Differing clinical impact of BRCA1 and BRCA2 mutations in serous ovarian cancer

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Abstract

A key function of BRCA1 and BRCA2 is the participation in dsDNAbreak repair via homologous recombination. BRCA1 and BRCA2 mutations, which occur in most hereditary ovarian cancers (OCs) and approximately 10% of all OC cases, are associated with defects in homologous recombination and genomic instability, a phenotype termed ‘BRCAness’. The clinical effects of BRCA1 and BRCA2 mutations have commonly been analyzed together; however, it is becoming increasingly apparent that these mutations do not have the same effects in OC. Recently, three major reports highlighted the unequal clinical characteristics of OCs with BRCA1 and BRCA2 mutations. All studies demonstrated that BRCA2-mutated patients are associated with better survival and therapeutic response than BRCA1-mutated and wild-type patients with serous OC. The differing prognostic effects of the BRCA2 and BRCA1 mutations is likely due to differing roles of BRCA1 and BRCA2 in homologous recombination repair and a stronger association between the BRCA2 mutation and a hypermutator phenotype. These new findings have potentially important implications for clinical management of patients with serous OC.

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Keywords

*BRCA* mutation; drug response; homologous recombination; ovarian cancer; PARP inhibitor; survival

Ovarian cancer (OC) is the second most common gynecological malignancy and the leading cause of death from gynecological cancer. Approximately 75–80% of patients present with advanced disease that is refractory to current therapies; the 5-year survival rate for advanced OC is approximately 30–40%. A family history of OC is one of the strongest risk factors for OC. To date, at least 16 genes have been associated with hereditary OC, and *BRCA1* and *BRCA2* (*BRCA1/2*) mutations are believed to account for the majority of hereditary OC [1]. More than 90% of early-onset cancers in families with breast cancer and OC histories are associated with *BRCA1* or *BRCA2* mutations. The risk of developing OC by 70 years of age is 40–50% for *BRCA1* mutation carriers and 10–20% for *BRCA2* mutation carriers [2,3].

The previous studies have demonstrated that *BRCA1* and *BRCA2* mutation-related OCs have distinct clinicopathological features; they tend to be more sensitive to platinum agents and possibly PARP inhibitors than wild-type *BRCA* OCs, and secondary *BRCA1* and *BRCA2* mutations that result in gain of *BRCA1* and *BRCA2* function are associated with platinum resistance [4,5]. Recently, three independent investigations have shown that among women with serous OC, *BRCA2* mutation is more significantly associated with improved patient survival than *BRCA1* mutation [6–8]; one study also showed that *BRCA2* mutation was more strongly associated with chemotherapy response and genome instability [6]. In addition, two other studies demonstrated the trend of favorable outcomes in *BRCA2* mutation patients [9,10] compared with *BRCA1* mutation. This article reviews recent progress in our understanding of *BRCA1* and *BRCA2* mutations in OC and how these emerging findings affect synthetic lethality-based therapeutics in OC.

**BRCA1 & BRCA2 mutations are associated with high-grade serous OC**

In the general population, an estimated one in 300–800 individuals carries a *BRCA1* or *BRCA2* mutation [11]. By contrast, 8–13% of women diagnosed with epithelial OC have a germline *BRCA1* or *BRCA2* mutation [12–14]. In total, 70% of OC are of the serous subtype, 16–21% of which have *BRCA1* or *BRCA2* mutations [12,14,15]. *BRCA1* and *BRCA2* mutations can be also found in primary fallopian tube and peritoneal cancers [16]. Many OCs are believed to originate in the fallopian tube [17].

High-grade serous (HGS) OCs are highly genomically unstable, with *TP53* gene mutations in up to 96% of cases in addition to mutations in *BRCA1, BRCA2, RAD51C* and other DNA-repair protein-encoding genes [18–20]. Other OC subtypes, such as clear-cell OCs, have fewer *TP53* mutations, but have high-prevalence mutations in the *ARID1A* and *PIK3CA* genes [21,22]. Endometrioid OCs commonly have *CTNNB1, ARID1A* and *PIK3CA* mutations, but fewer *TP53* mutations [23]. Mucinous OC have a greater prevalence of *KRAS* mutations [24].

The majority of OCs in women with inherited *BRCA1* and *BRCA2* mutations are HGS OC [25,26]. Among nonfamilial HGS OCs, somatic mutations or methylation also occur in *BRCA1* or *BRCA2* and other members of the BRCA1 and BRCA2 homologous recombination pathway, including RAD51, cCHK1, cCHK2, ATM, ATR and FANCF [27–31]. Homologous recombination defects occur in up to 50% of HGS OCs [19].

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BRCA2 mutations are associated with longer survival & better therapy response than BRCA1 mutations

It has been thought that BRCA1- and BRCA2-mutated OCs are part of characteristic ‘BRCA syndrome’, with a constellation of clinicopathological features: younger age at onset [32,33], HGS histologic type (i.e., under-representation of mucinous cancers) [25,26,34], advanced stage at presentation, high probability of durable remission with platinum therapy and better prognosis [35–38]. A recent study reported that BRCA1- and BRCA2-mutated OCs metastasize to viscera more often than BRCA1 and BRCA2 wild-type OCs, suggesting that visceral metastasis is a feature of the BRCA syndrome phenotype [39].

The authors identified 26 studies that assessed the association between BRCA1 and BRCA2 mutations and clinicopathological features (Table 1); most of the studies combined BRCA1 and BRCA2 mutation carriers because of the relative rarity of BRCA1 and BRCA2 mutations [6–10,35–37,40–57]. Among these studies, six analyzed the relationship between chemosensitivity and BRCA1 and BRCA2 mutation, with inconsistent results [35–37,41,50,57]. Although most of the previous studies found that BRCA1- and BRCA2-mutated OCs were associated with better outcomes than were wild-type OCs, many of these studies were limited by small sample sizes, inadequate adjustment for known prognostic factors (such as stage, age at diagnosis, histologic type and extent of surgical debulking), short follow-up and nonuniform therapy in cases and controls. Nine studies analyzed the impact of BRCA1 and BRCA2 mutations separately on OC patient survival, and reported inconsistent conclusions [6–10,36,51,52,54].

In 2003, Cass and colleagues studied the clinical characteristics and treatment responses of Ashkenazi Jewish women with hereditary OC and found that among 18 BRCA1 and 11 BRCA2 mutation patients, BRCA2 carriers had marginally longer disease-free intervals than BRCA1 carriers (57 vs 40 months, respectively; p = 0.2) [45]. In 2007, Pal and colleagues found a statistically significant difference in the 4-year survival rate between six BRCA2 carriers and 115 noncarriers (p = 0.013), but not between 14 BRCA1 carriers and noncarriers (p = 0.17) [51]. In 2008, Chetrit et al. reported on the outcomes of BRCA1-associated and sporadic OC as part of the National Israeli Study of Ovarian Cancer [46]. Among 605 patients of Ashkenazi origin, median survival durations of 45.1 and 52.5 months were observed among BRCA1 and BRCA2 mutation carriers, respectively, versus 33.5 months in noncarriers. Vencken et al. compared first-line chemotherapy (including platinum- and nonplatinum-based regimens) response among 99 BRCA1- and 13 BRCA2-mutated and 115 noncarrier epithelial OC patients and found a nonstatistically significant trend towards longer progression-free and overall survival durations for BRCA2 mutation patients than in BRCA1 mutation patients [36].

These studies prompted several larger scale analyses that sought a definitive conclusion regarding the differential clinical associations of BRCA1 and BRCA2 mutations in OC. In a recent report, the authors performed integrated analyses of the multidimensional genomic and clinical data from 316 HGS OC patients in a project for The Cancer Genome Atlas (TCGA) and found that patients with BRCA1 and BRCA2 mutations had differing clinical features. Specifically, patients with BRCA1 mutations were younger at diagnosis (mean age: 55.9 vs 61.8 years for wild-type [p = 0.006] and 60.9 years for BRCA2 [p = 0.03]) [6]. The 5-year survival rate of BRCA2 mutation carriers was significantly higher than that of wild-type cases (61 vs 25%, respectively; p = 0.02). Among BRCA2 mutation carriers, 100% were platinum sensitive (i.e., a complete or partial response to adjuvant chemotherapy) compared with 80% of BRCA1-mutated and 85% of wild-type cases (p = 0.05 and p = 0.02, respectively). Similarly, BRCA2 mutation patients had longer platinum-free survival durations than BRCA1 and wild-type patients. The availability of genomic data (i.e.,
somatic mutations, DNA copy-number alterations and methylation) in TCGA project for all the analyzed cases allowed the authors to evaluate molecular correlates in a quantitative manner. The result of this analysis led to the determination that BRCA2 cases have a more pronounced ‘mutator phenotype’, as defined by the number of total mutations across the whole exome. BRCA1-mutated cancers exhibited no significant enrichment of mutations.

The results of quantitative analysis of the relationships between BRCA1 and BRCA2 mutations and genomic instability in OC suggest BRCA2 plays a more important role in the BRCA dsDNA break-repair pathway. Thus, BRCA2 inactivation would result in extensive gene mutations in cancer cells, making them vulnerable to DNA-damaging chemotherapy drugs. It should be noted that TCGA data set provides a more representative spectrum of BRCA mutations in the general population than previous studies, given that only 7% of patients in TCGA data set are of Ashkenazi Jewish origin. The detailed location of the mutations relative to the known functional domains of BRCA1/2 is shown in Figure 1.

Subsequent to our report, two independent studies also provided supporting evidence that BRCA2 mutations are associated with a better prognosis of OC [7,8]. Hyman and colleagues demonstrated that among 143 BRCA-nonmutated, 30 BRCA1-mutated and 17 BRCA2-mutated stage III or IV serous ovarian, fallopian tube or primary peritoneal cancer patients, the 3-year survival rates were 69.4, 90.7 and 100%, respectively [7]. A multivariate analysis revealed that BRCA2 mutations (p = 0.007), but not BRCA1 mutations (p = 0.31), were associated with improved overall survival compared with wild-type.

Recently, a pooled observational study interrogated a total of 3739 epithelial OC cases (909 BRCA1 mutation carriers, 304 BRCA2 mutation carriers and 2666 noncarriers) from the USA, Europe, Israel, Hong Kong, Canada, Australia and the UK, and concluded that BRCA2 mutation carriers had the best prognosis [8]. Specifically, the 5-year overall survival was 36% for noncarriers, 44% for BRCA1 carriers and 52% for BRCA2 carriers. In a Cox proportional-hazards regression model, BRCA2 mutation carriers had more survival advantages than BRCA1 mutation carriers (hazard ratio [HR]: 0.73 for BRCA1; 95% CI: 0.64–0.84, HR: 0.49 for BRCA2; 95% CI: 0.39–0.61). The result of these studies suggested that BRCA2 inactivation by mutation resulted in better survival than BRCA1 inactivation and wild-type. Consistent with these findings, the result of a recent study demonstrated that BRCA2 overexpression is associated with shorter progression-free survival in OC [58].

Next, Liu et al. identified that among 197 BRCA-related OC patients, 5-year overall survival was 75% in 49 BRCA2-mutated patients versus 61% in 148 BRCA1-mutated patients, and there was a trend toward improved outcomes in BRCA2-associated OCs in advanced-stage patients (p = 0.08) [9]. Similarly, Reitsma et al. evaluated clinico-pathological features and survival of 55 BRCA1- and 16 BRCA2-related adnexal cancer, and also found a nonsignificant trend of more favorable outcomes in BRCA2-mutated patients with fewer relapse (38 vs 58%) and a longer time to first time relapse (42 vs 25 months) than BRCA1 carriers [10].

The results of recent studies suggest that BRCA2 mutations have a stronger impact on synthetic lethality-associated sensitivity to chemotherapy compared with BRCA1 mutations, which may underlie their increased survival advantage; however, the role of BRCA1 is nevertheless important. First, in most reported studies, BRCA1-mutated OCs are diagnosed approximately 5–10 years earlier than BRCA2-mutated and non-BRCA-mutated cancers (median age, 50–55 years vs 60, respectively) [8,36,43,45,52,54]. Therefore, inactivation of BRCA1 likely plays a more important role in OC initiation than platinum sensitivity. This observation should probably be attributed to heterogeneity of the functional outcomes of different BRCA1 mutations. BRCA1 plays a versatile role in tumor suppression through its
ability to participate in the DNA-damage response, checkpoint control, mitotic spindle assembly, sister chromatid decatenation and centrosome duplication [59–63]. The failure of one of these functions could predispose BRCA1-mutated cells to tumorigenesis, but not necessarily render the developed cancer cell sensitive to DNA-damaging agents such as cisplatin. Indeed, Bolton et al. observed that survival association of BRCA1 mutation carriers depended on the mutation location, with N-terminal mutations of the BRCA1 protein associated with worse survival and C-terminal mutations found to be associated with better survival [8]. Consistent with this finding, a recent study demonstrated that a mutation in the RING-type zinc finger (RING) domain (N-terminal) of BRCA1 showed poor response to cisplatin and PARP inhibitors [64]. The authors’ analysis of TCGA data and the study of Hyman et al. both revealed a nonstatistically significant trend toward better survival in BRCA1 mutation carriers compared with noncarrier patients. The HR for BRCA1 carriers reported in the TCGA analysis (0.76) [6] and in an analysis by the Memorial Sloan-Kettering Cancer Center (0.70) [7] was very similar to those from Bolton et al. (0.73). However, with a larger sample size, the Bolton et al. study observed a statistically significant survival advantage for the BRCA1-mutated cases, although it is clear that BRCA2-mutated cases had the best survival advantage.

Other differing associations of BRCA1 & BRCA2 mutations

Unlike BRCA1 mutations, which are almost exclusively associated with female breast cancer and OC, BRCA2 mutations also confer a higher risk for pancreatic, prostate, male breast cancers and melanoma [65–68]. Women with BRCA1-associated breast cancer are more likely to have estrogen receptor-negative disease and significantly poorer overall prognoses than noncarrier sand BRCA2-associated breast cancer [69–71]. Evidence indicates that considerable differences in OC risk exist between women with BRCA1 mutations and those with BRCA2 mutations. Specifically, the lifetime risk for OC in patients with BRCA1 mutations is 39–46% compared with 10–27% in patients with BRCA2 mutations [2,72–74]. Furthermore, only 2–3% of women with BRCA2 mutations will develop OC by 50 years of age versus 10–21% of women with BRCA1 mutations.

Different roles of BRCA1 & BRCA2 in DNA-repair pathway

The observed differences in clinical outcome basis of BRCA1 versus BRCA2 mutations may be rooted in different functions of these proteins in dsDNA-repair pathway. BRCA1 was first localized to chromosome 17 via a genetic linkage analysis [75] and was cloned in 1994 [76]. The C-terminus of BRCA1 contains a BRCA1 C-terminal (BRCT) domain, which facilitates phosphoprotein binding. The N-terminus has a RING domain, which has E3 ubiquitin ligase activity. BRCA1 interacts with PALB2 through a domain toward the C-terminal region. Because PALB2 also interacts with BRCA2, BRCA1 may affect BRCA2 function through PALB2 [77]. BRCA2 was found to be related to hereditary breast cancer in 1995 [78]. BRCA2 contains a DNA-binding domain, which binds both ssDNA and dsDNA. BRCA2 has eight BRC repeats that bind RAD51. The C-terminus of BRCA2 also binds RAD51 in a phosphorylation-regulated manner (Figure 1) [79–81].

Both BRCA1 and BRCA2 have been reported to play key roles in DNA-damage repair; however, they appear to have distinct but complementary functions. BRCA1 plays more diverse roles including sensing DNA damage and replication stress, mediating signaling responses, signaling cell cycle checkpoints and mediating other transcriptional responses to DNA damage [82]. In the homologous recombination pathway, BRCA1 is mainly a scaffold protein, enabling interactions between different components of the homologous recombination machinery, and is required for the initial steps of the dsDNA break-repair response and signal amplification. By contrast, BRCA2 is directly involved in loading
RAD51 to damage sites or stalled replication forks [83,84]. BRCA2 acts by navigating RAD51 to ssDNA, enabling RAD51 to displace replication protein-A from ssDNA and stabilizing RAD51–ssDNA filaments by blocking ATP hydrolysis, which is a key regulatory step in DNA pairing [85,86]. RAD51 plays a central role in recombination, assembling onto ssDNA as a nucleoprotein filament and catalyzing the exchange of homologous DNA sequences [87].

BRCA2’s more direct involvement in homologous recombination is consistent with the association of \textit{BRCA2} mutations and hypermutator phenotype that the authors found in OC. Most \textit{BRCA2} mutations found in TCGA study were in the RAD51-binding domain or caused truncations that would delete the RAD51-binding region (Figure 1); therefore, these mutations are expected to attenuate or abolish the interaction with RAD51, resulting in failure to load RAD51 to DNA-damage sites. BRCA1 is also implicated in RAD51 recruitment to the sites of DNA damage through its interactions with PALB2 and BRCA2. This interaction appears to be dependent on CHK2-mediated phosphorylation of S988 on BRCA1 [82]. Interestingly, most \textit{BRCA1} mutations do not result in deletion of S988 or the PALB2 interaction region that regulates BRCA2 (Figure 1); thus, \textit{BRCA1} mutation may have less impact on RAD51-mediated homologous recombination. Consistent with this notion, mutations on the C-terminal region of BRCA1, including the PALB2-binding region, were found to be correlated with better survival advantage by Bolton \textit{et al.} [8]. Thus, this group of \textit{BRCA1}-mutated cases may impact survival in a manner similar to that \textit{BRCA2}-mutated bases because of the effect of these mutants on BRCA2.

**Implications for \textit{BRCA}-related OC treatment**

\textit{BRCA2} mutation status may be a genetic marker for predicting prognosis and chemotherapy response. Because \textit{BRCA2} mutations are associated with longer platinum-free survival durations than \textit{BRCA1} mutations and BRCA wild-type, a patient’s BRCA status may influence the choice of chemotherapy agents for recurrent disease. Whether \textit{BRCA1}- and \textit{BRCA2}-mutated OC patients would experience different responses to chemotherapy drugs other than cisplatin remains unclear. It should be noted that \textit{BRCA2}-deficient tumor cells manifest a strong response to melphanal \textit{in vivo} and \textit{in vitro} [88,89].

The differences in survival and chemotherapy responses among \textit{BRCA1} and \textit{BRCA2} mutation and noncarriers have important implications for the future of OC clinical trial designs. Because \textit{BRCA1} and \textit{BRCA2} mutations, especially \textit{BRCA2} mutations, have a clear impact on survival, any clinical trial that evaluates effectiveness of new therapeutic agents should consider \textit{BRCA1} and \textit{BRCA2} mutations status and perform multivariant analyses with this mutation status as a variable; for \textit{BRCA2}, it is relatively simple. For \textit{BRCA1}, the situation is more complicated because mutations at the N-terminal and C-terminal region of the proteins have opposite association with survival. Further analysis will be needed to stratify the \textit{BRCA1} mutations. Without a balanced \textit{BRCA} mutation distribution, any survival difference observed in different arms of the clinical trials can be at least partially attributed to difference in distributions.

Recent findings demonstrate that PARP inhibitors have cytotoxic effects on BRCA1- or BRCA2-deficient cells [90,91]. The prevailing explanation for these findings is a phenomenon called synthetic lethality [92]. Promising results from clinical trials in BRCA-associated carcinomas (including OC) have been reported (Table 2) [93–98]. An important consideration is whether \textit{BRCA1}- and \textit{BRCA2}-mutated OCs’ differing response to platinum-based chemotherapy, as observed in recent studies, may also result in differing sensitivity to agents that target the resultant homologous recombination defects. Some preclinical data suggest that \textit{BRCA2}−/− cells respond better to PARP inhibitors than...
BRCA1−/− cells [90,99]. Although current trials of PARP inhibitors have not been large enough to detect differences in efficacy among the BRCA gene mutations, trends can be observed. In Gelmon et al.’s study, which included 11 BRCA1- and five BRCA2-mutated OC patients treated by PARP inhibitors, a 60% (three out of five) response rate for BRCA2 versus 24% (11 out of 60) for BRCA-wild-type and 36% (four out of 11) for BRCA1 was observed [96]. A similar trend was seen in the cohort that received 400 mg of olaparib twice daily in Audeh et al.’s study [94]. These promising yet early results indicate that further stratification is needed to evaluate the differing effects of PARP inhibitors treatment in individuals with BRCA2 and BRCA1 mutations. In addition, upcoming trials of PARP inhibitors that specifically enrich for BRCA1 and BRCA2 carriers may be at particular risk for bias if differences between these two biologically distinct groups are not considered. Knowing the differing role of BRCA1 and BRCA2 in DNA-damage repair, the authors anticipate that BRCA2-mutated cases will also render OC more sensitive to PARP inhibitors.

BRCA2 mutation carriers experience better response to chemotherapy; however, it is challenging to identify therapeutic strategies for non-BRCA2 carriers and carriers with secondary resistance to DNA damaging drugs or PARP inhibitors. Understanding the homologous recombination pathway and the impact of mutations in genes in the pathway should provide important insight into areas for future explorations and drug development that mimic BRCA2 mutation in tumor cells. Recently, Issaeva et al. found that cisplatin-resistant breast cancer cells with BRCA2 secondary mutations are still sensitive to 6-thioguanine [100]. In addition, proteasome inhibitors [101], cyclin-dependent kinase inhibitors [102] and HSP90 inhibitors [103] have been reported to inhibit RAD51 foci formation. These drugs may re-sensitize drug-resistant cancers with secondary BRCA2 mutations by inhibiting homologous recombination.

It has been estimated that more than 50% of HGS epithelial OC could show dysfunction of BRCA1 or BRCA2 through genetic or epi-genetic events. There are reports that epithelial OC cases with somatic BRCA1/2 mutations or deficient expression show a survival advantage over noncarriers [15,47,57]; however, data from TCGA and others suggest that silencing of BRCA1 through promoter methylation does not result in an improved overall survival [19,104]. Larger studies that include comprehensive genomic screening of BRCA1 and BRCA2 in primary epithelial OCs will be needed to determine if alterations at the somatic and epigenetic level have similar clinical effects to germline mutations.

**Conclusion & future perspective**

Over the past two decades, significant progress has been made in elucidating the functions of BRCA1 and BRCA2 and their mutations on cancer risk and prognosis. Given the growing awareness of the prognostic importance of BRCA2 mutations and how their sensitivity differs from that of BRCA1 mutations and wild-type, as well as the potential of PARP inhibitors to change how OC is treated, it is increasingly likely that knowing patients’ BRCA1 mutation status will be important making informed treatment recommendations and clinical trial designs. BRCA mutation detection by sequencing is readily available to OC and breast cancer patients in the USA and Europe. The recent findings on BRCA2 mutations should encourage those in other countries to adopt the use of this molecular marker in OC treatment [105]. Other BRCA2 mutations cancer types may manifest similar clinical features to those of OC. Finally, for cancers that are not associated with BRCA2 mutations, efforts should be made to develop agents that mimic BRCA2 mutation as a new class of targeted therapeutics that can be specifically delivered to cancer cells.
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Papers of special note have been highlighted as:

- of interest
- of considerable interest


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97. Kaye SB, Lubinski J, Matulonis U, et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and


Executive summary

- *BRCA1* and *BRCA2* mutations are associated with high-grade serous ovarian cancer (OC).

- The clinical effects of *BRCA1* and *BRCA2* mutations have commonly been analyzed together; however, it is becoming increasingly apparent that these mutations do not have the same effects in OC. Recent reports demonstrated that *BRCA2* mutations are associated with better survival and therapeutic response than *BRCA1*-mutated and wild-type serous OC patients.

- *BRCA1* and *BRCA2* have different roles in homologous recombination repair.

- It is critical to understand the difference of these two genes mutation in OC and the potentially important implications for future clinical management of patients with OC.
Figure 1. Diagrams of BRCA1 and BRCA2 proteins, including functional domains and interacting proteins
The mutations identified in the The Cancer Genome Atlas project are indicated. Germline and somatic mutations in (A) BRCA1 and (B) BRCA2. Mutations are mapped to the corresponding exons of BRCA1 and BRCA2. The pie chart on top of each mutated location indicates the distribution of age at diagnosis of patients with the mutation. The size of each pie chart is based on the number of mutations in that location.

aa: Amino acids; BRCT: BRCA1 C-terminal; RING: RING-type zinc finger.
Table 1

Summary of studies reporting chemosensitivity or survival in ovarian cancer cases with mutations in BRCA1/2 compared with nonmutations or sporadic ovarian cancer.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Mutation-positive population</th>
<th>Carriers</th>
<th>Sporadic/noncarriers</th>
<th>Survival results</th>
<th>p-value</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubin et al. (1996)</td>
<td>Consecutive cases; BRCA1; stages III and IV; matched controls by age, stage, grade and histologic type</td>
<td>43</td>
<td>NA</td>
<td>Median survival (months): BRCA1 carriers, 77; controls, 29</td>
<td>p &lt; 0.001</td>
<td>[55]</td>
</tr>
<tr>
<td>Aida et al. (1998)</td>
<td>High-risk families; BRCA1</td>
<td>13</td>
<td>29</td>
<td>5-year survival (%): BRCA1 carriers, 78.6; controls, 30.3</td>
<td>p &lt; 0.05</td>
<td>[40]</td>
</tr>
<tr>
<td>Jóhannsson et al. (1998)</td>
<td>Familial BRCA1 carriers; age- and stage-matched controls</td>
<td>38</td>
<td>97</td>
<td>Hazard ratio: 1.2; 95% CI: 0.5–2.8</td>
<td>NS</td>
<td>[48]</td>
</tr>
<tr>
<td>Pharaoh et al. (1999)</td>
<td>High-risk families; sporadic cases</td>
<td>151 (BRCA1: 127; BRCA2: 24)</td>
<td>119</td>
<td>5-year survival (%): BRCA1 carriers, 21; BRCA2 carriers, 25; noncarriers, 19</td>
<td>NS</td>
<td>[52]</td>
</tr>
<tr>
<td>Boyd et al. (2000)</td>
<td>Consecutive cases; BRCA1/2 tissues; Jewish origin</td>
<td>88 (BRCA1: 67; BRCA2: 21)</td>
<td>101</td>
<td>5-year survival (%): BRCA1/2 carriers, ~47; noncarriers, ~22</td>
<td>BRCA1/2 vs noncarriers: p = 0.004</td>
<td>[43]</td>
</tr>
<tr>
<td>Zweemer et al. (2001)</td>
<td>Familial cases; BRCA1/2</td>
<td>23 (BRCA1: 20; BRCA2: 3)</td>
<td>17</td>
<td>5-year survival (%): BRCA1/2 carriers, ~40; noncarriers, ~46</td>
<td>NS</td>
<td>[56]</td>
</tr>
<tr>
<td>Ramsus et al. (2001)</td>
<td>Consecutive cases; Jewish origin; BRCA1/2</td>
<td>27 (BRCA1: 15; BRCA2: 12)</td>
<td>71</td>
<td>Median survival (months): BRCA1 carriers, 52; BRCA2 carriers, 49; noncarriers, 35</td>
<td>NS</td>
<td>[54]</td>
</tr>
<tr>
<td>Ben David et al. (2002)</td>
<td>Incidence cases; Jewish origin; BRCA1/2</td>
<td>229 (BRCA1: 171; BRCA2: 58)</td>
<td>549</td>
<td>3-year survival (%): BRCA1/2 carriers, 65.8; noncarriers, 51.9</td>
<td>p &lt; 0.001</td>
<td>[42]</td>
</tr>
<tr>
<td>Buller et al. (2002)</td>
<td>Incidence cases; BRCA1 carriers; stage-matched noncarriers</td>
<td>24</td>
<td>24</td>
<td>Median survival (years): BRCA1 carriers, 4.5; noncarriers, 4.6</td>
<td>NS</td>
<td>[44]</td>
</tr>
<tr>
<td>Cass et al. (2003)</td>
<td>Consecutive cases; BRCA1/2; Ashkenazi Jewish; stages III and IV</td>
<td>34 (BRCA1: 22; BRCA2: 12)</td>
<td>25</td>
<td>Median survival (months): BRCA1/2 carriers, 91; noncarriers, 54</td>
<td>p = 0.046</td>
<td>[45]</td>
</tr>
<tr>
<td>Kringen et al. (2005)</td>
<td>Familial cases; BRCA1</td>
<td>30</td>
<td>100</td>
<td>5-year survival (%): BRCA1 carriers, 33; noncarriers, 23</td>
<td>NS</td>
<td>[49]</td>
</tr>
<tr>
<td>Pal et al. (2007)</td>
<td>Population-based sample; BRCA1/2</td>
<td>32 (BRCA1: 20; BRCA2: 12)</td>
<td>200</td>
<td>4-year survival (%): BRCA1 carriers, 37; BRCA2 carriers, 83; noncarriers, 12</td>
<td>BRCA1 vs noncarriers: p = 0.17; BRCA2 vs noncarriers: p = 0.013</td>
<td>[51]</td>
</tr>
<tr>
<td>Chetrit et al. (2008)</td>
<td>Case–control; Ashkenazi Jewish; BRCA1/2</td>
<td>213 (BRCA1: 159; BRCA2: 54)</td>
<td>392</td>
<td>Median survival (months): BRCA1/2 carriers, 53.7; noncarriers, 37.9</td>
<td>5-year survival for stage III and IV (%): BRCA1/2 carriers, 38.1; noncarriers, 24.5</td>
<td>Median survival: p = 0.002; 5-year survival for stage III and IV: p &lt; 0.001</td>
</tr>
<tr>
<td>Tan et al. (2008)</td>
<td>Case–control; BRCA1/2</td>
<td>22 (BRCA1: 17; BRCA2: 5)</td>
<td>44</td>
<td>Median OS (years): BRCA1 carriers, 8.4; noncarriers, 2.9</td>
<td>Time of first relapse (years): BRCA1 carriers, 5; noncarriers, 1.6</td>
<td>Median OS: p &lt; 0.002; Time of first relapse: p &lt; 0.001</td>
</tr>
<tr>
<td>Study (year)</td>
<td>Mutation-positive population</td>
<td>Carriers</td>
<td>Sporadic/noncarriers</td>
<td>Survival results</td>
<td>p-value</td>
<td>Ref.</td>
</tr>
<tr>
<td>-------------</td>
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<tr>
<td>Hennessy et al. (2010)</td>
<td>Incidence case; BRCA1/2</td>
<td>43 (BRCA1: 31; BRCA2: 13)</td>
<td>192</td>
<td>Median PFS (months): BRCA1/2 20.1; nonmutations, 13.8</td>
<td>p = 0.032</td>
<td>[47]</td>
</tr>
<tr>
<td>Artioli et al. (2010)</td>
<td>Retrospective study; Italian; BRCA1/2</td>
<td>48 (BRCA1: 34; BRCA2: 14)</td>
<td>40</td>
<td>Median survival (months): BRCA1/2 145; noncarriers, 280</td>
<td>NS</td>
<td>[41]</td>
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<tr>
<td>Lacroix et al. (2011)</td>
<td>Non-Ashkenazi Jewish; BRCA1/2</td>
<td>95 (BRCA1: 62; BRCA2: 33)</td>
<td>183</td>
<td>OS (months): BRCA mutation carriers, 101.7; sporadic mutation carriers, 54.3; PFS (months): BRCA1 mutation carriers, 279; sporadic mutation carriers, 17.9</td>
<td>OS: p &lt; 0.0001; PFS: p &lt; 0.0003</td>
<td>[50]</td>
</tr>
<tr>
<td>Ragupathy et al. (2011)</td>
<td>Retrospective analysis; BRCA1/2</td>
<td>12 (BRCA1: 4; BRCA2: 8)</td>
<td>0</td>
<td>Response to platinum-based chemotherapy (%): 100, 50 and 50 for first-, second- and third-line, respectively 3-year survival (%): 92 OS (%): 83</td>
<td>–</td>
<td>[53]</td>
</tr>
<tr>
<td>Vencken et al. (2011)</td>
<td>Retrospective study; BRCA1 and BRCA2 separated</td>
<td>112 (BRCA1: 99; BRCA2: 13)</td>
<td>222</td>
<td>Median OS (years): BRCA1, 5.9; BRCA2, more than 10; sporadic, 2.9</td>
<td>p &lt; 0.01</td>
<td>[36]</td>
</tr>
<tr>
<td>Gallagher et al. (2011)</td>
<td>Incidence case; stage III and IV; BRCA1/2</td>
<td>36 (BRCA1: 20; BRCA2: 16)</td>
<td>74</td>
<td>Median OS (months): carriers, not reached; noncarriers, 67.8</td>
<td>p = 0.002</td>
<td>[37]</td>
</tr>
<tr>
<td>Yang et al. (2011)</td>
<td>Observational study; BRCA1/2 mutation and BRCA1 methylation</td>
<td>Mutations: 62 (BRCA1: 35; BRCA2: 27; methylation: 33)</td>
<td>219</td>
<td>5-year survival (%): BRCA1, 44; BRCA2, 61; wild-type, 25</td>
<td>BRCA1 vs wild-type: p = 0.003</td>
<td>[6]</td>
</tr>
<tr>
<td>Hyman et al. (2011)</td>
<td>Retrospective study; BRCA1 and BRCA2 separated</td>
<td>47 (BRCA1: 30; BRCA2: 17)</td>
<td>143</td>
<td>3-year survival (%): BRCA1, 90.7; BRCA2, 100; wild-type, 69.4</td>
<td>BRCA1 vs wild-type: p = 0.007</td>
<td>[7]</td>
</tr>
<tr>
<td>Bolton et al. (2012)</td>
<td>Observational study; BRCA1/2 mutation</td>
<td>3879 (BRCA1: 909; BRCA2: 304)</td>
<td>2666</td>
<td>5-year survival (%): BRCA1, 44; BRCA2, 52; wild-type, 36</td>
<td>BRCA1 vs noncarriers: p &lt; 0.01; BRCA2 vs noncarriers: p &lt; 0.01; BRCA1 vs BRCA2: p = 0.003</td>
<td>[8]</td>
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<tr>
<td>Liu et al. (2012)</td>
<td>Retrospective study</td>
<td>197 (BRCA1: 148; BRCA2: 49)</td>
<td>0</td>
<td>5-year survival (%): BRCA1, 61; BRCA2, 75</td>
<td>Advanced-stage patients: BRCA1, p = 0.17; BRCA2 p = 0.08</td>
<td>[9]</td>
</tr>
<tr>
<td>Dann et al. (2012)</td>
<td>Retrospective study</td>
<td>15 (BRCA1: 12; BRCA2: 3)</td>
<td>38</td>
<td>Median PFS (months): BRCA1-mutant tumor, 21; wild-type, 5</td>
<td>–</td>
<td>[57]</td>
</tr>
<tr>
<td>Reitma et al. (2012)</td>
<td>Retrospective study</td>
<td>71 (BRCA1: 55; BRCA2: 16)</td>
<td>–</td>
<td>Disease-free survival (months): BRCA1, 65 months; BRCA2, 95 OS (months): BRCA1, 71; BRCA2 116</td>
<td>Disease-free survival: p = 0.34; OS: p = 0.56</td>
<td>[10]</td>
</tr>
</tbody>
</table>

NA: Not available; NS: No significance; OS: Overall survival; PFS: Progression-free survival.
Clinical trials of PARP inhibitors including ovarian cancer patients.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study population</th>
<th>Phase</th>
<th>Treatment</th>
<th>Patients (n)</th>
<th>RR (%) †</th>
<th>CBR (%)</th>
<th>PFS or RD</th>
<th>Toxicity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fong et al. (2009)</td>
<td>Refractory solid tumors (OC, breast, colorectal, melanoma, sarcoma and others)</td>
<td>I</td>
<td>Olaparib: dose escalation and expansion at 600 mg twice daily</td>
<td>60 (OC: 21)</td>
<td>53</td>
<td>60</td>
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<td>Grade 1 or 2</td>
<td>[93]</td>
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<tr>
<td>Audeh et al. (2010)</td>
<td>BRCA-associated recurrent advanced OC</td>
<td>II</td>
<td>Olaparib: 400 mg twice daily and 100 mg twice daily</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
<td>Mainly grade 2</td>
<td>[94]</td>
</tr>
<tr>
<td>Fong et al. (2010)</td>
<td>BRCA-associated OC that progressed after platinum agent</td>
<td>II</td>
<td>Olaparib: dose escalation and expansion at 200 mg twice daily</td>
<td>50</td>
<td></td>
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<td>Mainly grade 2</td>
<td>[95]</td>
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<tr>
<td>Gelmon et al. (2011)</td>
<td>Advanced high-grade serous undifferentiated OC; triple-negative breast cancer</td>
<td>II</td>
<td>Olaparib: 400 mg twice daily</td>
<td>91 (OC: 65)</td>
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<td></td>
<td></td>
<td>36% grade 23</td>
<td>[96]</td>
</tr>
<tr>
<td>Kaye et al. (2012)</td>
<td>Recurred within 12 months of prior platinum treatment; BRCA1/2-mutated OC</td>
<td>II</td>
<td>Olaparib: 400 mg or 200 mg twice daily, or PLD 50 mg/m² every 28 days</td>
<td>97</td>
<td></td>
<td></td>
<td></td>
<td>Generally grade 2</td>
<td>[97]</td>
</tr>
<tr>
<td>Ledermann et al. (2012)</td>
<td>Platinum-sensitive, relapsed, high-grade serous OC</td>
<td>II</td>
<td>Olaparib 400 mg twice daily or placebo</td>
<td>265</td>
<td></td>
<td></td>
<td></td>
<td>Most grade 1 or 2</td>
<td>[98]</td>
</tr>
</tbody>
</table>

*RR according to RECIST criteria unless stated otherwise.

CBR: Clinical benefit rate (response rate + stable disease); GCIG: Gynecologic Cancer Intergroup; OC: Ovarian cancer; PFS: Progression-free survival; PLD: Pegylated liposomal doxorubicin; RD: Response duration; RECIST: Response Evaluation Criteria In Solid Tumors; RR: Response rate (complete + partial responses).