Germline Mutation in BRCA1 or BRCA2 and Ten-Year Survival for Women Diagnosed with Epithelial Ovarian Cancer

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Abstract

Purpose: To analyze the effect of germline mutations in BRCA1 and BRCA2 on mortality in patients with ovarian cancer up to 10 years after diagnosis.

Experimental Design: We used unpublished survival time data for 2,242 patients from two case-control studies and extended survival time data for 4,314 patients from previously reported studies. All participants had been screened for deleterious germline mutations in BRCA1 and BRCA2. Survival time was analyzed for the combined data using Cox proportional hazard models with BRCA1 and BRCA2 as time-varying covariates. Competing risks were analyzed using Fine and Gray model.

Results: The combined 10-year overall survival rate was 30% (95% confidence interval [CI], 28%–31%) for non-carriers, 25% (95% CI, 22%–28%) for BRCA1 carriers, and 35% (95% CI, 30%–41%) for BRCA2 carriers. The HR for BRCA1 was 0.53 at time zero and increased over time becoming greater than one at 4.8 years. For BRCA2, the HR was 0.42 at time zero and increased over time (predicted to become greater than 1 at 10.5 years). The results were similar when restricted to 3,202 patients with high-grade serous tumors and to ovarian cancer-specific mortality.

Conclusions: BRCA1/2 mutations are associated with better short-term survival, but this advantage decreases over time and in BRCA1 carriers is eventually reversed. This may have important implications for therapy of both primary and relapsed disease and for analysis of long-term survival in clinical trials of new agents, particularly those that are effective in BRCA1/2 mutation carriers. Clin Cancer Res; 21(3); 652–7. ©2014 AACR.
Translational Relevance

Previous studies show consistent association between *BRCA1* or *BRCA2* germline mutations and improved 5-year survival rate in ovarian cancer. However, recent studies suggested that this survival advantage did not persist after 5 years. This is a large and comprehensive study, which has investigated the role of *BRCA1*/*2* status on long-term survival of patients with ovarian cancer. We confirmed the HRs for death associated with *BRCA1*/*2* germline mutations is lower than 1.0 at diagnosis, however, it increases over time. These findings were independent of other clinical prognostic factors, including histologic subtype. These results are of fundamental importance for counseling patients about their prognosis and in interpreting results of clinical trials involving *BRCA1*/*2* carriers.

Introduction

Epithelial ovarian cancer (EOC) is the most fatal gynecologic malignancy, resulting in about 140,000 deaths worldwide per year (1). EOC is a heterogeneous disease with multiple histopathologic subtypes that is usually treated using a combination of cytoreductive surgery and platinum-based chemotherapy (2). However, women often present with advanced-stage disease and the prognosis is generally poor. Clinical management of the disease might be improved by a more personalized approach to treatment based on likely treatment response.

Germline mutations in *BRCA1* and *BRCA2* are associated with a high risk of EOC, predominantly of the high-grade serous subtype (HGSOC). Mutations in these genes account for 5% to 15% of all cases of EOC (3–6). There is substantial evidence that patients with HGSOC with *BRCA1* or *BRCA2* germline mutations have better short-term survival than noncarriers (6, 7), but recent studies suggested that this survival advantage did not persist after 5 years (8, 9).

We have recently sequenced *BRCA1* and *BRCA2* in 2 large EOC case series to estimate the contribution of these genes to EOC in the general population (10). Long-term outcome data were available for these cases. In the study reported by Bolton and colleagues (7), cause-specific mortality data were not available, those analyses had been restricted to the first 5 years after diagnosis when it was assumed that most deaths would be due to ovarian cancer. Alsop and colleagues considered disease-specific mortality with 5.3 years of median follow-up (6). However, long-term all-cause mortality data are also available for both studies. The aim of the current analysis was to determine the effect of *BRCA1* and *BRCA2* mutation status on long-term survival in women with EOC.

Patients and Methods

Patients

We used survival time data for 6,556 EOC cases from 27 studies. Two case–control studies, the population-based SEARCH study (*n* = 1,419) and the clinic-based Mayo clinic study (*n* = 823), were screened for deleterious mutations in *BRCA1* and *BRCA2* using multiplexed 48.48 Fluidigm access arrays for targeted sequence library preparation followed by sequencing on an Illumina HiScan sequencer (10). In addition, we used extended survival time data for 3,325 cases previously reported by Bolton and colleagues (7) and for 989 cases from the Australian Ovarian Cancer Study (AOCs; ref. 6). Some cases from SEARCH and the Mayo Clinic study were included in the Bolton and colleagues analysis. These duplicates excluded for this analysis. The number of individuals by *BRCA* status and references describing each study design is given in Supplementary Table S1.

We considered protein-truncating insertion/deletion variants, consensus splice-site variants, and missense variants with reported damaging effect on protein function to be deleterious. For the purpose of our analysis, *BRCA1* and *BRCA2* mutation status were recorded simply as mutation-positive or -negative, with no distinction between different mutation types by location or functional effect.

Statistical analysis

We used standard Cox regression with a primary endpoint of death from all causes for the survival analysis. Survival time was from the date of diagnosis until the date of death. For the 3,075 cases from 12 studies with cause of death available, we used Fine and Gray competing risks regressions to predict 10-year probability of death from ovarian cancer subdistribution HRs (SHR) for ovarian cancer. The Fine and Gray model is a multivariable time-to-event model, which accounts for the fact that individuals can only have one competing event. The model also accounts for censoring among those who do not have an event during follow-up (11). Participants were recruited at a variable time after diagnosis, which was allowed for in the analyses by treating time at risk from the date of recruitment (left truncation). This
results in an unbiased estimate of the HR provided the proportional hazard assumption is valid (12). In preliminary analyses, tests of the proportional hazards assumption using Schoenfeld residuals showed that the assumption was seriously violated for both BRCA1 and BRCA2, which would be expected if the HR changes over time as suggested by McLaughlin and colleagues (8). We therefore modeled the HRs for BRCA1 and BRCA2 by treating them as time-varying covariates such that the log HR varies linearly with time. The HR at time $t$ is then given by

$$HR(t) = \exp(\beta x + \delta t)$$

where $x$ is the predictor variable (BRCA1 or BRCA2 status), $\beta$ is the $\beta$ coefficient, and $\delta$ is the time-varying coefficient. Under the proportional hazards assumption, $\delta$ equals zero.

All analyses were stratified by year of diagnosis (before 1990; 1990–1995; 1996–1999; 2000 and after) and study. The covariates in multivariable models were age at diagnosis (measured in years), clinical stage [localized (IA, IB), regional (IC and II), and distant (III/IV)], histopathologic grade (low = grade I/well-differentiated or high = grade II/grade III/poorly differentiated), and morphologic subtype (serous or nonserous).

There was missing data for a substantial proportion of cases for stage (12%) and grade (17%). Multiple imputation has been shown to be the method for the handling of missing data that is least likely to be biased across a wide range of assumptions. We therefore imputed 20 complete datasets for each study using multivariate imputation by chained equations (13). The imputation model included BRCA1 and BRCA2 mutation status, year of diagnosis, age at diagnosis, morphologic subtype, outcome, time of follow-up, and study. Each imputed data set was analyzed separately and the parameter estimates were combined according to “Rubin’s rules” (14).

Differences in time elapsed from diagnosis to entry in study, follow-up time, year of diagnosis, proportion of deaths from ovarian cancer, tumor histology, grade, stage, and age at diagnosis were tested using $t$ and $\chi^2$ tests.

Statistical analysis was conducted using STATA/SE version 13 (StataCorp).

**Results**

The characteristics of the patients are shown in Table 1. In the SEARCH case series, there were 41 BRCA1 mutation carriers, 59 BRCA2 mutation carriers, and 1,319 cases without a mutation in either gene. In the Mayo Clinic case series, there were 38 BRCA1 mutation carriers, 27 BRCA2 mutation carriers, and 758 cases without a mutation in either gene. In the AOCs case series, there were 89 BRCA1 mutation carriers, 54 BRCA2 mutation carriers, and 846 cases without a mutation in either gene (6). There were 890 BRCA1 carriers, 298 BRCA2 carriers, and 2,137 noncarriers from the study previously published by Bolton and colleagues (7).

The crude 5-year overall survival rate was 42% (95% confidence interval (CI), 41%–44%) for noncarriers, 45% (95% CI, 41%–48%) for BRCA1 carriers, and 54% (95% CI, 48%–59%) for BRCA2 carriers. The 10-year overall survival rate was 30% (95% CI, 28%–31%) for noncarriers, 25% (95% CI, 22%–28%) for BRCA1 carriers, and 35% (95% CI, 30%–41%) for BRCA2 carriers (Fig. 1). On the basis of the multivariable analysis of the imputed data, the HR for BRCA1 at time zero ($t_0$) was 0.53 (0.43–0.66, $P < 0.001$) which increased significantly with time (coefficient for time-by-covariate interaction = 1.14; 95% CI, 1.08–1.20, $P < 0.001$; Table 2). The HR for BRCA1 positivity at time $t$ is thus given by the formula

$$HR(t) = \exp(-0.63 + 0.13t)$$

This means that the HR for BRCA1 is less than one from $t = 0$ to $t = 4.8$ years and is greater than one after $t = 4.8$ years.

The multivariable-adjusted HR for BRCA2 at $t_0$ was 0.42 (0.30–0.59, $P < 0.001$) and this increased significantly with time (coefficient for time-by-covariate interaction = 1.09; 95% CI, 1.01–1.19, $P = 0.048$; Table 2). The HR for BRCA2 positivity at time $t$ is thus given by the formula

$$HR(t) = \exp(-0.87 + 0.08t)$$

This means that the HR for BRCA2 is less than one from $t = 0$ to $t = 10.5$ years and is greater than one after $t = 10.5$ years.

### Table 1. Characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Noncarriers ($n = 5,060$)</th>
<th>BRCA1 mutation ($n = 1,058$)</th>
<th>BRCA2 mutation ($n = 438$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>3,052 (65)</td>
<td>553 (73)</td>
<td>254 (77)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>271 (6)</td>
<td>5 (0.7)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>587 (12)</td>
<td>91 (12)</td>
<td>27 (8)</td>
</tr>
<tr>
<td>Clear cell</td>
<td>306 (6)</td>
<td>14 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Mixed cell</td>
<td>150 (3)</td>
<td>8 (1)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>345 (7)</td>
<td>82 (10)</td>
<td>32 (90)</td>
</tr>
<tr>
<td>Unknown</td>
<td>349 (–)</td>
<td>305 (–)</td>
<td>110 (–)</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>491 (11)</td>
<td>19 (2)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>High</td>
<td>3,778 (88)</td>
<td>801 (98)</td>
<td>331 (96)</td>
</tr>
<tr>
<td>Unknown</td>
<td>791 (–)</td>
<td>238 (–)</td>
<td>94 (–)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>967 (21)</td>
<td>97 (12)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>Regional</td>
<td>818 (18)</td>
<td>101 (12)</td>
<td>55 (15)</td>
</tr>
<tr>
<td>Distant</td>
<td>2,808 (61)</td>
<td>622 (76)</td>
<td>274 (76)</td>
</tr>
<tr>
<td>Unknown</td>
<td>467 (–)</td>
<td>238 (–)</td>
<td>80 (–)</td>
</tr>
<tr>
<td>Age at EOC diagnosis, mean (SD), y</td>
<td>59 (11)</td>
<td>52 (10)</td>
<td>59 (10)</td>
</tr>
</tbody>
</table>

NOTE: The cases with unknown histology, grade, and stage were not included in the calculation of proportions.
The large sample size of the current study, including previously unpublished data on 165 *BRCA1* or *BRCA2* mutation carriers and 2,077 noncarriers in addition to data on 4,714 cases that were previously published as part of an analysis of short-term survival, is a major strength of the current analysis. The large sample size allowed us to analyze data from the subset of patients with high-grade serous cancer, thereby excluding low-grade cases that can have more indolent disease and are less likely to carry mutations in *BRCA1* or *BRCA2*. Hence, it is unlikely that contamination by low-grade tumors, which may have been simply cured surgically, contributed to the favorable long-term survival of noncarriers.

We have no information on recurrence for a large number of the cases and cause of death was not available for 13 studies (3,481 cases); consequently, primary analyses were based on all-cause mortality. The proportion of deaths from causes other than ovarian cancer was small in the studies with data on cause-specific mortality, as has been reported in other ovarian cancer case series (18). It is likely that the majority of deaths occurring in the first 5 years after diagnosis were due to ovarian cancer and so any misclassification will have been minimal. The comparison of all-cause mortality by *BRCA1* and *BRCA2* carrier status over the long term may not reflect differences in ovarian cancer specific mortality if non–ovarian cancer mortality also differs between carriers and noncarriers. This is likely to be true as carriers are also at increased risk of other cancers. However, over the longer term, competing causes of mortality become more important. We therefore performed an analysis restricting the data to those cases with information on cause-specific mortality using an analytic approach that allows for competing risks. The findings were

### Table 2. Ten years’ estimated HRs for death in patients with ovarian cancer

<table>
<thead>
<tr>
<th>Variable (reference)</th>
<th>Conventional Cox model</th>
<th>Cox model with time-varying effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.02 (1.02–1.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade (ref: low)</td>
<td>1.66 (1.40–1.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regional (ref: localized)</td>
<td>2.89 (2.41–3.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distant (ref: localized)</td>
<td>6.64 (5.58–7.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serous (ref: nonserous)</td>
<td>1.08 (0.99–1.17)</td>
<td>0.30</td>
</tr>
<tr>
<td><em>BRCA1</em> (ref: noncarriers)</td>
<td>0.83 (0.74–0.93)</td>
<td>0.002</td>
</tr>
<tr>
<td><em>BRCA2</em> (ref: noncarriers)</td>
<td>0.55 (0.47–0.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>BRCA1</em> t</td>
<td>1.19 (1.10–1.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>BRCA2</em> t</td>
<td>1.24 (1.18–1.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>_t, time-varying HR.</td>
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<td></td>
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</tbody>
</table>

*Discussion*

Consistent with previously published studies (8), (15–17), we found that patients with EOC carrying *BRCA1* or *BRCA2* mutations have better short-term survival (5 years) than noncarriers. This survival advantage was lost over time, and after approximately 5 years, *BRCA1* carriers had a higher risk of dying than noncarriers. Also, consistent with the generally better short-term survival of *BRCA2* carriers compared with germline *BRCA1* mutation carriers, a survival advantage persisted longer in *BRCA2* patients and did not cross-over with noncarriers until approximately 9 years after diagnosis.

The large sample size of the current study, including previously unpublished data on 165 *BRCA1* or *BRCA2* mutation carriers and 2,077 noncarriers in addition to data on 4,714 cases that were previously published as part of an analysis of short-term survival, is a major strength of the current analysis. The large sample size allowed us to analyze data from the subset of patients with high-grade serous cancer, thereby excluding low-grade cases that can have more indolent disease and are less likely to carry mutations in *BRCA1* or *BRCA2*. Hence, it is unlikely that contamination by low-grade tumors, which may have been simply cured surgically, contributed to the favorable long-term survival of noncarriers.
broadly similar to the results for all-cause mortality suggesting that differences in non–ovarian cancer mortality do not account for the time-dependent effect for BRCA1 and BRCA2 carriers. The primary studies are heterogeneous in design and patient management is likely to have varied substantially across studies. This heterogeneity is a strength, as it suggests that our findings are robust and generalizable. However, lack of detailed data on treatment limits our ability to investigate interactions between mutation status and specific treatments. In particular, investigation of hypotheses regarding revertant mutations or intratumoral heterogeneity need detailed progression-free survival and response data. These data may be available in the future from retrospective analysis of large multicentre trials such as ICON7 and ICON8.

Exclusion of important prognostic factors from a Cox model may result in other variables behaving as time-varying covariates (19). Our findings may therefore be due to the fact that we did not include residual disease as a covariate in the prognostic models (these data were not available in our case series). However, simulations excluding other important prognostic variables, such as clinical stage, had little impact on the magnitude of the coefficients for the time-dependent effects (data not shown), suggesting that exclusion of other covariates is unlikely to be an explanation for our findings.

The reasons why BRCA1/2 carriers have only a short-term survival advantage are not clear. However, while 10 years’ survival may reflect the cure from their disease, 5-year survival would allow for a proportion of patients who are still alive with incurable disease. BRCA1 and BRCA2 are important in double-strand break DNA repair by homologous recombination (20, 21) and cell lines deficient in BRCA1 and BRCA2 function are more sensitive to platinum (22, 23). Furthermore, presence of germline and somatic homologous recombination mutations is predictive of primary platinum sensitivity in women with EOC (24). Carrier status may initially segregate those patients with platinum sensitivity from patients with high-grade serous cancer whose tumors lack homologous recombination defects, such as those with CCNE1 amplification (25), who are frequently resistant to primary therapy and have poor outcomes (26).

Intragenic reversion of germline alleles that restore BRCA1 and BRCA2 function in tumor cell lines (27) and in recurrent ovarian carcinomas (28) has been observed and it is possible that this is associated with a time-dependent loss of the survival advantage associated with germline mutation. A minority of patients with HGSC achieve long-term remissions following optimal debulking surgery and chemotherapy, where presumably adjuvant treatment is able to successfully eradicate any cancer repopulating cells remaining after surgery. Our findings may reflect differences between carriers and noncarriers in the abundance of cancer stem cells or the ability of those cells to be ablated by adjuvant treatment or host immunologic factors. Indeed, expansion of the breast luminal progenitor population is observed in BRCA1 mutation carriers (29), suggesting that partial loss of HR function can influence the stem cell kinetics. Intratumor genetic heterogeneity at the time of primary treatment may comprise an alternative mechanism for acquired platinum resistance.

Despite the advances in the understanding of the genetics and biology of ovarian cancer during the past 10 years, the clinical management of the disease remains challenging. Our findings confirm that germline genotype is an important predictor of response to treatment in both the short- and long-term and emphasizes the need to identify novel approaches to the management of the disease that target the underlying biology.

Disclosure of Potential Conflicts of Interest
A. de Fazio reports receiving speakers bureau honoraria from Roche and is a consultant/advisory board member for AstraZeneca. S. Neuhausen reports receiving royalties from the University of Utah on patents related to discoveries of BRCA1 and BRCA2. R. Nussbaum provided expert testimony for Ambry on patent infringement and Aruna on patenting the use of cell-free DNA in maternal serum to make inferences about fetus. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.C. Larson, E. Dick, P. Harrington, S.J. Ramus, S. Fereday, A. Chetrit, E. Hodgall, M. Daly, J.T. Loud, K. Moysich, S. Ellis.
Study supervision: S.K. Kjaer, R. Nussbaum, J.T. Loud.

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