Published in final edited form as:

Pharmacogenomics. 2012 October ; 13(13): 1523–1535. doi:10.2217/pgs.12.137.

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

Guoyan Liu^{1,2}, Da Yang¹, Yan Sun^{1,3}, Ilya Shmulevich⁴, Fengxia Xue², Anil K Sood^{5,6}, and Wei Zhang^{1,*}

¹Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

²Department of Gynecology & Obstetrics, Tianjin Medical University General Hospital, Tianjin, China

³Department of Pathology, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China

⁴Institute for Systems Biology, Seattle, WA, USA

⁵Department of Cancer Biology & Center for RNAi & Non-Coding RNA, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

⁶Department of Gynecologic Oncology, & Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract

A key function of *BRCA1* and *BRCA2* is the participation in dsDNA break 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.

© 2012 Future Medicine Ltd

*Author for correspondence: Tel.: +1 713 745 1103, Fax: +1 713 792 5549, wzhang@mdanderson.org.

For reprint orders, please contact: reprints@futuremedicine.com

Financial & competing interests disclosure

This study was supported by a grant from the NIH (U24CA143835) to I Shmulevich and W Zhang, a grant from the Blanton-Davis Ovarian Cancer Research Program to W Zhang, an Ovarian Cancer SPORE grant (P50 CA083639) to AK Sood and a grant supported by National Natural Science Foundation of China (grant no. 81101673) to G Liu. D Yang is an Odyssey Fellow at MD Anderson Cancer Center, and supported by The Diane Denson Tobola Fellowship in Ovarian Cancer Research fellowship and The Harold C and Mary L Daily Endowment Fund. Y Sun is supported by The Linda K Manning Fellowship in Ovarian Cancer and The A Lavoy Moore Endowment Fund. G Liu is a New Century outstanding fellow at Tianjin Medical University General Hospital. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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*, *CHK1*, *CHK2*, *ATM*, *ATR* and *FANCF* [27–31]. Homologous recombination defects occur in up to 50% of HGS OCs [19].

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 *BRCA*-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 and *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 *BRCA2* mutations and hypermutator phenotype that the authors found in OC. Most *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 *BRCA1* mutations do not result in deletion of S988 or the PALB2 interaction region that regulates BRCA2 (Figure 1); thus, *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 *et al.* [8]. Thus, this group of *BRCA1*-mutated cases may impact survival in a manner similar to that *BRCA2*-mutated bases because of the effect of these mutants on BRCA2.

Implications for *BRCA*-related OC treatment

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

The differences in survival and chemotherapy responses among *BRCA1* and *BRCA2* mutation and noncarriers have important implications for the future of OC clinical trial designs. Because *BRCA1* and *BRCA2* mutations, especially *BRCA2* mutations, have a clear impact on survival, any clinical trial that evaluates effectiveness of new therapeutic agents should consider *BRCA1* and *BRCA2* mutations status and perform multivariate analyses with this mutation status as a variable; for BRCA2, it is relatively simple. For 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 *BRCA1* mutations. Without a balanced *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 *BRCA1*- and *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 *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 *BRCA1*-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' *BRCA* 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.

Acknowledgments

The authors would like to thank A Sutton in the Department of Scientific Publications (The University of Texas MD Anderson Cancer Center, TX, USA) for editing this manuscript.

References

Papers of special note have been highlighted as:

■ of interest

■ ■ of considerable interest

1. Pennington KP, Swisher EM. Hereditary ovarian cancer: beyond the usual suspects. *Gynecol Oncol*. 2012; 124(2):347–353. [PubMed: 22264603]
2. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in *BRCA1* and *BRCA2*. *Science*. 2003; 302(5645):643–646. [PubMed: 14576434]
3. Chen S, Parmigiani G. Meta-analysis of *BRCA1* and *BRCA2* penetrance. *J Clin Oncol*. 2007; 25(11):1329–1333. [PubMed: 17416853]
4. Sakai W, Swisher EM, Karlan BY, et al. Secondary mutations as a mechanism of cisplatin resistance in *BRCA2*-mutated cancers. *Nature*. 2008; 451(7182):1116–1120. [PubMed: 18264087]
5. Swisher EM, Sakai W, Karlan BY, Wurz K, Urban N, Taniguchi T. Secondary *BRCA1* mutations in *BRCA1*-mutated ovarian carcinomas with platinum resistance. *Cancer Res*. 2008; 68(8):2581–2586. [PubMed: 18413725]
- 6■. Yang D, Khan S, Sun Y, et al. Association of *BRCA1* and *BRCA2* mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. *JAMA*. 2011; 306(14):1557–1565. A comprehensive analysis of The Cancer Genome Atlas data on different effect of *BRCA1* and *BRCA2* mutations on drug response and hypermutator phenotype in ovarian cancer. [PubMed: 21990299]
- 7■. Hyman DM, Zhou Q, Iasonos A, et al. Improved survival for *BRCA2*-associated serous ovarian cancer compared with both *BRCA*-negative and *BRCA1*-associated serous ovarian cancer. *Cancer*. 2011; 118(15):3703–3709. Another important report of improved survival of *BRCA2*-mutated ovarian cancer patients. [PubMed: 22139894]
- 8■ ■. Bolton, KI; Chenevix-Trench, G.; Goh, C., et al. Association between *BRCA1* and *BRCA2* mutations and survival in women with invasive epithelial ovarian cancer. *JAMA*. 2012; 307(4): 382–390. Large multicenter study on differing effect of *BRCA1* and *BRCA2* mutations on ovarian cancer survival. [PubMed: 22274685]
9. Liu J, Cristea MC, Frankel P, et al. Clinical characteristics and outcomes of BRCA-associated ovarian cancer: genotype and survival. *Cancer Genet*. 2012; 205(1–2):34–41. [PubMed: 22429596]
10. Reitsma W, de Bock GH, Oosterwijk JC, Ten Hoor KA, Hollema H, Mourits MJ. Clinicopathologic characteristics and survival in *BRCA1*- and *BRCA2*-related adnexal cancer: are they different? *Int J Gynecol Cancer*. 2012; 22(4):579–585. [PubMed: 22274543]
11. Whittemore AS, Gong G, Itnyre J. Prevalence and contribution of *BRCA1* mutations in breast cancer and ovarian cancer: results from three U.S. population-based case-control studies of ovarian cancer. *Am J Hum Genet*. 1997; 60(3):496–504. [PubMed: 9042908]
12. Risch HA, McLaughlin JR, Cole DE, et al. Prevalence and penetrance of germline *BRCA1* and *BRCA2* mutations in a population series of 649 women with ovarian cancer. *Am J Hum Genet*. 2001; 68(3):700–710. [PubMed: 11179017]
13. Rubin SC, Blackwood MA, Bandera C, et al. *BRCA1*, *BRCA2*, and hereditary nonpolyposis colorectal cancer gene mutations in an unselected ovarian cancer population: relationship to family history and implications for genetic testing. *Am J Obstet Gynecol*. 1998; 178(4):670–677. [PubMed: 9579428]
14. Pal T, Permuth-Wey J, Betts JA, et al. *BRCA1* and *BRCA2* mutations account for a large proportion of ovarian carcinoma cases. *Cancer*. 2005; 104(12):2807–2816. [PubMed: 16284991]

15. Press JZ, De Luca A, Boyd N, et al. Ovarian carcinomas with genetic and epigenetic *BRCA1* loss have distinct molecular abnormalities. *BMC Cancer*. 2008; 8:17. [PubMed: 18208621]
16. Levine DA, Argenta PA, Yee CJ, et al. Fallopian tube and primary peritoneal carcinomas associated with *BRCA* mutations. *J Clin Oncol*. 2003; 21(22):4222–4227. [PubMed: 14615451]
17. Crum CP, Drapkin R, Miron A, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. *Curr Opin Obstet Gynecol*. 2007; 19(1):3–9. [PubMed: 17218844]
18. Norquist BM, Garcia RL, Allison KH, et al. The molecular pathogenesis of hereditary ovarian carcinoma: alterations in the tubal epithelium of women with *BRCA1* and *BRCA2* mutations. *Cancer*. 2010; 116(22):5261–5271. [PubMed: 20665887]
19. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011; 474(7353):609–615. [PubMed: 21720365]
20. Bowtell DD. The genesis and evolution of high-grade serous ovarian cancer. *Nat Rev Cancer*. 2010; 10(11):803–808. [PubMed: 20944665]
21. Kuo KT, Mao TL, Jones S, et al. Frequent activating mutations of *PIK3CA* in ovarian clear cell carcinoma. *Am J Pathol*. 2009; 174(5):1597–1601. [PubMed: 19349352]
22. Jones S, Wang TL, Shih Ie M, et al. Frequent mutations of chromatin remodeling gene *ARID1A* in ovarian clear cell carcinoma. *Science*. 2010; 330(6001):228–231. [PubMed: 20826764]
23. Wiegand KC, Shah SP, Al-Agha OM, et al. *ARID1A* mutations in endometriosis-associated ovarian carcinomas. *N Engl J Med*. 2010; 363(16):1532–1543. [PubMed: 20942669]
24. Cuatrecasas M, Villanueva A, Matias-Guiu X, Prat J. *K-RAS* mutations in mucinous ovarian tumors: a clinicopathologic and molecular study of 95 cases. *Cancer*. 1997; 79(8):1581–1586. [PubMed: 9118042]
25. Gilks CB, Prat J. Ovarian carcinoma pathology and genetics: recent advances. *Hum Pathol*. 2009; 40(9):1213–1223. [PubMed: 19552940]
26. Piek JM, Torrença B, Hermesen B, et al. Histopathological characteristics of *BRCA1*- and *BRCA2*-associated intraperitoneal cancer: a clinic-based study. *Fam Cancer*. 2003; 2(2):73–78. [PubMed: 14574155]
27. Geisler JP, Hatterman-Zogg MA, Rathe JA, Buller RE. Frequency of *BRCA1* dysfunction in ovarian cancer. *J Natl Cancer Inst*. 2002; 94(1):61–67. [PubMed: 11773283]
28. Hilton JL, Geisler JP, Rathe JA, Hattermann-Zogg MA, Deyoung B, Buller RE. Inactivation of *BRCA1* and *BRCA2* in ovarian cancer. *J Natl Cancer Inst*. 2002; 94(18):1396–1406. [PubMed: 12237285]
29. Lim, SI; Smith, P.; Syed, N., et al. Promoter hypermethylation of *FANCF* and outcome in advanced ovarian cancer. *Br J Cancer*. 2008; 98(8):1452–1456. [PubMed: 18414472]
30. Wang Z, Li M, Lu S, Zhang Y, Wang H. Promoter hypermethylation of *FANCF* plays an important role in the occurrence of ovarian cancer through disrupting Fanconi anemia–BRCA pathway. *Cancer Biol Ther*. 2006; 5(3):256–260. [PubMed: 16418574]
31. D'Andrea AD. The Fanconi anemia/BRCA signaling pathway: disruption in cisplatin-sensitive ovarian cancers. *Cell Cycle*. 2003; 2(4):290–292. [PubMed: 12851475]
32. Soegaard M, Kjaer SK, Cox M, et al. *BRCA1* and *BRCA2* mutation prevalence and clinical characteristics of a population-based series of ovarian cancer cases from Denmark. *Clin Cancer Res*. 2008; 14(12):3761–3767. [PubMed: 18559594]
33. Risch HA, McLaughlin JR, Cole De, et al. Population *BRCA1* and *BRCA2* mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. *J Natl Cancer Inst*. 2006; 98(23):1694–1706. [PubMed: 17148771]
34. Shaw PA, McLaughlin JR, Zweemer RP, et al. Histopathologic features of genetically determined ovarian cancer. *Int J Gynecol Pathol*. 2002; 21(4):407–411. [PubMed: 12352190]
35. Tan DS, Rothermundt C, Thomas K, et al. 'BRCAness' syndrome in ovarian cancer: a case–control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with *BRCA1* and *BRCA2* mutations. *J Clin Oncol*. 2008; 26(34):5530–5536. [PubMed: 18955455]
36. Vencken PM, Kriege M, Hoogwerf D, et al. Chemosensitivity and outcome of *BRCA1*- and *BRCA2*-associated ovarian cancer patients after first-line chemotherapy compared with sporadic ovarian cancer patients. *Ann Oncol*. 2011; 22(6):1346–1352. [PubMed: 21228333]

37. Gallagher DJ, Konner JA, Bell-McGuinn KM, et al. Survival in epithelial ovarian cancer: a multivariate analysis incorporating *BRCA* mutation status and platinum sensitivity. *Ann Oncol*. 2011; 22(5):1127–1132. [PubMed: 21084428]
38. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. *Nat Rev Cancer*. 2004; 4(10):814–819. [PubMed: 15510162]
39. Gourley C, Michie Co, Roxburgh P, et al. Increased incidence of visceral metastases in Scottish patients with *BRCA1/2*-defective ovarian cancer: an extension of the ovarian BRCAness phenotype. *J Clin Oncol*. 2010; 28(15):2505–2511. [PubMed: 20406939]
40. Aida H, Takakuwa K, Nagata H, et al. Clinical features of ovarian cancer in Japanese women with germ-line mutations of *BRCA1*. *Clin Cancer Res*. 1998; 4(1):235–240. [PubMed: 9516977]
41. Artioli G, Borgato L, Cappetta A, et al. Overall survival in *BRCA*-associated ovarian cancer: case-control study of an Italian series. *Eur J Gynaecol Oncol*. 2010; 31(6):658–661. [PubMed: 21319511]
42. Ben David Y, Chetrit A, Hirsh-Yechezkel G, et al. Effect of *BRCA* mutations on the length of survival in epithelial ovarian tumors. *J Clin Oncol*. 2002; 20(2):463–466. [PubMed: 11786575]
43. Boyd J, Sonoda Y, Federici MG, et al. Clinicopathologic features of *BRCA*-linked and sporadic ovarian cancer. *JAMA*. 2000; 283(17):2260–2265. [PubMed: 10807385]
44. Buller RE, Shahin MS, Geisler JP, Zogg M, De Young BR, Davis CS. Failure of *BRCA1* dysfunction to alter ovarian cancer survival. *Clin Cancer Res*. 2002; 8(5):1196–1202. [PubMed: 12006538]
45. Cass I, Baldwin RL, Varkey T, Moslehi R, Narod SA, Karlan BY. Improved survival in women with *BRCA*-associated ovarian carcinoma. *Cancer*. 2003; 97(9):2187–2195. [PubMed: 12712470]
46. Chetrit A, Hirsh-Yechezkel G, Ben-David Y, Lubin F, Friedman E, Sadetzki S. Effect of *BRCA1/2* mutations on long-term survival of patients with invasive ovarian cancer: the national Israeli study of ovarian cancer. *J Clin Oncol*. 2008; 26(1):20–25. [PubMed: 18165636]
47. Hennessy BT, Timms KM, Carey MS, et al. Somatic mutations in *BRCA1* and *BRCA2* could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. *J Clin Oncol*. 2010; 28(22):3570–3576. [PubMed: 20606085]
48. Jóhannsson OT, Rånstam J, Borg A, Olsson H. Survival of *BRCA1* breast and ovarian cancer patients: a population-based study from southern Sweden. *J Clin Oncol*. 1998; 16(2):397–404. [PubMed: 9469321]
49. Kringen P, Wang Y, Dumeaux V, et al. *TP53* mutations in ovarian carcinomas from sporadic cases and carriers of two distinct *BRCA1* founder mutations; relation to age at diagnosis and survival. *BMC Cancer*. 2005; 5:134. [PubMed: 16229746]
50. Lacour RA, Westin SN, Meyer LA, et al. Improved survival in non-Ashkenazi Jewish ovarian cancer patients with *BRCA1* and *BRCA2* gene mutations. *Gynecol Oncol*. 2011; 121(2):358–363. [PubMed: 21276604]
51. Pal T, Permuth-Wey J, Kapoor R, Cantor A, Sutphen R. Improved survival in *BRCA2* carriers with ovarian cancer. *Fam Cancer*. 2007; 6(1):113–119. [PubMed: 17160431]
52. Pharoah PD, Easton DF, Stockton DL, Gayther S, Ponder BA. Survival in familial, *BRCA1*-associated, and *BRCA2*-associated epithelial ovarian cancer. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) Familial Ovarian Cancer Study Group. *Cancer Res*. 1999; 59(4):868–871. [PubMed: 10029077]
53. Ragupathy K, Ferguson M. Pattern and chemosensitivity of ovarian cancer in patients with *BRCA1/2* mutations. *J Obstet Gynaecol*. 2011; 31(2):178–179. [PubMed: 21281038]
54. Ramus SJ, Fishman A, Pharoah PD, Yarkoni S, Altaras M, Ponder BA. Ovarian cancer survival in Ashkenazi Jewish patients with *BRCA1* and *BRCA2* mutations. *Eur J Surg Oncol*. 2001; 27(3):278–281. [PubMed: 11373105]
55. Rubin SC, Benjamin I, Behbakht K, et al. Clinical and pathological features of ovarian cancer in women with germ-line mutations of *BRCA1*. *N Engl J Med*. 1996; 335(19):1413–1416. [PubMed: 8875917]
56. Zweemer RP, Verheijen RH, Coebergh JW, et al. Survival analysis in familial ovarian cancer, a case control study. *Eur J Obstet Gynecol Reprod Biol*. 2001; 98(2):219–223. [PubMed: 11574135]

57. Dann RB, Deloia JA, Timms KM, et al. *BRCA1/2* mutations and expression: response to platinum chemotherapy in patients with advanced stage epithelial ovarian cancer. *Gynecol Oncol.* 2012; 125(3):677–682. [PubMed: 22406760]
58. Mankoo PK, Shen R, Schultz N, Levine DA, Sander C. Time to recurrence and survival in serous ovarian tumors predicted from integrated genomic profiles. *PLoS ONE.* 2011; 6(11):e24709. [PubMed: 22073136]
59. Yarden RI, Pardo-Reoyo S, Sgagias M, Cowan KH, Brody LC. *BRCA1* regulates the G2/M checkpoint by activating Chk1 kinase upon DNA damage. *Nat Genet.* 2002; 30(3):285–289. [PubMed: 11836499]
60. Joukov V, Groen AC, Prokhorova T, et al. The *BRCA1/BARD1* heterodimer modulates ran-dependent mitotic spindle assembly. *Cell.* 2006; 127(3):539–552. [PubMed: 17081976]
61. Lou Z, Minter-Dykhouse K, Chen J. *BRCA1* participates in DNA decatenation. *Nat Struct Mol Biol.* 2005; 12(7):589–593. [PubMed: 15965487]
62. Sankaran S, Crone DE, Palazzo RE, Parvin JD. *BRCA1* regulates gamma-tubulin binding to centrosomes. *Cancer Biol Ther.* 2007; 6(12):1853–1857. [PubMed: 18087219]
63. Starita LM, Machida Y, Sankaran S, et al. *BRCA1*-dependent ubiquitination of gamma-tubulin regulates centrosome number. *Mol Cell Biol.* 2004; 24(19):8457–8466. [PubMed: 15367667]
64. Drost R, Bouwman P, Rottenberg S, et al. *BRCA1* RING function is essential for tumor suppression but dispensable for therapy resistance. *Cancer Cell.* 2011; 20(6):797–809. Important study on different domain mutations of *BRCA1* inducing different effects on tumor suppression and therapy resistance. [PubMed: 22172724]
65. Narod SA, Neuhausen S, Vichodez G, et al. Rapid progression of prostate cancer in men with a *BRCA2* mutation. *Br J Cancer.* 2008; 99(2):371–374. [PubMed: 18577985]
66. Ferrone CR, Levine DA, Tang LH, et al. *BRCA* germline mutations in Jewish patients with pancreatic adenocarcinoma. *J Clin Oncol.* 2009; 27(3):433–438. [PubMed: 19064968]
67. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in *BRCA1* or *BRCA2*: a review of the literature. *J Clin Oncol.* 2004; 22(4):735–742. [PubMed: 14966099]
68. Hahn SA, Greenhalf B, Ellis I, et al. *BRCA2* germline mutations in familial pancreatic carcinoma. *J Natl Cancer Inst.* 2003; 95(3):214–221. [PubMed: 12569143]
69. Moller P, Evans DG, Reis MM, et al. Surveillance for familial breast cancer: Differences in outcome according to *BRCA* mutation status. *Int J Cancer.* 2007; 121(5):1017–1020. [PubMed: 17471561]
70. Lee EH, Park SK, Park B, et al. Effect of *BRCA1/2* mutation on short-term and long-term breast cancer survival: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2010; 122(1):11–25. [PubMed: 20376556]
71. Foulkes WD, Metcalfe K, Sun P, et al. Estrogen receptor status in *BRCA1*- and *BRCA2*-related breast cancer: the influence of age, grade, and histological type. *Clin Cancer Res.* 2004; 10(6): 2029–2034. [PubMed: 15041722]
72. Satagopan JM, Boyd J, Kauff ND, et al. Ovarian cancer risk in Ashkenazi Jewish carriers of *BRCA1* and *BRCA2* mutations. *Clin Cancer Res.* 2002; 8(12):3776–3781. [PubMed: 12473589]
73. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with *BRCA1* or *BRCA2* mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet.* 2003; 72(5):1117–1130. [PubMed: 12677558]
74. Anglian Breast Cancer Study Group. Prevalence and penetrance of *BRCA1* and *BRCA2* mutations in a population-based series of breast cancer cases. *Br J Cancer.* 2000; 83(10):1301–1308. [PubMed: 11044354]
75. Hall JM, Lee Mk, Newman B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science.* 1990; 250(4988):1684–1689. [PubMed: 2270482]
76. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1*. *Science.* 1994; 266(5182):66–71. [PubMed: 7545954]
77. Sy SM, Huen MS, Chen J. PALB2 is an integral component of the *BRCA* complex required for homologous recombination repair. *Proc Natl Acad Sci USA.* 2009; 106(17):7155–7160. [PubMed: 19369211]

78. Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene *BRCA2*. *Nature*. 1995; 378(6559):789–792. [PubMed: 8524414]
79. Esashi F, Christ N, Gannon J, et al. CDK-dependent phosphorylation of *BRCA2* as a regulatory mechanism for recombinational repair. *Nature*. 2005; 434(7033):598–604. [PubMed: 15800615]
80. Ayoub N, Rajendra E, Su X, Jeyasekharan AD, Mahen R, Venkitaraman AR. The carboxyl terminus of *BRCA2* links the disassembly of Rad51 complexes to mitotic entry. *Curr Biol*. 2009; 19(13):1075–1085. [PubMed: 19540122]
81. Davies OR, Pellegrini L. Interaction with the *BRCA2* C terminus protects RAD51-DNA filaments from disassembly by BRC repeats. *Nat Struct Mol Biol*. 2007; 14(6):475–483. [PubMed: 17515903]
82. Roy R, Chun J, Powell SN. *BRCA1* and *BRCA2*: different roles in a common pathway of genome protection. *Nat Rev Cancer*. 2011; 12(1):68–78. Comprehensive and well-written review highlighting the different roles of *BRCA1* and *BRCA2* in homologous recombination. [PubMed: 22193408]
83. Lou Z, Chini CC, Minter-Dykhouse K, Chen J. Mediator of DNA damage checkpoint protein 1 regulates *BRCA1* localization and phosphorylation in DNA damage checkpoint control. *J Biol Chem*. 2003; 278(16):13599–13602. [PubMed: 12611903]
84. Hashizume R, Fukuda M, Maeda I, et al. The RING heterodimer *BRCA1*–*BARD1* is a ubiquitin ligase inactivated by a breast cancer-derived mutation. *J Biol Chem*. 2001; 276(18):14537–14540. [PubMed: 11278247]
85. Jensen RB, Carreira A, Kowalczykowski SC. Purified human *BRCA2* stimulates RAD51-mediated recombination. *Nature*. 2010; 467(7316):678–683. [PubMed: 20729832]
86. Holloman WK. Unraveling the mechanism of *BRCA2* in homologous recombination. *Nat Struct Mol Biol*. 2011; 18(7):748–754. [PubMed: 21731065]
87. Baumann P, Benson FE, West SC. Human Rad51 protein promotes ATP-dependent homologous pairing and strand transfer reactions *in vitro*. *Cell*. 1996; 87(4):757–766. [PubMed: 8929543]
88. Osher DJ, Kushner YB, Arseneau J, Foulkes WD. Melphalan as a treatment for *BRCA*-related ovarian carcinoma: can you teach an old drug new tricks? *J Clin Pathol*. 2011; 64(10):924–926. [PubMed: 21378390]
89. Evers B, Schut E, van der Burg E, et al. A high-throughput pharmaceutical screen identifies compounds with specific toxicity against *BRCA2*-deficient tumors. *Clin Cancer Res*. 2009; 16(1): 99–108. [PubMed: 20008842]
90. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy. *Nature*. 2005; 434(7035):917–921. [PubMed: 15829967]
91. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of *BRCA2*-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*. 2005; 434(7035):913–917. [PubMed: 15829966]
92. Chen A. PARP inhibitors: its role in treatment of cancer. *Chin J Cancer*. 2011; 30(7):463–471. [PubMed: 21718592]
93. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N Engl J Med*. 2009; 361(2):123–134. [PubMed: 19553641]
94. Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet*. 2010; 376(9737):245–251. [PubMed: 20609468]
95. Fong PC, Yap TA, Boss DS, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in *BRCA* carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol*. 2010; 28(15):2512–2519. [PubMed: 20406929]
96. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a Phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*. 2011; 12(9):852–861. [PubMed: 21862407]
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

- pegylated liposomal doxorubicin in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer. *J Clin Oncol*. 2012; 30(4):372–379. [PubMed: 22203755]
98. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012; 366(15):1382–1392. [PubMed: 22452356]
99. Turner NC, Lord CJ, Iorns E, et al. A synthetic lethal siRNA screen identifying genes mediating sensitivity to a PARP inhibitor. *EMBO J*. 2008; 27(9):1368–1377. [PubMed: 18388863]
100. Issaeva N, Thomas HD, Djureinovic T, et al. 6-thioguanine selectively kills *BRCA2*-defective tumors and overcomes PARP inhibitor resistance. *Cancer Res*. 2010; 70(15):6268–6276. [PubMed: 20631063]
101. Jacquemont C, Taniguchi T. Proteasome function is required for DNA damage response and fanconi anemia pathway activation. *Cancer Res*. 2007; 67(15):7395–7405. [PubMed: 17671210]
102. Deans AJ, Khanna KK, Mcnees CJ, Mercurio C, Heierhorst J, Mcarthur GA. Cyclin-dependent kinase 2 functions in normal DNA repair and is a therapeutic target in *BRCA1*-deficient cancers. *Cancer Res*. 2006; 66(16):8219–8226. [PubMed: 16912201]
103. Dungey FA, Caldecott KW, Chalmers AJ. Enhanced radiosensitization of human glioma cells by combining inhibition of poly(ADP-ribose) polymerase with inhibition of heat shock protein 90. *Mol Cancer Ther*. 2009; 8(8):2243–2254. [PubMed: 19671736]
104. Chiang JW, Karlan BY, Cass L, Baldwin RL. *BRCA1* promoter methylation predicts adverse ovarian cancer prognosis. *Gynecol Oncol*. 2006; 101(3):403–410. [PubMed: 16360812]
105. Liu GY, Zhang W. Will Chinese ovarian cancer patients benefit from knowing the *BRCA2* mutation status? *Chin J Cancer*. 2012; 31(1):1–4. [PubMed: 22176776]

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.

Study (year)	Mutation-positive population	Carriers	Sporadic/noncarriers	Survival results	p-value	Ref.
Rubin <i>et al.</i> (1996)	Consecutive cases; <i>BRCA1</i> ; stages III and IV; matched controls by age, stage, grade and histologic type	43	NA	Median survival (months): <i>BRCA1</i> carriers, 77; controls, 29	$p < 0.001$	[55]
Aida <i>et al.</i> (1998)	High-risk families; <i>BRCA1</i>	13	29	5-year survival (%): <i>BRCA1</i> carriers, 78.6; controls, 30.3	$p < 0.05$	[40]
Johannsson <i>et al.</i> (1998)	Familial <i>BRCA1</i> carriers; age- and stage-matched controls	38	97	Hazard ratio: 1.2; 95% CI: 0.5–2.8	NS	[48]
Pharaoh <i>et al.</i> (1999)	High-risk families; sporadic cases	151 (<i>BRCA1</i> : 127; <i>BRCA2</i> : 24)	119	5-year survival (%): <i>BRCA1</i> carriers, 21; <i>BRCA2</i> carriers, 25; noncarriers, 19	NS	[52]
Boyd <i>et al.</i> (2000)	Consecutive cases; <i>BRCA1/2</i> tissues; Jewish origin	88 (<i>BRCA1</i> : 67; <i>BRCA2</i> : 21)	101	5-year survival (%): <i>BRCA1/2</i> carriers, ~47; noncarriers, ~22	<i>BRCA1/2</i> vs noncarriers: $p = 0.004$	[43]
Zweemer <i>et al.</i> (2001)	Familial cases; <i>BRCA1/2</i>	23 (<i>BRCA1</i> : 20; <i>BRCA2</i> : 3)	17	5-year survival (%): <i>BRCA1/2</i> carriers, ~40; noncarriers, ~46	NS	[56]
Ramus <i>et al.</i> (2001)	Consecutive cases; Jewish origin; <i>BRCA1/2</i>	27 (<i>BRCA1</i> : 15; <i>BRCA2</i> : 12)	71	Median survival (months): <i>BRCA1</i> carriers, 52; <i>BRCA2</i> carriers, 49; noncarriers, 35	NS	[54]
Ben David <i>et al.</i> (2002)	Incidence cases; Jewish origin; <i>BRCA1/2</i>	229 (<i>BRCA1</i> : 171; <i>BRCA2</i> : 58)	549	3-year survival (%): <i>BRCA1/2</i> carriers, 65.8; noncarriers, 51.9	$p < 0.001$	[42]
Buller <i>et al.</i> (2002)	Incidence cases; <i>BRCA1</i> carriers; stage-matched noncarriers	24	24	Median survival (years): <i>BRCA1</i> carriers, 4.5; noncarriers, 4.6	NS	[44]
Cass <i>et al.</i> (2003)	Consecutive cases; <i>BRCA1/2</i> ; Ashkenazi Jewish; stages III and IV	34 (<i>BRCA1</i> : 22; <i>BRCA2</i> : 12)	25	Median survival (months): <i>BRCA1/2</i> carriers, 91; noncarriers, 54	$p = 0.046$	[45]
Kringen <i>et al.</i> (2005)	Familial cases; <i>BRCA1</i>	30	100	5-year survival (%): <i>BRCA1</i> carriers, 33; noncarriers, 23	NS	[49]
Pal <i>et al.</i> (2007)	Population-based sample; <i>BRCA1/2</i>	32 (<i>BRCA1</i> : 20; <i>BRCA2</i> : 12)	200	4-year survival (%): <i>BRCA1</i> carriers, 37; <i>BRCA2</i> carriers, 83; noncarriers, 12	<i>BRCA1</i> vs noncarriers: $p = 0.17$; <i>BRCA2</i> vs noncarriers: $p = 0.013$	[51]
Chetrit <i>et al.</i> (2008)	Case-control; Ashkenazi Jewish; <i>BRCA1/2</i>	213 (<i>BRCA1</i> : 159; <i>BRCA2</i> : 54)	392	Median survival (months): <i>BRCA1/2</i> , 53.7; noncarriers, 37.9 5-year survival for stage III and IV (%): carriers, 38.1; noncarriers, 24.5	Median survival: $p = 0.002$ 5-year survival for stage III and IV: $p < 0.001$	[46]
Tan <i>et al.</i> (2008)	Case-control; <i>BRCA1/2</i>	22 (<i>BRCA1</i> : 17; <i>BRCA2</i> : 5)	44	Median OS (years): <i>BRCA</i> carriers, 8.4; noncarriers, 2.9 Time of first relapse (years): <i>BRCA</i> carriers, 5; noncarriers, 1.6	Median OS: $p < 0.002$ Time of first relapse: $p < 0.001$	[35]

Study (year)	Mutation-positive population	Carriers	Sporadic/noncarriers	Survival results	p-value	Ref.
Hennessy <i>et al.</i> (2010)	Incidence case; <i>BRCA1/2</i>	43 (<i>BRCA1</i> : 31; <i>BRCA2</i> : 13)	192	Median PFS (months): <i>BRCA1/2</i> , 20.1; nonmutations, 13.8	p = 0.032	[47]
Arioli <i>et al.</i> (2010)	Retrospective study; Italian; <i>BRCA1/2</i>	48 (<i>BRCA1</i> : 34; <i>BRCA2</i> : 14)	40	Median survival (months): <i>BRCA1/2</i> , 145; noncarriers, 280	NS	[41]
Lacour <i>et al.</i> (2011)	Non-Ashkenazi Jewish; <i>BRCA1/2</i>	95 (<i>BRCA1</i> : 62; <i>BRCA2</i> : 33)	183	OS (months): <i>BRCA</i> mutation carriers, 101.7; sporadic mutation carriers, 54.3 PFS (months): <i>BRCA</i> mutation carriers, 27.9; sporadic mutation carriers, 17.9	OS: p < 0.0001 PFS: p < 0.0003	[50]
Ragupathy <i>et al.</i> (2011)	Retrospective analysis; <i>BRCA1/2</i>	12 (<i>BRCA1</i> : 4; <i>BRCA2</i> : 8)	0	Response to platinum-based chemotherapy (%): 100, 50 and 50 for first-, second- and third-line, respectively 3-year survival (%): 92 OS (%): 83	–	[53]
Vencken <i>et al.</i> (2011)	Retrospective study; <i>BRCA1</i> and <i>BRCA2</i> separated	112 (<i>BRCA1</i> : 99; <i>BRCA2</i> : 13)	222	Median OS (years): <i>BRCA1</i> , 5.9; <i>BRCA2</i> , more than 10; sporadic, 2.9	p < 0.01	[36]
Gallagher <i>et al.</i> (2011)	Incidence case; stage III and IV; <i>BRCA1/2</i>	36 (<i>BRCA1</i> : 20; <i>BRCA2</i> : 16)	74	Median OS (months): carriers, not reached; noncarriers, 67.8	p = 0.002	[37]
Yang <i>et al.</i> (2011)	Observational study; <i>BRCA1/2</i> mutation and <i>BRCA1</i> methylation	Mutations: 62 (<i>BRCA1</i> : 35; <i>BRCA2</i> : 27; methylation: 33)	219	5-year survival (%): <i>BRCA1</i> , 44; <i>BRCA2</i> , 61; wild-type, 25	<i>BRCA2</i> vs wild-type: p = 0.003	[6]
Hyman <i>et al.</i> (2011)	Retrospective study; <i>BRCA1</i> and <i>BRCA2</i> separated	47 (<i>BRCA1</i> : 30; <i>BRCA2</i> : 17)	143	3-year survival (%): <i>BRCA1</i> , 90.7; <i>BRCA2</i> , 100; wild-type, 69.4	<i>BRCA2</i> vs wild-type: p = 0.007	[7]
Bolton <i>et al.</i> (2012)	Observational study; <i>BRCA1/2</i> mutation	3879 (<i>BRCA1</i> : 909; <i>BRCA2</i> : 304)	2666	5-year survival (%): <i>BRCA1</i> , 44; <i>BRCA2</i> , 52; wild-type, 36	<i>BRCA1</i> vs noncarriers: p < 0.01; <i>BRCA2</i> vs noncarriers: p < 0.01; <i>BRCA1</i> vs <i>BRCA2</i> : p = 0.003	[8]
Liu <i>et al.</i> (2012)	Retrospective study	197 (<i>BRCA1</i> : 148; <i>BRCA2</i> : 49)	0	5-year survival (%): <i>BRCA1</i> , 61; <i>BRCA2</i> , 75	Advanced-stage patients: <i>BRCA1</i> , p = 0.17; <i>BRCA2</i> , p = 0.08	[9]
Dann <i>et al.</i> (2012)	Retrospective study	15 (<i>BRCA1</i> : 12; <i>BRCA2</i> : 3)	38	Median PFS (months): <i>BRCA</i> -mutant tumor, 21; wild-type, 5	–	[57]
Reitsma <i>et al.</i> (2012)	Retrospective study	71 (<i>BRCA1</i> : 55; <i>BRCA2</i> : 16)	–	Disease-free survival (months): <i>BRCA1</i> , 65 months; <i>BRCA2</i> , 95 OS (months): <i>BRCA1</i> , 71; <i>BRCA2</i> , 116	Disease-free survival: p = 0.34 OS: p = 0.56	[10]

NA: Not available; NS: No significance; OS: Overall survival; PFS: Progression-free survival.

Table 2

Clinical trials of PARP inhibitors including ovarian cancer patients.

Study (year)	Study population	Phase	Treatment	Patients (n)	RR (%) [†]	CBR (%)	PFS or RD	Toxicity	Ref.
Fong <i>et al.</i> (2009)	Refractory solid tumors (OC, breast, colorectal, melanoma, sarcoma and others)	I	Olaparib: dose escalation and expansion at 600 mg twice daily	60 (OC: 21)	53	60	–	Grade 1 or 2	[93]
Audeh <i>et al.</i> (2010)	<i>BRCA</i> -associated recurrent advanced OC	II	Olaparib: 400 mg twice daily and 100 mg twice daily	57	400 mg dose: RECIST, 33; RECIST/GCIG, 61; 100 mg dose: RECIST, 13; RECIST/GCIG, 17	400 mg dose: 66; 100 mg dose: 42	PFS (months): olaparib 400 mg dose, 5.8; 100 mg dose, 1.9	Mainly grade 2	[94]
Fong <i>et al.</i> (2010)	<i>BRCA</i> -associated OC that progressed after platinum agent	II	Olaparib: dose escalation and expansion at 200 mg twice daily	50	RECIST/GCIG, 40	Overall: 46; platinum sensitive: 69; platinum resistant: 46; platinum refractory: 23 (p < 0.05)	RD of all responding patients (weeks): 28	Mainly grade 2	[95]
Gelmon <i>et al.</i> (2011)	Advanced high-grade serous undifferentiated OC; triple-negative breast cancer	II	Olaparib: 400 mg twice daily	91 (OC: 65)	Total: 29; <i>BRCA</i> /2 mutations: 41; non- <i>BRCA</i> : 24	Total: 67; <i>BRCA</i> /2 mutations: 76; non- <i>BRCA</i> : 63	PFS (days): total, 219; <i>BRCA</i> /2 mutations, 221; non- <i>BRCA</i> , 192	36% grade 3	[96]
Kaye <i>et al.</i> (2012)	Recurred within 12 months of prior platinum treatment; <i>BRCA</i> /2-mutated OC	II	Olaparib: 400 mg or 200 mg twice daily, or PLD 50 mg/m ² every 28 days	97	Olaparib 400 mg: RECIST, 31; RECIST/GCIG, 59 200 mg: RECIST, 25; RECIST/GCIG, 38 PLD: RECIST, 18; RECIST/GCIG, 39	Olaparib 400 mg: 59 200 mg: 47 PLD: 52	PFS (months): olaparib 400 mg, 8.8; 200 mg, 6.5; PLD 50 mg/m ² , 7.1	Generally grade 2	[97]
Ledermann <i>et al.</i> (2012)	Platinum-sensitive, relapsed, high-grade serous OC	II	Olaparib 400 mg twice daily or placebo	265	Olaparib 12; Placebo 4	Olaparib: 53; placebo: 25	PFS (months): olaparib, 8.4; placebo, 4.8	Most grade 1 or 2	[98]

[†]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).