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

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For editorial comment see p 408.

Context Approximately 10% of women with invasive epithelial ovarian cancer (EOC) carry deleterious germline mutations in *BRCA1* or *BRCA2*. A recent article 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 with noncarriers and to determine whether *BRCA1* and *BRCA2* carriers show similar survival patterns.

Design, Setting, and Participants A pooled analysis of 26 observational studies on the survival of women with ovarian cancer, which included data from 1213 EOC cases with pathogenic germline mutations in *BRCA1* (n=909) or *BRCA2* (n=304) and from 2666 noncarriers recruited and followed up at variable times between 1987 and 2010 (the median year of diagnosis was 1998).

Main Outcome Measure Five-year overall mortality.

Results 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. After adjusting for study and year of diagnosis, *BRCA1* and *BRCA2* mutation carriers showed a more favorable survival than noncarriers (for *BRCA1*: hazard ratio [HR], 0.78; 95% CI, 0.68-0.89; $P<.001$; and for *BRCA2*: HR, 0.61; 95% CI, 0.50-0.76; $P<.001$). These survival differences remained after additional adjustment for stage, grade, histology, and age at diagnosis (for *BRCA1*: HR, 0.73; 95% CI, 0.64-0.84; $P<.001$; and for *BRCA2*: HR, 0.49; 95% CI, 0.39-0.61; $P<.001$). The *BRCA1* HR estimate was significantly different from the HR estimated in the adjusted model (*P* for heterogeneity=.003).

Conclusion Among patients with invasive EOC, having a germline mutation in *BRCA1* or *BRCA2* was associated with improved 5-year overall survival. *BRCA2* carriers had the best prognosis.

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Germline mutations in the tumor suppressor genes *BRCA1* (NCBI Entrez Gene 672) and *BRCA2* (NCBI Entrez Gene 675) are the strongest known genetic risk factors for both breast and epithelial ovarian cancer (EOC) and are found in 6% to 15% 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 noncarriers. *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 noncarriers is unclear. A

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recent article[8] 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[6,7,9] compared with noncarriers, whereas other studies have reported no significant difference.[10,11] Several factors may account for these divergent results. Most studies contained less than 50 carriers 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.[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 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.[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 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*[16] or the Ovarian Cancer Association Consortium.[17]

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[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 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.

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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 adjusted for study site. We used Cox proportional hazards 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 χ^2 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

Characteristics	Noncarriers (n = 2666)	*BRCA1* (n = 909)	*BRCA2* (n = 304)	*P* Value: *BRCA1* vs Noncarriers	*P* Value: *BRCA2* vs Noncarriers	*P* Value: *BRCA1* vs *BRCA2*
Diagnosis to study entry, median (IQR), mo	0.5 (0-13)	2 (0-18)	2 (0-17)			
Follow-up, median (IQR), mo	38 (18-83)	35 (18-66)	39 (21-75)			
Year of EOC diagnosis, median (range)	1998 (1981-2009)	1998 (1986-2010)	1999 (1986-2009)			
Deaths within 5 y of EOC diagnosis, No. (%)	1249 (46.8)	409 (45.0)	108 (35.5)			
Histology, No. (%)						
Serous	1769 (67)	617 (74)	213 (80)	.001	.002	.20
Mucinous	214 (8)	7 (1)	0 (0)	<.001	.02	.33
Endometroid	324 (12)	105 (13)	24 (9)	.85	.39	.16
Clear cell	119 (4)	15 (2)	6 (2)	.13	.14	.42
Other	45 (2)	10 (1)	5 (2)			
Carcinoma, not otherwise specified	187 (7)	80 (10)	18 (7)			
Missing[a]	8 (0.3)	75 (8)	38 (13)			
Grade, No. (%)						
Well differentiated	298 (13)	18 (3)	8 (4)			
Poorly differentiated	543 (24)	129 (19)	28 (13)	<.001	<.001	.37
Undifferentiated	1382 (62)	533 (78)	184 (84)			
Missing[a]	443 (17)	229 (25)	84 (28)			
Stage (FIGO), No. (%)						
I	501 (21.0)	84 (12.3)	22 (9.5)			
II	213 (8.9)	71 (10.4)	13 (5.6)	.03	.007	.02
III	1286 (54.0)	436 (64.0)	170 (73.3)			
IV	382 (16.0)	90 (13.2)	27 (11.6)			
Missing[a]	284 (11)	228 (25)	72 (24)			
Age at EOC diagnosis, mean (SD), y	58 (12)	52 (10)	60 (11)	<.001	.04	<.001

Abbreviations: EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range.
[a]The proportion of tumors in various categories of a variable was calculated among study participants with nonmissing data for that variable.

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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.

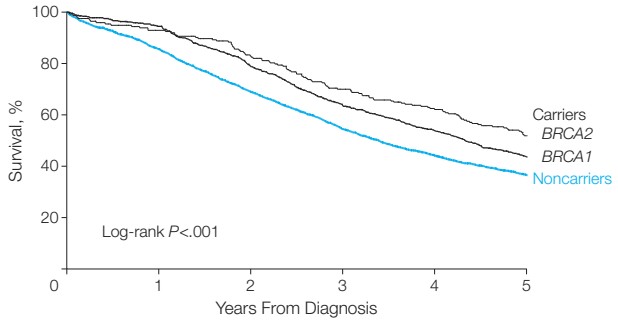
RESULTS

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

Figure. Kaplan-Meier Estimates of Cumulative Survival According to *BRCA1/2* Status



No. at risk						
Noncarriers	1047	1687	1540	1395	1225	1044
Carriers						
BRCA1	327	593	569	490	408	342
BRCA2	117	199	192	179	164	125

Kaplan-Meier analysis was adjusted for year of diagnosis and study.

Table 2. Cox Proportional Hazards Regression Models for Effect of *BRCA* Status on All-Cause Mortality Using Imputed Data[a]

Comparison Groups	Unadjusted				Adjusted			
	Total No. (No. of Deaths)		Hazard Ratio (95% CI)	*P* Value	Total No. (No. of Deaths)		Hazard Ratio (95% CI)	*P* Value
	Carriers	Noncarriers			Carriers	Noncarriers		
BRCA1 vs noncarriers	909 (409)	2666 (1249)	0.78 (0.68-0.89)	<.001	909 (409)	2666 (1249)	0.73 (0.64-0.84)	<.001
BRCA2 vs noncarriers	304 (108)	2666 (1249)	0.61 (0.50-0.76)	<.001	304 (108)	2666 (1249)	0.49 (0.39-0.61)	<.001

[a] Noncarriers 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.

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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 tumor 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 5′ 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 3. Effect of *BRCA1/2* Mutations on All-Cause Mortality in Adjusted Models Stratified by Selected Subgroups

	BRCA1 vs Noncarriers					*BRCA2* vs Noncarriers				
	Total No. (No. of Deaths)					Total No. (No. of Deaths)				
Subgroups	Carriers	Noncarriers	Hazard Ratio (95% CI)	*P* Value	*P* for Heterogeneity	Carriers	Noncarriers	Hazard Ratio (95% CI)	*P* Value	*P* for Heterogeneity
Stage										
Localized (I/II)	208 (51)	856 (130)	0.85 (0.53-1.37)	.51	.53	55 (11)	856 (130)	0.65 (0.53-1.37)	.31	.51
Advanced (III/IV)	701 (358)	1810 (1119)	0.73 (0.63-0.84)	<.001		249 (97)	1810 (1119)	0.49 (0.39-0.61)	<.001	
Grade										
Well differentiated	28 (11)	364 (82)	2.66 (0.86-8.17)	.09	.02	8 (5)	364 (82)	3.86 (0.59-25.15)	.16	.03
Poorly/undifferentiated	881 (398)	2302 (1167)	0.71 (0.61-0.82)	<.001		296 (103)	2302 (1167)	0.47 (0.38-0.59)	<.001	
Histology										
Nonserous[a]	127 (5)	657 (184)	0.68 (0.45-1.04)	.07	.76[b]	30 (11)	657 (184)	0.70 (0.36-1.37)	.30	.19[b]
Serous	617 (286)	1769 (939)	0.73 (0.62-0.86)	<.001		213 (74)	1769 (939)	0.43 (0.33-0.56)	<.001	
High-grade serous	598 (278)	1602 (887)	0.72 (0.61-0.85)	<.001		206 (69)	1602 (887)	0.41 (0.31-0.53)	<.001	
Breast cancer before or during study period										
No	551 (273)	1171 (683)	0.86 (0.72-1.02)	.08	.75	165 (73)	1171 (683)	0.62 (0.47-0.82)	<.001	.61
Yes	214 (89)	61 (25)	0.77 (0.41-1.45)	.42		75 (21)	61 (25)	0.50 (0.24-1.07)	.08	

[a] Includes tumors of mucinous, clear cell, and endometroid histology.
[b] Test for heterogeneity is for differences between nonserous and serous subtypes.

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Table 4. Cox Proportional Hazards Regression for Effect of *BRCA* Status on All-Cause Mortality by Study Type[a]

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

[a]Noncarriers 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.[5,27] 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.[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 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 al[8] (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 RAD51C[30]) 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.

Our findings could have relevance to an even higher proportion of patients with EOC if somatic mutations and epi-

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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 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 noncarriers,[33] but data from TCGA and others suggest that silencing of *BRCA1* through promoter methylation does not result in an improved overall survival.[34,35] Larger studies that include comprehensive genomic screening of *BRCA1* and *BRCA2* in primary EOCs will be needed to determine if alterations at the somatic and epigenetic level have similar clinical effects to germline mutations.

Our study results have potentially important implications for the clinical management of patients with EOC. Most immediately, our findings can be used by health care professionals for patient counseling regarding expected survival. *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 patients could be stratified based on their *BRCA* status, their treatment could be tailored to reflect this, with noncarriers 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 DNA repair pathway, creating a synthetic lethal phenotype. 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 response to Olparib in *BRCA1* vs *BRCA2* carriers and it is not known whether they will show similar levels of response. Epithelial ovarian cancer 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 groups 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.

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