Association Between BRCA1 and BRCA2 Mutations and Survival in Women With Invasive Epithelial Ovarian Cancer

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recent article found a more favorable outcome for BRCA2 mutation carriers, with no significant difference in outcome for BRCA1 mutation carriers compared with noncarriers. However, some studies have demonstrated a more favorable prognosis for BRCA1 and BRCA2 carriers compared with noncarriers, whereas other studies have reported no significant difference. Several factors may account for these divergent results. Most studies contained less than 50 cases and all contained less than 250 carriers, resulting in imprecise survival estimates. Small sample sizes have also resulted in the grouping of BRCA1 and BRCA2 carriers together for analysis, despite potential prognostic differences. In addition, adjustment for prognostic factors known to differ by carrier status has varied among studies. In addition, few studies used appropriate statistical methods to account for the potential bias resulting from the inclusion of prevalent cases. The mechanism driving the association between BRCA1/2 mutations and survival is not known but some retrospective studies suggested that the survival advantage of carriers could be mediated through improved response to platinum-based agents. This is consistent with in vitro studies showing that BRCA1 and BRCA2 deficient cells are hypersensitive to drugs, which induce double-strand DNA breaks such as platinum-based agents.

The goal of our study was to collate the data from multiple EOC case series with data on BRCA1 and BRCA2 mutation status to provide definitive evidence of the relative effect of germline BRCA1 and BRCA2 mutations on prognosis. The results could provide insight into the biology of BRCA1/2 mutations, improve clinical management of mutation carriers, and have implications for clinical trial design, particularly for agents targeting BRCA1/2 dysfunction, such as poly (ADP-ribose) polymerase inhibitors.

**METHODS**

**Study Design**

Study participants were women with confirmed invasive EOC, both with and without pathogenic mutations in BRCA1 and BRCA2. Participants were drawn from 26 studies (10 from the United States, 6 from Europe, 2 from Israel, 1 from Hong Kong, 1 from Canada, 1 from Australia, and 5 from the United Kingdom). Participants were recruited and enrolled in clinical research protocols between 1987 and 2010 that were approved by local institutional review boards. Written consent was obtained from all living patients. Most participating studies were affiliated with either the Consortium of Investigators of Modifiers of BRCA1/2 or the Ovarian Cancer Association Consortium. Investigators submitted data on patient demographics, tumor pathology, vital status, and treatment to the coordinating group in Cambridge, England. In some studies, EOC cases were recruited based on a strong family history of ovarian, breast cancer (family-based), or both, while other cases used population-based sampling or enrolled a consecutive series of cases treated at a single or multiple institutions. In all studies, BRCA1/2 carriers and noncarriers were enrolled into the study using the same criteria.

Mutations were considered pathogenic if they met criteria defined by the Breast Cancer Information Core and were grouped into categories based on their predicted functional effect. Women with variants of unknown significance in BRCA1 or BRCA2 were excluded. Class I mutations are the most frequent and represent loss-of-function mutations predicted to result in reduced transcript or protein level due to mRNA nonsense-mediated RNA decay, translational retention, or absence of expression. Class II contains those mutations likely to generate stable proteins that may have some normal or dominant negative function. This includes missense substitutions and mutations generating a premature stop codon in the last exon.

All participants were screened for both BRCA1 and BRCA2 mutations with 3 exceptions. In 3 family-based studies, the Kathleen Cuningham Consortium for Research into Familial Breast Cancer, the UK Gilda Radner Familial Ovarian Cancer Registries, and the National Cancer Institute study, some EOC cases were not tested for BRCA1/2 and BRCA1/2 status was assumed to be the same as that of affected family members who had been tested. The noncarrier group from the Royal Marsden Hospital study contained some untested EOC cases but who reported no family history of breast or ovarian cancer and were therefore considered unlikely to harbor mutations. In addition, in the Stanford Genetic Epidemiology of Ovarian Cancer study, only BRCA1 mutation testing was performed. A variety of methods were used to perform mutation testing (eTable 1, available at http://www.jama.com).

Data on tumor pathology, vital status, and treatment were obtained through a combination of medical records, local cancer registries, and death certificates. Infrequently, vital status was determined through direct contact with a physician or family member of the patient. In a subset of studies, information regarding residual disease following primary surgery was available from medical records. Optimal debulking was defined as residual disease of 1 cm or less and suboptimal debulking as residual disease of more than 1 cm.

**BRCA1/2 status** may modify response to platinum-based chemotherapy, which became standard of care in most countries around 1990. Among the 36% of patients with chemotherapy data, 95% of cases diagnosed after 1990 were reported to have received a platinum-based agent. We therefore excluded women diagnosed before 1990 if chemotherapy regime was unknown, and those known not to have received platinum-based chemotherapy.
Statistical Analysis
The primary end point was overall survival up to 5 years following EOC diagnosis. We chose this end point to minimize the influence of non-EOC–related deaths. Time-to-event (death or censoring) was calculated from the date of diagnosis. However, cases were recruited at variable times after diagnosis and so time under observation was calculated from date of recruitment (left truncation) in order to prevent the bias that could result from the inclusion of prevalent cases. Effect estimates from left-truncated data are considered to be unbiased if the event time and delayed entry time are independent, given the covariates.24

Differences in tumor stage, grade, histology, and age at diagnosis between BRCA1, BRCA2, and noncarriers were tested using logistic regression models to estimate hazard ratios (HR) and 95% CIs. All models were adjusted for year of EOC diagnosis (<1990, 1990-1995, 1996-2000, and 2000-2010) and stratified by study site. In stratified survival analyses, strata with small numbers of deaths can lead to unreliable estimates. For this reason, 4 studies with less than 30 cases were placed in the same strata as other studies sharing similar study designs and baseline survival rates.

We performed analyses with and without adjustment for stage, grade, histology, and age at diagnosis. The Cox proportional hazards assumption was tested for each covariate analytically using Schoenfeld residuals. Age at diagnosis and histology violated the proportional hazards assumption; therefore, additional covariates were included to allow for time-dependent effects.

Differences in the HR estimates for the survival effect of BRCA1 and BRCA2 by different clinical factors were tested using Cochrane Q-test (Q-test) for heterogeneity. To assess the effect of possible competing mortality from breast cancer on effect estimates, we compared analyses

Table 1. Characteristics of 3879 Study Participants by BRCA1/2 Germline Mutation Status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BRCA1 (n = 909)</th>
<th>BRCA2 (n = 304)</th>
<th>BRCA1 vs Noncarriers</th>
<th>BRCA2 vs Noncarriers</th>
<th>BRCA1 vs BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis to study entry, median (IQR), mo</td>
<td>0.5 (0-13) 2 (0-18) 2 (0-17)</td>
<td>38 (18-63) 35 (18-66) 39 (21-75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year of EOC diagnosis, median (range)</td>
<td>1249 (46.8)</td>
<td>409 (45.0)</td>
<td>108 (35.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths within 5 y of EOC diagnosis, No. (%)</td>
<td>1769 (67)</td>
<td>617 (74)</td>
<td>213 (80)</td>
<td>.001</td>
<td>.002</td>
</tr>
<tr>
<td>Histology, No. (%)</td>
<td>214 (8)</td>
<td>7 (1)</td>
<td>0 (0)</td>
<td>&lt;.001</td>
<td>.02</td>
</tr>
<tr>
<td>Serous</td>
<td>324 (12)</td>
<td>105 (13)</td>
<td>24 (9)</td>
<td>.85</td>
<td>.39</td>
</tr>
<tr>
<td>Mucinous</td>
<td>119 (4)</td>
<td>15 (2)</td>
<td>6 (2)</td>
<td>.13</td>
<td>.14</td>
</tr>
<tr>
<td>Clear cell</td>
<td>45 (2)</td>
<td>10 (1)</td>
<td>5 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoma, not otherwise specified</td>
<td>187 (7)</td>
<td>80 (10)</td>
<td>18 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missinga</td>
<td>8 (0.3)</td>
<td>75 (8)</td>
<td>38 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade, No. (%)</td>
<td>298 (13)</td>
<td>18 (3)</td>
<td>8 (4)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Well differentiated</td>
<td>543 (24)</td>
<td>129 (19)</td>
<td>28 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>1382 (62)</td>
<td>533 (78)</td>
<td>184 (84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>443 (17)</td>
<td>229 (25)</td>
<td>84 (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage (FIGO), No. (%)</td>
<td>501 (21.0)</td>
<td>84 (12.3)</td>
<td>22 (9.5)</td>
<td>.03</td>
<td>.007</td>
</tr>
<tr>
<td>I</td>
<td>213 (8.9)</td>
<td>71 (10.4)</td>
<td>13 (5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1286 (54.0)</td>
<td>436 (64.0)</td>
<td>170 (73.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>382 (16.0)</td>
<td>90 (13.2)</td>
<td>27 (11.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missinga</td>
<td>284 (11)</td>
<td>228 (25)</td>
<td>72 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at EOC diagnosis, mean (SD), y</td>
<td>58 (12)</td>
<td>52 (10)</td>
<td>60 (11)</td>
<td>&lt;.001</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; IQR, Interquartile range.

The proportion of tumors in various categories of a variable was calculated among study participants with nonmissing data for that variable.
restricted to women with and without a diagnosis of breast cancer before or in the 5 years following EOC diagnosis. We tested for heterogeneity by study in the HR estimates through the inclusion of an interaction term between study and BRCA1/2 mutation status.

Some participants were missing data for stage (19%), grade (22%), and histology (5%). To decrease potential bias and loss of power due to missingness, we performed multiple imputation for these 3 variables (eMethods). All analyses, except for comparison of pathological characteristics and Kaplan-Meier estimation of survival, were performed on the imputed data. The results using nonimputed data were similar to those presented herein using imputed data. For comparison, the main results using nonimputed data are shown in eTable 2. All analyses were performed using STATA/SE version 11 (StataCorp). Statistical significance was defined as $P < .05$. Statistical tests were 2 sided.

**RESULTS**

Data were available for 3879 EOC cases (909 BRCA1 and 304 BRCA2 mutation carriers and 2666 noncarriers). The median number of months from ascertainment to diagnosis for participants was 1 month (interquartile range, 0-15 months). Women were under active follow-up for a median time of 38 months (interquartile range, 18-77 months). The proportion of cases with censored survival time (not followed up to death or 5 years after diagnosis) was 15%. After controlling for study site, there was no significant difference in the proportion of cases with censored survival time among BRCA1 ($P = .22$) or BRCA2 ($P = .41$) carriers compared with noncarriers. The median year of EOC diagnosis was 1998 (range, 1981-2010). During the 5 years following EOC diagnosis, 1766 deaths occurred.

Several significant differences in the clinical features of BRCA1 and BRCA2 carriers compared with noncarriers were found (Table 1). Tumors in BRCA1 and BRCA2 carriers were more likely to be of serous histology and less likely to be of mucinous histology than tumors in noncarriers. BRCA1 and BRCA2 carriers were more likely to have stage III/IV tumors and poorly differentiated or undifferentiated tumors than noncarriers. Compared with BRCA1 carriers, BRCA2 carriers were more likely to have stage III/IV tumors. Although BRCA1 carriers were younger at diagnosis than noncarriers, BRCA2 carriers were slightly older.

The 5-year overall survival was 36% (95% CI, 34%-38%) for noncarriers, 44% (95% CI, 40%-48%) for BRCA1 carriers, and 52% (95% CI, 46%-58%) for BRCA2 carriers (Figure and eFigure). In a Cox proportional hazards regression model only adjusted for study site and year of diagnosis, BRCA1 carriers showed a more favorable survival than noncarriers did ($HR, 0.78; 95\% CI, 0.68-0.89; P < .001$) (Table 2). This improved slightly after additional adjustment for stage, grade, histology, and age at diagnosis ($HR, 0.73; 95\% CI, 0.64-0.84; P < .001$). BRCA2 carriers showed a greater survival advantage compared with noncarriers ($HR, 0.61; 95\% CI, 0.50-0.76; P < .001$), particularly after adjusting for other prognostic factors ($HR, 0.49; 95\% CI, 0.39-0.61; P < .001$). The BRCA1 HR estimates were significantly different from

Table 2. Cox Proportional Hazards Regression Models for Effect of BRCA Status on All-Cause Mortality Using Imputed Dataa

<table>
<thead>
<tr>
<th>Comparison Groups</th>
<th>Total No. (No. of Deaths)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Total No. (No. of Deaths)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carriers</td>
<td>Noncarriers</td>
<td>Carriers</td>
<td>Noncarriers</td>
<td>Carriers</td>
<td>Noncarriers</td>
</tr>
<tr>
<td>BRCA1 vs noncarriers</td>
<td>909 (409)</td>
<td>2666 (1249)</td>
<td>0.78 (0.68-0.89)</td>
<td>&lt;.001</td>
<td>909 (409)</td>
<td>2666 (1249)</td>
</tr>
<tr>
<td>BRCA2 vs noncarriers</td>
<td>304 (108)</td>
<td>2666 (1249)</td>
<td>0.61 (0.50-0.76)</td>
<td>&lt;.001</td>
<td>304 (108)</td>
<td>2666 (1249)</td>
</tr>
</tbody>
</table>

aNoncarriers are the referent group. The unadjusted model was stratified by study site, adjusted for year of ovarian cancer diagnosis. The adjusted model was stratified by study site and tumor stage, adjusted for year of ovarian cancer diagnosis, grade, histology, and age at ovarian cancer diagnosis.
the BRCA2 HR estimates in unadjusted (P for heterogeneity ≤ .05) and adjusted models (P for heterogeneity ≤ .003).

We studied the effect of BRCA1/2 mutation status on all-cause mortality after stratifying patients by other clinical features (Table 3). In analyses stratified by grade and adjusted for other prognostic factors, the HRs were more than 1 for both BRCA1 vs noncarriers and BRCA2 vs noncarriers in low-grade cases but less than 1 in high-grade cases. No significant differences were found in the HRs for BRCA1 vs noncarriers or BRCA2 vs noncarriers when stratified according to stage, histology, or history of breast cancer before or during the study period. The survival advantage of BRCA1 and BRCA2 carriers compared with noncarriers was found to be attenuated in women with ovarian cancer selected based on family history of ovarian, breast cancer, or both (Table 4). However, the difference in survival between BRCA1 and BRCA2 carriers did not depend on ascertainment (for BRCA2 vs BRCA1: HR, 0.71; 95% CI, 0.52-0.98; and for familial and unselected cases: HR, 0.64; 95% CI, 0.45-0.91; P for heterogeneity = .65). There was no evidence of study-specific heterogeneity in the HR estimates for mutation status among family-based studies (BRCA1, P = .22; and BRCA2, P = .92) or unselected studies (BRCA1, P = .73; and BRCA2, P = .57).

The proportion of mutation carriers with the Ashkenazi Jewish founder mutations 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2 was 26%. We did not find any significant differences in the adjusted HRs for BRCA1 vs noncarriers among carriers by mutation type (class I vs class II mutation, P for heterogeneity = .10). However, the survival advantage of BRCA1 mutation carriers with class I mutations differed depending on mutation location; worse survival was associated with mutations on the 3′ end compared with the 3′ end of BRCA1 (P for heterogeneity = .03) (eMethods and eTable 3).

A subset of 1129 patients had information on residual disease following primary surgery. We assessed the effect of lack of adjustment for these variables in our main analysis by comparing results with and without adjustment for residual disease in this subgroup. Optimal debulking occurred in 85% of noncarriers, 87% of BRCA1 carriers, and 91% of BRCA2 carriers. After adjusting for study site and year of diagnosis, there was no significant difference in the likelihood of optimal debulking between noncarriers and BRCA1 (P = .74) or BRCA2 (P = .46) carriers. Adjustment for residual disease did not substantially change the HR estimates for the relative survival of either BRCA1 or BRCA2 carriers compared with noncarriers (eTable 4).

**COMMENT**

Our data demonstrate an improved survival in patients with EOC with germline BRCA1 and BRCA2 mutations relative to noncarriers, with BRCA2 carriers having the best prognosis. BRCA1 carriers presented with EOC at an earlier age than BRCA2 carriers, which is consistent with the age-specific penetrances for BRCA1 compared with...
Table 4. Cox Proportional Hazards Regression for Effect of BRCA Status on All-Cause Mortality by Study Typea

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Total No. (No. of Deaths)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Main Effect</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 vs noncarriers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected for family history</td>
<td>556 (254)</td>
<td>283 (126)</td>
<td>1.03 (0.79-1.35)</td>
<td>.83</td>
<td>.002</td>
</tr>
<tr>
<td>Unselected for family history</td>
<td>353 (155)</td>
<td>2383 (1123)</td>
<td>0.62 (0.52-0.75)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>BRCA2 vs noncarriers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected for family history</td>
<td>179 (63)</td>
<td>283 (126)</td>
<td>0.71 (0.49-1.03)</td>
<td>.07</td>
<td>.04</td>
</tr>
<tr>
<td>Unselected for family history</td>
<td>125 (45)</td>
<td>2383 (1123)</td>
<td>0.43 (0.32-0.58)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

aNoncarriers are the referent group. Models were stratified by study site and tumor stage, adjusted for year of ovarian cancer diagnosis, grade, histology, and age at ovarian cancer diagnosis.

BRCA2 carriers. The pathological characteristics of BRCA1- and BRCA2-related tumors are similar to each other, but differ from those of tumors in noncarriers. This contrasts with breast cancer, in which substantial differences between BRCA1- and BRCA2-associated disease are present.25,26 The differences in grade, stage, and histology by mutation status are consistent with previously reported data.2,3,7 The effect of BRCA1 and BRCA2 mutations on survival appeared to be similar among patients with both localized and advanced stage tumors and among both serous and nonserous tumors. The lack of a survival advantage for BRCA1 and BRCA2 mutation carriers with low-grade disease suggests that disruptions of the BRCA1/2 pathways may not be as important in the etiology of these tumors, supporting evidence of etiologic heterogeneity between high-grade and low-grade serous carcinoma from other studies.20,28 However, these results were based on small numbers and require confirmation in larger studies.

Our findings confirm the findings of recent analysis of data from The Cancer Genome Atlas (TCGA) project, which reported an improved prognosis for BRCA2 carriers.8 In contrast, we also found an improved prognosis for BRCA1 carriers, whereas the TCGA data suggested no difference between BRCA1 carriers and noncarriers. The most likely reason for this difference is the lack of power to detect a moderate difference in survival in the TCGA data. Indeed, the HR for BRCA1 carriers compared with noncarriers reported by Yang et al8 (multivariate-adjusted HR, 0.76) was very similar to that from our analysis (multivariate-adjusted HR, 0.73).

We found a smaller survival effect of BRCA1 and BRCA2 in the subset of studies in which participants were selected based on a strong family history of ovarian, breast cancer, or both. This could have been due to misclassification of noncarriers in these studies. The sensitivity of mutation testing is likely to be similar across all studies, but the proportion of false-negative carriers will be higher in familial cases. Alternatively, cases from BRCA1/2 wild-type families could carry germline mutations in genes in the same pathway as BRCA1/2 (such as RAD51C30) or in different pathways that produce similar clinical features.

The improved survival of BRCA1/2 carriers relative to noncarriers, and the survival advantage of BRCA2 carriers relative to BRCA1 carriers, could be related to intrinsic biological differences, their response to therapeutic agents, or both. In addition to differences in stage, grade, and histology, BRCA1/2 carriers could have differences in other aspects of tumor biology that were not measured in our study. For example, BRCA1 and BRCA2 carriers have been recently shown to differ from each other and from sporadic EOC in the incidence of visceral metastasis.31 The most notable advantage as well as disadvantage of our study is the fact that it is based on a heterogeneous population; these data were taken from studies containing different ethnic groups, using different mutation screening methodologies and case ascertainment. By including a wide variety of studies, we were able to generate a large enough sample size to adequately address the issue of heterogeneity of the survival effect between BRCA1 and BRCA2 carriers. However, differences in study design and population may limit the specificity of the conclusions drawn. Additionally, varying levels of misclassification of BRCA status and other variables of interest may have led to some bias of our estimates toward the null. However, the absence of heterogeneity in study-specific effects (after accounting for selection on family history) suggests that these results are generalizable to many populations. Furthermore, the magnitude of the differences we observed between BRCA1 and BRCA2 carriers and noncarriers, despite the presence of heterogeneity, provide further testament to their robustness. Even at the lower bounds of our effect estimates, BRCA2 carriers would be predicted to show a 64% decreased risk of death in the 5 years following diagnosis compared with noncarriers.

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genetic silencing of BRCA1 and BRCA2 show similar effects on prognosis to germline mutations. It has been estimated that approximately 30% of EOC and more than 50% of high-grade se-
rous EOC could show dysfunction of BRCA1 or BRCA2 through genetic or epigenetic events.32,33 There is evidence that EOC cases with somatic BRCA1/2 mutations show a survival advan-
tage over noncarriers,31 but data from TCGA and others suggest that sil-
encing of BRCA1 through promoter methylation does not result in an im-
proved overall survival.19,34 Larger studies that include comprehensive ge-
nomic screening of BRCA1 and BRCA2 in primary EOCs will be needed to
determine if alterations at the somatic and epigenetic level have similar clinical ef-
gs to germline mutations.

Our study results have potentially important implications for the clinical manage-
ment of patients with EOC. Most immediately, our findings can be used by health care professionals for pa-
tient counseling regarding expected sur-
vival. BRCA1 and BRCA2 carriers with EOC respond better than noncarriers to platinum-based chemotherapies and have improved survival despite the fact that the disease is generally diagnosed at a later stage and higher grade. If pa-
tients could be stratified based on their BRCA status, their treatment could be
tailored to reflect this, with noncarri-
ers targeted for more aggressive treat-
ment. Our data provide further sup-
port that there may be different func-
tional mechanisms involved in the epi-
tiology of different subtypes of EOCs and, therefore, different therapeutic tar-
gets based on germline and somatic ge-
netic variation. For example, the func-
tional characterization of BRCA1 and 
BRCA2 led to the development of a 
noval therapy in BRCA1/2 carriers based 
on inhibition of the poly (ADP-
ribose) polymerase DNA repair path-
way, creating a synthetic lethal phen-
type. Recently, phase 1 and 2 trials have 
shown anti-tumor activity of the poly 
(ADP-ribose) polymerase inhibitor Olparib in BRCA1/2 mutation carriers with EOC.15,36,37 These trials were not 
large enough to detect differences in re-
response to Olparib in BRCA1 vs BRCA2 
carriers and it is not known whether they will show similar levels of re-
sponse. Epithelial ovarian cancer clin-
cial trials should be stratified by BRCA 
status, not only to more appropriately 
target therapy but also to avoid the po-
tential bias introduced by unequal num-
bers of carriers in treatment groups or 
within study cohorts. Furthermore, 
given the important prognostic infor-
mation provided by BRCA1 and BRCA2 
status and the potential for personal-
ized treatment in carriers, the routine 
testing of women presenting with high-
grade serous EOC may now be war-
ranted.

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