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


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Access to data
Kelly Leigh Bolton had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Abstract

Context—Approximately 10 percent of women with invasive epithelial ovarian cancer (EOC) carry deleterious germline mutations in BRCA1 or BRCA2. A recent report suggested that BRCA2-related EOC was associated with an improved prognosis, but the effect of BRCA1 remains unclear.

Objective—to characterize the survival of BRCA carriers with EOC compared to non-carriers and to determine whether BRCA1 and BRCA2 carriers show similar survival patterns.

Design, Setting, and Participants—we pooled data from 26 studies on the survival of women with ovarian cancer. This included data on 1,213 EOC cases with pathogenic germline
mutations in BRCA1 (909) or BRCA2 (304) and 2,666 non-carriers recruited and followed for variable times between 1987 and 2010; the median year of diagnosis was 1998.

**Main Outcome Measures**—Five year overall mortality.

**Results**—The five-year overall survival was 36 percent (95% CI: 34–38) for non-carriers, 44 percent (95% CI: 40–48) for BRCA1 carriers and 52 percent (95% CI: 46–58) for BRCA2 carriers. After adjusting for study and year of diagnosis, BRCA1 and BRCA2 carriers showed a more favorable survival than non-carriers (BRCA1, HR=0.78; 95% CI=0.68–0.89, P=2×10^{-4}; BRCA2, HR = 0.61; 95% CI=0.50–0.76, P=6×10^{-6}). These survival differences remained after additional adjustment for stage, grade, histology and age at diagnosis (BRCA1, HR=0.73, 95% CI=0.64–0.84, P=2×10^{-5}; BRCA2, HR = 0.49, 95% CI=0.39–0.61, P=3×10^{-10}).

**Conclusions**—Among patients with invasive epithelial ovarian cancer, having a germline mutation in BRCA1 or BRCA2 was associated with improved 5-year overall survival.

**Introduction**

Germline mutations in the genes BRCA1 and BRCA2 are the strongest known genetic risk factors for both breast and epithelial ovarian cancer (EOC) and are found in 6–15 percent of women with EOC1–3. BRCA1 is involved in DNA repair, cell-cycle checkpoint control, chromatin remodeling, transcriptional regulation and mitosis and BRCA2 has an important role in homologous recombination 4. The clinical characteristics of EOCs among BRCA1/2 carriers differ from that of non-carriers. BRCA1 related disease is more likely to be of serous histology5, high grade6 and advanced stage3. Less data are available for BRCA2-related EOC due to their lower prevalence and lower EOC penetrance relative to BRCA1 but a similar pattern is generally reported5;7.

The relative prognosis of BRCA1/2 carriers and non-carriers is unclear. A recent report found a more favorable outcome for BRCA2 mutation carriers, with no significant difference in outcome for BRCA1 mutation carriers compared to non-carriers8. However, some studies have demonstrated a more favorable prognosis for BRCA1 and BRCA2 carriers6;7;9 compared to non-carriers whereas others have reported no significant difference10;11. Several factors may account for these divergent results. Most studies contained fewer than 50 carriers and all contained fewer 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. Finally, few studies employed appropriate statistical methods to account for the potential bias that results from the inclusion of prevalent cases12. 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 agents7;13. 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 agents14.

The aim of this study was to collate the data from multiple EOC case series with data on BRCA1 and BRCA2 mutation status in order 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 (PARP) inhibitors15.
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 USA, six from Europe, two from Israel, one from Hong Kong, one from Canada, one from Australia and five from the UK. Participants were 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 (CIMBA) or the Ovarian Cancer Association Consortium (OCAC). Investigators submitted data on patient demographics, tumor pathology, vital status and treatment to the coordinating group in Cambridge. In some studies, EOC cases were recruited based on a strong family history of ovarian and/or breast cancer (family-based), while others used population-based sampling or enrolled a consecutive series of cases treated at a single or multiple institution(s). In all studies, BRCA1/2 carriers and non-carriers 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 three exceptions. In three 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 member(s) who had been tested. The non-carrier group from the RMH 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. Finally, 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 (etTable 1).

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 =<1cm and suboptimal debulking as residual disease > 1cm.

BRCA1/2 status may modify response to platinum based chemotherapy which became standard of care in most countries around 1990. Among the 36 percent of subjects with chemotherapy data, 95 percent 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 endpoint was overall survival (OS) up to five years following EOC diagnosis. We chose this endpoint in order 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. Differences in tumor stage, grade, histology and age at diagnosis between BRCA1, BRCA2 and non-carriers were tested using logistic regression adjusted for study site. We used Cox proportional-hazards models to estimate hazard ratios (HR) and 95 percent confidence intervals (CI). All models were adjusted for year of EOC diagnosis (<1990, 1990–1995, 1996–2000, 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, four 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 proportional hazards assumption was tested for each covariate analytically using Schoenfeld residuals. Age at diagnosis and histology violated the PH assumption so additional covariates were included to allow for time-dependent effects.

Differences in the HR estimates for the survival impact of BRCA1 and BRCA2 by different clinical factors were tested using Cochrane’s chi-square test (Q-test) for heterogeneity. To assess the impact of possible competing mortality from breast cancer on effect estimates, we compared analyses restricted to women with and without a diagnosis of breast cancer before or in the five 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%). In order to decrease potential bias and loss of power due to missingness, we performed multiple imputation for these three 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 non-imputed data were similar to those presented here using imputed data; for comparison, the main results using non-imputed data are presented in eTable 2. All analyses were performed using STATA/SE version 11 (StataCorp, College Station, TX, USA). Statistical significance was defined as a P value of less than 0.05. Statistical tests were two sided.

**Results**

Data were available for 3,879 EOC cases; 909 BRCA1 and 304 BRCA2 mutation carriers and 2,666 non-carriers. The median number of months from ascertainment to diagnosis for participants was 1 month (25th–75th percentile: 0–15 months). Women were under active follow-up for a median time of 38 months (25th–75th percentile: 18–77 months). The proportion of cases with censored survival time (not followed to death or 5 years after diagnosis) was 15 percent. After controlling for study site, there was no significant difference in the proportion of cases with censored survival time among BRCA1 (p=0.22) or BRCA2 (p=0.41) carriers compared to non-carriers. The median year of diagnosis was 1998 (range: 1981–2010). During the five years following EOC diagnosis, 1,766 deaths occurred. We found several significant differences in the clinical features of BRCA1 and BRCA2 carriers compared to non-carriers (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 non-carriers. BRCA1 and BRCA2 carriers were more likely to have stage III/IV tumors and poorly differentiated/undifferentiated tumors than non-carriers. Compared to BRCA1 carriers, BRCA2 carriers were more likely to have stage III/IV tumors. While BRCA1 carriers were younger at diagnosis than non-carriers, BRCA2 carriers were slightly older.

The five-year overall survival was 36 percent (95% CI: 34–38) for non-carriers, 44 percent (95% CI: 40–48) for BRCA1 carriers and 52 percent (95% CI: 46–58) for BRCA2 carriers (Figure 1 and eFigure 1). In a Cox regression model only adjusted for study and year of diagnosis, BRCA1 carriers showed a more favorable survival than non-carriers (HR=0.78; 95% CI=0.68–0.89; P=2x10^{-4}) (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=2x10^{-5}). BRCA2 carriers showed a greater survival advantage compared to non-carriers (HR = 0.61; 95% CI=0.50–0.76, P=6x10^{-6}), particularly after adjusting for other prognostic factors (HR = 0.49; 95% CI=0.39–0.61, P=3x10^{-10}). The BRCA1 HR estimates were significantly different from the BRCA2 HR estimates in unadjusted (P_{het}=0.05) and adjusted models (P_{het}=0.003).

We studied the impact 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 >1 for both BRCA1 vs. non-carriers and BRCA2 vs. non-carriers in low grade cases but <1 in high grade cases. There were no significant differences in the HRs for BRCA1 vs. non-carriers or BRCA2 vs. non-carriers when stratified according to tumor stage, histology or history of breast cancer before or during the study period. The survival advantage of BRCA1 and BRCA2 carriers compared to non-carriers was found to be attenuated in women with ovarian cancer selected based on family history of ovarian and/or breast cancer (Table 4). However, the difference in survival between BRCA1 and BRCA2 carriers did not depend on ascertainment (HR for BRCA2 vs. BRCA1: 0.71, 95% CI=0.52–0.98 and 0.64, 95% CI=0.45–0.91 for familial and unselected cases respectively; P_{het}=0.65). There was no evidence of study-specific heterogeneity in the HR estimates for mutation status among family-based studies (BRCA1, p=0.22; BRCA2, p=0.92) or unselected studies (BRCA1, p=0.73; BRCA2, p=0.57).

The proportion of mutation carriers with the Ashkenazi Jewish founder mutations 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2 was 26 percent. We did not find any significant differences in the adjusted HRs for BRCA1 vs. non-carriers among carriers by mutation type (Class I vs. Class II mutation P_{het}=0.10). 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 5′ end compared to the 3′ end of BRCA1 (P=0.03) (eMethods and eTable 3).

A subset of 1129 patients had information on residual disease following primary surgery. We assessed the impact 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 non-carriers, 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 non-carriers and BRCA1 (p=0.74) or BRCA2 (p=0.46) carriers. Adjustment for residual disease did not substantially change the HR estimates for the relative survival of either BRCA1 or BRCA2 carriers compared to non-carriers (eTable 4).
Discussion

Our data demonstrate an improved survival in EOC patients with germline BRCA1 and BRCA2 mutations relative to non-carriers, 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 to BRCA2 carriers. The pathological characteristics of BRCA1 and BRCA2 related tumors are similar to each other, but differ from those of tumors in non-carriers. This contrasts with breast cancer, in which substantial differences between BRCA1 and BRCA2-associated disease are present.

The differences in grade, stage and histology by mutation status are consistent with previously reported data. The impact 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 non-serous 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. 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. In contrast we also found an improved prognosis for BRCA1 carriers, whereas the TCGA data suggested no difference between BRCA1 carriers and non-carriers. 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 hazard ratio for BRCA1 carriers compared to non-carriers reported by Yang and colleagues (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 where participants selected based on a strong family history of ovarian and/or breast cancer. This could have been due to misclassification of non-carriers 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 RAD51C) or in different pathways that produce similar clinical features.

The improved survival of BRCA1/2 carriers relative to non-carriers, 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 the current 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.

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, employing 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. But, differences in study design and population may limit the specificity of the conclusions drawn. Additionally, varying levels of misclassification of BRCA4 status and other variables of interest may have led to some bias of our estimates towards 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*, *BRCA2* carriers and non-carriers, 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 five years following diagnosis compared to non-carriers.

Our findings could have relevance to an even higher proportion of EOC patients if somatic
mutations and epigenetic silencing of *BRCA1* and *BRCA2* show similar effects on
prognosis to germline mutations. It has been estimated that roughly 30% of EOC and over
half of high-grade serous EOC could show dysfunction of *BRCA1* or *BRCA2* through
genetic or epigenetic events. There is evidence that EOC cases with somatic *BRCA1/2*
mutations show a survival advantage over non-carriers, but data from The Cancer Genome
Atlas and others suggest that silencing of *BRCA1* through promoter methylation does not
result in an improved OS. Larger studies that include comprehensive genomic screening
of *BRCA1* and *BRCA2* in primary EOCs will be needed determine if alterations at the
somatic and epigenetic level have similar clinical effects to germline mutations.

The results of this study have potentially important implications for the clinical management
of patients with EOC. Most immediately, our findings can be used by health care
professions for patient counseling regarding expected survival. *BRCA1* and *BRCA2* carriers
with EOC respond better than non carriers 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 patients could be stratified based on their *BRCA* status, their treatment
could be tailored to reflect this, with non-carriers targeted for more aggressive treatments.
Our data provide further support that there may be different functional mechanisms involved
in the etiology of different subtypes of EOCs, and therefore different therapeutic targets
based on germline and somatic genetic variation. For example, the functional
characterization of *BRCA1* and *BRCA2* led to the development of a novel therapy in
*BRCA1/2* carriers based on inhibition of the poly (ADP-ribose) polymerase (PARP) DNA
repair pathway, creating a synthetic lethal phenotype. Recently, phase I and II trials have
shown anti-tumor activity of the PARP inhibitor Olparib in *BRCA1/2* mutation carriers with
EOC. These trials were not large enough to detect differences in response to Olparib in
*BRCA1* vs. *BRCA2* carriers and it is not known whether they will show similar levels of
response. EOC clinical trials should be stratified by *BRCA* status not only to more
appropriately target therapy but also to avoid the potential bias introduced by unequal
numbers of carriers in treatment arms or between study cohorts. Furthermore, given the
important prognostic information provided by *BRCA1* and *BRCA2* status and the potential
for personalized treatment in carriers, the routine testing of women presenting with high-
grade serous EOC may now be warranted.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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None of the sponsors described above had any role in the design or conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Reference List

Figure 1. Kaplan Meier Estimates of Cumulative Survival According to $BRCA1/2$ status
Caption: Kaplan Meier analysis was adjusted for year of diagnosis and study.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-carriers (n=2666)</th>
<th>BRCA1 (n=909)</th>
<th>BRCA2 (n=304)</th>
<th>P (BRCA1 vs non-carriers)</th>
<th>No.</th>
<th>P (BRCA2 vs non-carriers)</th>
<th>P (BRCA1 vs BRCA2 carriers)</th>
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<td>2 (0–18)</td>
<td>2 (0–17)</td>
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<td>Median (25–75%)</td>
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<td>Months of Follow-up:</td>
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<td>35 (18–66)</td>
<td>39 (21–75)</td>
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<tr>
<td>Median (Max-Min)</td>
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<td>Deaths within 5 years of EOC diagnosis</td>
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<td>409</td>
<td>108</td>
<td></td>
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<td>617(74)</td>
<td>213(80)</td>
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<td>2x10^{-3}</td>
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<td>7(1)</td>
<td>0(0)</td>
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<td>6(2)</td>
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<td></td>
<td>0.14</td>
<td>0.42</td>
</tr>
<tr>
<td>Other</td>
<td>45(2)</td>
<td>10(1)</td>
<td>5(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoma, NOS</td>
<td>187(7)</td>
<td>80(10)</td>
<td>18(7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing *</td>
<td>8(0.3)</td>
<td>75(8)</td>
<td>38(13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9x10^{-7}</td>
<td>6x10^{-4}</td>
<td>0.37</td>
</tr>
<tr>
<td>Well differentiated</td>
<td>298(13)</td>
<td>18(3)</td>
<td>8(4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>543(24)</td>
<td>129(19)</td>
<td>28(13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Un-differentiated</td>
<td>1382(62)</td>
<td>533(78)</td>
<td>184(84)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing *</td>
<td>443(17)</td>
<td>229(25)</td>
<td>84(28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage (FIGO)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
<td>7x10^{-3}</td>
<td>0.02</td>
</tr>
<tr>
<td>I</td>
<td>501(21.0)</td>
<td>84(12.3)</td>
<td>22(9.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>213(8.9)</td>
<td>71(10.4)</td>
<td>13(5.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1286(54.0)</td>
<td>436(64.0)</td>
<td>170(73.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Characteristics</td>
<td>Non-carriers (n=2666)</td>
<td>BRCA1 (n=909)</td>
<td>BRCA2 (n=304)</td>
<td>P (BRCA1 vs non-carriers)</td>
<td>P (BRCA2 vs non-carriers)</td>
<td>P (BRCA1 vs BRCA2 carriers)</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>--------------------------</td>
<td>---------------------------</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>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing*</td>
<td>284 (11)</td>
<td>228 (25)</td>
<td>72 (24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at EOC Diagnosis:</td>
<td>58 (12)</td>
<td>52 (10)</td>
<td>60 (11)</td>
<td>8 × 10^{-18}</td>
<td>0.04</td>
<td>1 × 10^{-17}</td>
<td></td>
</tr>
</tbody>
</table>

*The proportion of tumors in various categories of a variable was calculated among subjects with non-missing data for that variable.
Table 2

Proportional hazards regression models for impact of BRCA status on all-cause mortality using imputed data.

<table>
<thead>
<tr>
<th>Comparison Groups</th>
<th>#Carriers (deaths)</th>
<th>#Ref (deaths)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>#Carriers (deaths)</th>
<th>#Ref (deaths)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 vs Non-Carriers (ref)</td>
<td>909 (409)</td>
<td>2666 (1249)</td>
<td>0.78 (0.68–0.89)</td>
<td>2.3×10⁻⁴</td>
<td>909 (409)</td>
<td>2666 (1249)</td>
<td>0.73 (0.64–0.84)</td>
<td>1.6×10⁻⁵</td>
</tr>
<tr>
<td>BRCA2 vs Non-Carriers (ref)</td>
<td>304 (108)</td>
<td>2666 (1249)</td>
<td>0.61 (0.50–0.76)</td>
<td>5.8×10⁻⁶</td>
<td>304 (108)</td>
<td>2666 (1249)</td>
<td>0.49 (0.39–0.61)</td>
<td>2.7×10⁻¹⁰</td>
</tr>
</tbody>
</table>

a Model was stratified by study site, and adjusted for year of ovarian cancer diagnosis.

b Model was stratified by study site and tumor stage, and adjusted for year of ovarian cancer diagnosis, grade, histology and age at ovarian cancer diagnosis.
Table 3

Impact of BRCA1/2 mutations on all-cause mortality in adjusted models stratified by selected subgroups.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>BRCA1 vs Non-carriers</th>
<th>BRCA2 vs Non-carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#Carriers (deaths)</td>
<td>#Ref (deaths)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized (I/II)</td>
<td>208 (51)</td>
<td>856 (130)</td>
</tr>
<tr>
<td>Advanced (III/IV)</td>
<td>701 (358)</td>
<td>1810 (1119)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>28 (11)</td>
<td>364 (82)</td>
</tr>
<tr>
<td>Poorly/Un-differentiated</td>
<td>881 (398)</td>
<td>2302 (1167)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-serous a</td>
<td>127 (5)</td>
<td>657 (184)</td>
</tr>
<tr>
<td>Serous</td>
<td>617 (286)</td>
<td>1769 (939)</td>
</tr>
<tr>
<td>High grade serous</td>
<td>598 (278)</td>
<td>1602 (887)</td>
</tr>
<tr>
<td>Breast Cancer before or during study period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>551 (273)</td>
<td>1171 (683)</td>
</tr>
<tr>
<td>Yes</td>
<td>214 (89)</td>
<td>61 (25)</td>
</tr>
</tbody>
</table>

aIncludes tumors of mucinous, clear cell and endometroid histology

bTest for heterogeneity is for differences between non-serous and serous subtypes
Table 4

Proportional hazards regression for impact of BRCA status on all-cause mortality by study type.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>#Carriers (deaths)</th>
<th>#Ref (deaths)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>Main effect</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 vs Non-Carriers (ref)</td>
<td></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>0.83</td>
<td>0.002</td>
<td></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>2.4×10⁻⁷</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA2 vs Non-Carriers (ref)</td>
<td></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>0.07</td>
<td>0.04</td>
<td></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>5.0×10⁻⁸</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Models were stratified by study site and tumor stage, and adjusted for year of ovarian cancer diagnosis, grade, histology and age at ovarian cancer diagnosis.
<table>
<thead>
<tr>
<th>Years</th>
<th>Non-carriers</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1047</td>
<td>327</td>
<td>117</td>
</tr>
<tr>
<td>1</td>
<td>1687</td>
<td>593</td>
<td>199</td>
</tr>
<tr>
<td>2</td>
<td>1540</td>
<td>569</td>
<td>192</td>
</tr>
<tr>
<td>3</td>
<td>1395</td>
<td>509</td>
<td>179</td>
</tr>
<tr>
<td>4</td>
<td>1225</td>
<td>490</td>
<td>164</td>
</tr>
<tr>
<td>5</td>
<td>1044</td>
<td>408</td>
<td>125</td>
</tr>
</tbody>
</table>

Table 5. Number at risk by carrier status for Figure 1.