Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer

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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, $P=2\times10^{-4}$; *BRCA2*, HR = 0.61; 95% CI=0.50–0.76, $P=6\times10^{-6}$). 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, $P=2\times10^{-5}$; *BRCA2*, HR = 0.49, 95% CI=0.39–0.61, $P=3\times10^{-10}$).

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 EOC[1–3]. 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 histology[5], high grade[6] and advanced stage[3]. 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 reported[5;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-carriers[8]. However, some studies have demonstrated a more favorable prognosis for *BRCA1* and *BRCA2* carriers[6;7;9] compared to non-carriers whereas others have reported no significant difference[10;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 cases[12]. 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[7;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 agents[14].

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) inhibitors[15].

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)[16] or the Ovarian Cancer Association Consortium (OCAC)[17]. 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[18;19] and were grouped into categories based on their predicted functional effect[20–23]. 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 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 (eTable 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[24]. 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; $P=2\times10^{-4}$) (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; $P=2\times10^{-5}$). *BRCA2* carriers showed a greater survival advantage compared to non-carriers (HR = 0.61; 95% CI=0.50–0.76, $P=6\times10^{-6}$), particularly after adjusting for other prognostic factors (HR = 0.49; 95% CI=0.39–0.61, $P=3\times10^{-10}$). 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[25;26]. The differences in grade, stage and histology by mutation status are consistent with previously reported data[5;27]. 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[28;29]. 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 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[30]) 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[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, 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 *BRCA* 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[32;33]. There is evidence that EOC cases with somatic *BRCA1/2* mutations show a survival advantage over non-carriers[33], but data from The Cancer Genome Atlas and others suggest that silencing of BRCA1 through promoter methylation does not result in an improved OS[34;35]. 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[15;36;37]. 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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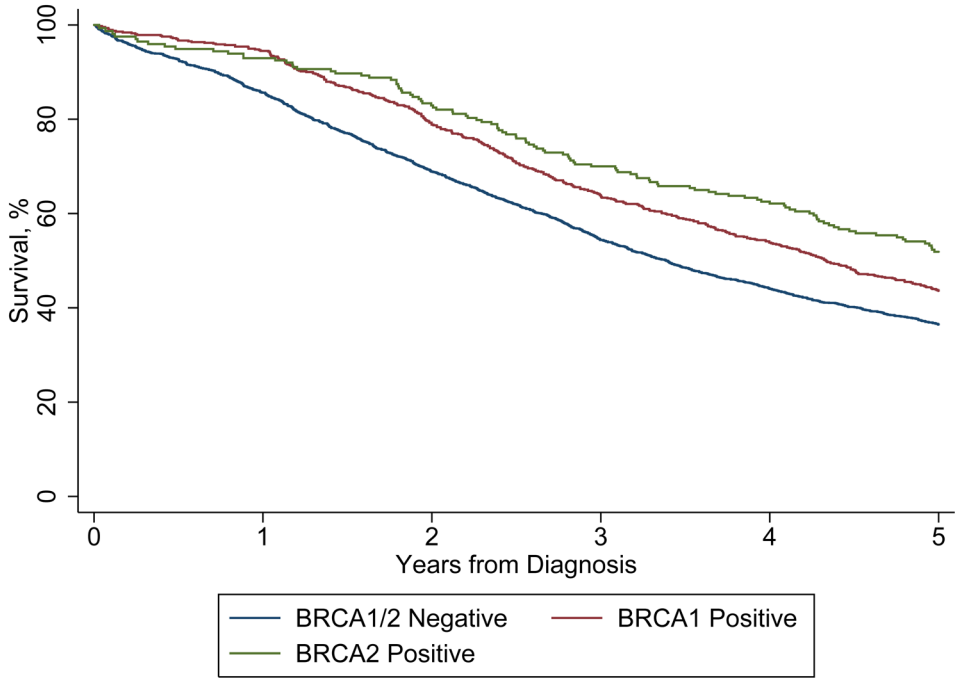

Figure 1. Kaplan Meier Estimates of Cumulative Survival According to *BRCA1/2* status
Caption: Kaplan Meier analysis was adjusted for year of diagnosis and study.

Table 1

Characteristics of 4,284 study participants by BRCA1/2 germline mutation status

	Non-carriers (n=2666)	*BRCA1* (n=909)		*BRCA2* (n=304)		
Characteristics	**No.**	**No.**	**P (*BRCA1* vs non-carriers)**	**No.**	**P (*BRCA2* vs non-carriers)**	**P (*BRCA1* vs *BRCA2* carriers)**
Months from Diagnosis to Study Entry: Median (25–75%)	0.5 (0–13)	2 (0–18)		2 (0–17)		
Months of Follow-up: Median (25–75%)	38 (18–83)	35 (18–66)		39 (21–75)		
Year of EOC Diagnosis: Median (Max-Min)	1998 (1981–2009)	1998 (1986–2010)		1999 (1986–2009)		
Deaths within 5 years of EOC diagnosis	1249	409		108		
Histology						
Serous	1769(67)	617(74)	1×10^{-3}	213(80)	2×10^{-3}	0.20
Mucinous	214(8)	7(1)	3×10^{-5}	0(0)	0.02	0.33
Endometroid	324(12)	105(13)	0.85	24(9)	0.39	0.16
Clear Cell	119(4)	15(2)	0.13	6(2)	0.14	0.42
Other	45(2)	10(1)	-	5(2)	-	
Carcinoma, NOS	187(7)	80(10)	-	18(7)	-	
Missing *	8(0.3)	75(8)	-	38(13)	-	
Grade			9×10^{-7}		6×10^{-4}	0.37
Well differentiated	298(13)	18(3)		8(4)		
Poorly differentiated	543(24)	129(19)		28(13)		
Un-differentiated	1382(62)	533(78)		184(84)		
Missing *	443(17)	229(25)		84(28)		
Stage (FIGO)			0.03		7×10^{-3}	0.02
I	501(21.0)	84(12.3)		22(9.5)		
II	213(8.9)	71(10.4)		13(5.6)		
III	1286(54.0)	436(64.0)		170(73.3)		

Characteristics	Non-carriers (n=2666) No.	*BRCA1* (n=909) No.	P (*BRCA1* vs non-carriers)	*BRCA2* (n=304) No.	P (*BRCA2* vs non-carriers)	P (*BRCA1* vs *BRCA2* carriers)
IV	382(16.0)	90(13.2)		27(11.6)		
Missing *	284(11)	228(25)		72(24)		
Age at EOC Diagnosis: Mean (SD)	58(12)	52(10)	8×10^{-18}	60(11)	0.04	1×10^{-17}

* 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.

	Unadjusted[a]				Adjusted[b]			
Comparison Groups	**#Carriers (deaths)**	**#Ref (deaths)**	**HR (95% CI)**	**P-value**	**#Carriers (deaths)**	**#Ref (deaths)**	**HR (95% CI)**	**P-value**
BRCA1 vs Non-Carriers (ref)	909 (409)	2666 (1249)	0.78 (0.68–0.89)	2.3×10^{-4}	909 (409)	2666 (1249)	0.73 (0.64–0.84)	1.6×10^{-5}
BRCA2 vs Non-Carriers (ref)	304 (108)	2666 (1249)	0.61 (0.50–0.76)	5.8×10^{-6}	304 (108)	2666 (1249)	0.49 (0.39–0.61)	2.7×10^{-10}

[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 ajusted for year of ovarian cancer diagnosis, grade, histology and age at ovarian cancer diagnsois.

Table 3

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

	***BRCA1* vs Non-carriers**					***BRCA2* vs Non-carriers**				
Subgroups	**#Carriers (deaths)**	**#Ref (deaths)**	**HR (95% CI)**	**P**	**P-het**	**#Carriers (deaths)**	**#Ref (deaths)**	**HR (95% CI)**	**P**	**P-het**
Stage										
Localized (I/II)	208 (51)	856 (130)	0.85 (0.53–1.37)	0.51	0.53	55 (11)	856 (130)	0.65 (0.53–1.37)	0.31	0.51
Advanced (III/IV)	701 (358)	1810 (1119)	0.73 (0.63–0.84)	2×10^{-5}		249 (97)	1810 (1119)	0.49 (0.39–0.61)	5×10^{-10}	
Grade										
Well differentiated	28 (11)	364 (82)	2.66 (0.86–8.17)	0.09	0.02	8 (5)	364 (82)	3.86 (0.59–25.15)	0.16	0.03
Pooly/Un-differentiated	881 (398)	2302 (1167)	0.71 (0.61–0.82)	3×10^{-5}		296 (103)	2302 (1167)	0.47 (0.38–0.59)	8×10^{-10}	
Histology										
Non-serous[a]	127 (5)	657 (184)	0.68 (0.45–1.04)	0.07	0.76[b]	30 (11)	657 (184)	0.70 (0.36–1.37)	0.30	0.19[b]
Serous	617 (286)	1769 (939)	0.73 (0.62–0.86)	2×10^{-4}		213 (74)	1769 (939)	0.43 (0.33–0.56)	3×10^{-10}	
High grade serous	598 (278)	1602 (887)	0.72 (0.61–0.85)	8×10^{-5}		206 (69)	1602 (887)	0.41 (0.31–0.53)	1×10^{-10}	
Breast Cancer before or during study peroid										
No	551 (273)	1171 (683)	0.86 (0.72–1.02)	0.08	0.75	165 (73)	1171 (683)	0.62 (0.47–0.82)	3×10^{-4}	0.61
Yes	214 (89)	61 (25)	0.77 (0.41–1.45)	0.42		75 (21)	61 (25)	0.50 (0.24–1.07)	0.08	

[a] Includes tumors of mucinous, clear cell and endometroid histology

[b] test 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.

				P-value	
Subgroup	**#Carriers (deaths)**	**#Ref (deaths)**	**HR (95% CI)**	**Main effect**	**Heterogeneity**
BRCA1 vs Non-Carriers (ref)					
Selected for Family History	556 (254)	283 (126)	1.03 (0.79–1.35)	0.83	0.002
Unselected for Family History	353 (155)	2383 (1123)	0.62 (0.52–0.75)	2.4×10^{-7}	
BRCA2 vs Non-Carriers (ref)					
Selected for Family History	179 (63)	283 (126)	0.71 (0.49–1.03)	0.07	0.04
Unselected for Family History	125 (45)	2383 (1123)	0.43 (0.32–0.58)	5.0×10^{-8}	

Models were stratified by study site and tumor stage, and ajusted for year of ovarian cancer diagnosis, grade, histology and age at ovarian cancer diagnsois

Table 5

Number at risk by carrier status for Figure 1

Years	Non-carriers	BRCA1	BRCA2
0	1047	327	117
1	1687	593	199
2	1540	569	192
3	1395	490	179
4	1225	408	164
5	1044	342	125