** Subgroup analyses regarding objective response rate in patients who received anti-microtubule agents with high BRCA1 expression vs. low BRCA1 expression. BRCA1, breast cancer susceptibility gene 1.

### Discussion

Due to its ubiquitous presence and importance in all cells, microtubules are one of the most validated intracellular targets in oncology (25). Because of this, the mechanism of resistance to anti-microtubule agents earn widespread concerns and many studies have reported on the subject. Several mechanisms explain the resistance, including decrease of the cellular accumulation mediated by P-glycoprotein (26) exportation and altered expression or post-translational modification of tubulin or other microtubule regulatory proteins (27).

Recently, some studies have reported on the relationship and mechanism between BRCA1 expression and chemotherapy outcomes for carcinoma, but the results were controversial. Therefore a meta-analysis is needed to incorporate all available results to give further insight on this conflicting issue. After combining the available data of the included studies, our results were in concordance with our initial hypothesis that increased BRCA1 expression might be associated with higher sensitivity of anti-
Since significant heterogeneity was observed in the overall analyses, we carried out additional subgroup analyses. Interestingly, our results show that using non-immunohistochemical (PCR and Relative cDNA quantification) detection methods offer the notable advantage of: (I) accurate quantification; (II) reliable sensitivity and specificity; (III) reducing pollution and automation, etc. Because of this, we believe that detection using mRNA might be a preferred technique over IHC. However, there are several limitations. First, it was based on retrospective analysis; prospective analysis is needed to further clarify these issues. Second, although our purpose is the prediction of BRCA1 for paclitaxel, we cannot eliminate the effects of the combination of the chemotherapeutic agents. In addition, we are unable to study the effects on each cancer separately and are therefore unable to distinguish the individual role of BRCA1. Further studies are necessary to validate our results.

In conclusion, although the predictive value of BRCA1 expression on the anti-microtubule chemotherapy remained uncertain based on overall results, our exploratory analyses suggested that detection using mRNA might be a preferred technique over IHC, however, further validation is required to substantiate our findings.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


28. Ramos-Vara JA, Miller MA. When tissue antigens and
antibodies get along: revisiting the technical aspects of immunohistochemistry--the red, brown, and blue technique. Vet Pathol 2014;51:42-87.


## Table S1: Characteristics of eligible studies evaluating BRCA1 level and clinical outcome

<table>
<thead>
<tr>
<th>Lead author [Y] (ref.)</th>
<th>Tumor type</th>
<th>No. of patients</th>
<th>Median age</th>
<th>Patient Stage</th>
<th>Chemotherapyregimen</th>
<th>BRCA1 detection</th>
<th>Antibody</th>
<th>Assessment</th>
<th>Evaluation</th>
<th>Cut off</th>
<th>BRCA1</th>
<th>CR + PR</th>
<th>SD + PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimling [2012] (8)</td>
<td>Malignant pleural Mesothelioma</td>
<td>49</td>
<td>64</td>
<td>Europe I-IV</td>
<td>Vinorelbine 25 mg/m² i.v. weekly and cisplatin 100 mg i.v. every 4 weeks</td>
<td>IHC</td>
<td>Mouse: monoclonal anti-human BRCA1</td>
<td>H-score</td>
<td>Positive: H-score ≥ upper quartile; Negative: H-score &lt; upper quartile</td>
<td>Using a cut-off value of 11.96</td>
<td>Negative</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Gao [2013] (14)</td>
<td>Esophageal Squamous cell Carcinoma</td>
<td>45</td>
<td>62</td>
<td>Asian II-IV</td>
<td>Docetaxel (60-75 mg/m²) plus 5-fluorouracil (500 mg/m², D1, D6)</td>
<td>qPCR</td>
<td>Relative cDNA quantification</td>
<td>Low BRCA1 expression: &lt;10% staining; normal: &gt;10% staining</td>
<td>BRCA1 was 2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papadaki [2011] (15)</td>
<td>NSCLC</td>
<td>131</td>
<td>60</td>
<td>Europe IIIB-IV</td>
<td>Docetaxel cisplatin; docetaxel gemcitabine</td>
<td>cDNA quantification</td>
<td>Ab-1 (MS110) provider: oncogene (Cambridge, MA)</td>
<td>Absence</td>
<td>Present</td>
<td>9</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Su [2011] (16)</td>
<td>NSCLC</td>
<td>85</td>
<td>60</td>
<td>Asian II-IV</td>
<td>Cisplatin (75 mg/m²) or carboplatin (AUC =5) plus vinorelbine (25 mg/m², D1, D6)</td>
<td>Real-time PCR</td>
<td>Rabbit polyclonal, Ab-1, Oncogene, Boston, MA, USA</td>
<td>Low</td>
<td>High</td>
<td>28</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim [2005] (17)</td>
<td>Breast cancer</td>
<td>60</td>
<td>NA</td>
<td>Asian</td>
<td>Docetaxel (60 mg/m², q3w), four cycles unless progressive disease</td>
<td>IHC</td>
<td>Rabbit polyclonal, Ab-1, Oncogene, Boston, MA, USA</td>
<td>Low</td>
<td>High</td>
<td>37</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurebayashi [2006] (18)</td>
<td>Breast cancer</td>
<td>19</td>
<td>58</td>
<td>Asian</td>
<td>13 patients received taxane (docetaxel or paclitaxel) alone, 3 patients taxane with medroxyprogesterone Acetate, 2 patients taxane with pamidronate and one taxane with trastuzumab</td>
<td>IHC</td>
<td>Rabbit polyclonal, Ab-1, Oncogene, Boston, MA, USA</td>
<td>Absence</td>
<td>Present</td>
<td>5</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhao [2014] (19)</td>
<td>SCLC</td>
<td>158</td>
<td>59</td>
<td>Asian</td>
<td>Cisplatin (75 mg/m², D1) or carboplatin (AUC =5, D1) plus gemcitabine (1,000 mg/m², D1, D8), vinorelbine (50 mg/m², D1, D8) or paclitaxel (175 mg/m², D1)</td>
<td>Fluorescence-based, real-time detection method</td>
<td>Mouse anti-BRCA1; monoclonal antibody (ZHGB BIO, China)</td>
<td>The median expression levels (4.3)</td>
<td>Low</td>
<td>54</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wan [2011] (20)</td>
<td>Breast cancer</td>
<td>87</td>
<td>NA</td>
<td>Asian</td>
<td>Taxanes (150 mg/m², D1) plus cisplatin (25 mg/m², D1-3)</td>
<td>IHC</td>
<td>Mouse anti-BRCA1; monoclonal antibody (ZHGB BIO, China)</td>
<td>According to the previous studies, positive: &gt;10% of the tumor cells negative: &lt;10% of the tumor cells</td>
<td>Low</td>
<td>22</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boukovinas [2008] (7)</td>
<td>NSCLC</td>
<td>95</td>
<td>60</td>
<td>Europe IIIB-IV</td>
<td>Gemcitabine (1,000 mg/m², D1, D6) plus docetaxel (100 mg/m² D8)</td>
<td>PCR</td>
<td>Mouse monoclonal antibody Ab-1 (Oncotech Inc., Tuslin, CA, USA)</td>
<td>Median mRNA expression levels (3.64)</td>
<td>Low</td>
<td>51</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesnock [2013] (21)</td>
<td>Ovarian cancer</td>
<td>393</td>
<td>NA White black and other</td>
<td>I-III</td>
<td>Intravenous paclitaxel and cisplatin or combination of intravenous paclitaxel and intraperitoneal cisplatin and paclitaxel</td>
<td>IHC</td>
<td>Mouse monoclonal BRCA1 antibody (MS110, Calbiochem, Darmstadt, Germany)</td>
<td>Low BRCA1 expression: &lt;10% staining; normal: &gt;10% staining</td>
<td>BRCA1 was 2.5</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Weberpals [2011] (22)</td>
<td>Ovarian carcinoma</td>
<td>116</td>
<td>57</td>
<td>Europe II-IV</td>
<td>Cisplatin plus topotecan followed by paclitaxel plus carboplatin or carboplatin plus paclitaxel</td>
<td>IHC</td>
<td>Mouse monoclonal BRCA1 antibody (MS110, Calbiochem, Darmstadt, Germany)</td>
<td>Low BRCA1 expression: &lt;10% staining; normal: &gt;10% staining</td>
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</tr>
<tr>
<td>Papadaki [2012] (23)</td>
<td>NSCLC</td>
<td>100</td>
<td>63</td>
<td>Europe IV</td>
<td>Docetaxel/gemcitabine or vinorelbine/gemcitabine</td>
<td>q-PCR</td>
<td>Mouse anti-BRCA1; monoclonal antibody (ZHGB BIO, China)</td>
<td>Median mRNA expression levels (4.28)</td>
<td>Cut-off point for BRCA1 was 4.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wei [2011] (24)</td>
<td>Gastric cancer</td>
<td>152</td>
<td>58</td>
<td>Asian</td>
<td>Docetaxel-based</td>
<td>q-PCR</td>
<td>Mouse anti-BRCA1; monoclonal antibody (ZHGB BIO, China)</td>
<td>Median mRNA expression levels (4.28)</td>
<td>Cut-off point for BRCA1 was 4.6</td>
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</table>

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; IHC, Immunohistochemistry; qPCR, real-time polymerase chain reaction; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; BRCA1, breast cancer susceptibility gene 1.