BRCA Mutations and Outcome in Epithelial Ovarian Cancer: Experience in Ethnically Diverse Groups

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Abstract

Variation in the worldwide prevalence of *BRCA1* and *BRCA2* mutations is well recognized. We analyzed *BRCA* mutation type variability in 585 *BRCA*-tested epithelial ovarian cancer patients from different ethnic populations. Of these patients, 98 (16.8%) were carriers of the *BRCA1* mutation, and 34 (5.8%) were carriers of *BRCA2*. Among the *BRCA1/2* carriers, there were 29 mutation types. The widest variation in mutation types was in non-Jewish Caucasians. Our analysis showed statistically improved overall survival and a tendency towards improved first progression-free survival across all *BRCA* mutation subtypes, compared to non-carriers.

Key words: *BRCA1* mutation, *BRCA2* mutation, epithelial ovarian cancer, mutation subtype, 185delAG, 5382insC, 6174del

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Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death from gynecological malignancies in the Western world.[1-3] The strongest known risk factors are mutations in either the *BRCA1* or *BRCA2* gene, which account for approximately 10% of EOC cases.[3-5]

BRCA1 and *BRCA2* are tumor suppressor genes involved in the regulation of cellular proliferation, chromosomal stability, and DNA repair by homologous recombination (HR).[5] Cells that cannot repair DNA double-strand breaks due to deficiencies in the HR pathway are more susceptible to malignant transformation.[5] Homologous recombination–deficient cells also cannot repair DNA damage induced by platinum adducts; therefore, they are particularly platinum-sensitive.[6]

BRCA mutation carriers represent a unique group of patients who are commonly diagnosed at a younger age, have improved sensitivity to platinum-based chemotherapy, and have an overall improved prognosis.[4,6]

Variation in the worldwide prevalence of *BRCA1* and *BRCA2* mutations is well recognized.[7-9] In the Ashkenazi Jewish (AJ) population, the *BRCA1/2* mutation spectrum is represented mainly by 185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*.[10] Other populations display a large variety of *BRCA* mutations, so that ethnicity-specific prevalences of *BRCA1/2* mutations are less clearly defined.

We previously described *BRCA* mutation type variability in a retrospective cohort comprising 190 stage IV *BRCA*-tested patients with EOC from New York City, Israel, and Italy diagnosed between 1995 and 2009.[11] The present paper is an update of that study; the analysis was extended to include 585 *BRCA*-tested patients with EOC from the same medical centers diagnosed between 1995 and 2014. The study objectives were to describe *BRCA* mutation type variability in different ethnic populations, and to compare progression-free survival (PFS) and overall survival (OS) among patients with nonhereditary EOC, *BRCA* mutation carriers, and subtypes of *BRCA* mutations.

Materials and Methods

We reviewed medical records of 1200 patients diagnosed with EOC between 1995 and 2014 at New York University (NYU) Cancer Institute, Tel Aviv Sourasky Medical Center (Israel), and Padova Clinical Cancer Centers (Italy). Patients with EOC or histologically confirmed extra-uterine Müllerian carcinoma (ovarian, tubal, and primary peritoneal) who were tested for BRCA mutation status were included in the analysis. Clinical data retrieved included institution, patient age at diagnosis, ethnicity, comorbidities, stage of disease, tumor histology, tumor grade, patient and family cancer history, *BRCA* mutation status, *BRCA* mutation type, prior surgical management, first-line chemotherapy, chemotherapy for recurrent disease, date of first relapse, platinum sensitivity, PFS, OS, and status at the most recent follow-up.

Statistical Methods

The characteristics of *BRCA* carriers were compared with those of the noncarriers (NCs). Progression-free survival

and OS were evaluated by Kaplan-Meyer and multivariate Cox proportional hazards regression models with adjustments for age at diagnosis, platinum sensitivity, stage at diagnosis, and histology to exclude dependency. All statistical analyses were performed using SAS version 9.2 statistical software.

Results

Patient Characteristics

BRCA mutations were assessed in 585 patients (median age, 58 years; range, 33-86 years) of 1200 EOC patient records reviewed. Of the patients assessed for mutations, 132 (22.5%) tested positive, 98 (16.8%) were carriers of the *BRCA1* mutation, and 34 (5.8%) were carriers of *BRCA2*. The clinical characteristics of the *BRCA* carriers and the NCs are shown in **Table 1**. The *BRCA* carrier population tended to be approximately 10 years younger than the NC population, as previously reported.[4]

More than half of the *BRCA* carriers (78/132, 59.1%) were of AJ descent. Other *BRCA* carriers were non-AJ, non-Jewish Caucasian, African American, Hispanic, and unknown.

Among the *BRCA1/2* carriers, there were 29 mutation types (**Table 2**). The widest variation was among non-Jewish Caucasians. The most common *BRCA1* mutations in AJ carriers were 185delAG (49 patients) and 5382insC (8 patients); the most common *BRCA2* mutation was 6174del (16 patients). Thirteen non-AJ patients had 185delAG mutations, and 3 of them had 6174delT mutations.

Assessment of Prognosis

As shown in **Figure 1**, median OS was significantly longer in *BRCA* carriers compared with NCs (82.5 vs 50.7 months; P =.0012).

Analysis of OS by mutation type showed a median OS of 74.8 months for 185delAG mutation carriers, 126.6 months for 5382insC carriers, and 56.2 months for all other mutation subtypes (combined). Median OS was statistically significantly longer in 185delAG, 617delT, and 5382insC mutation carriers compared with NCs (P = .02, P = .03, and P = .02, respectively; **Figure 2**).

Analysis of PFS by mutation type showed a median PFS of 16.7 months for 185delAG, 9.1 months for 6174delT, 16.7 months for 5382insC, and 10.5 months for all other mutation subtypes compared with a median PFS of 9.6 months in NCs (**Figure 3**).

Discussion and Conclusions

The results of the present work show the large variety of *BRCA* mutations in our ethnically diverse EOC population. The non-AJ population, specifically non-Jewish Caucasians, represented approximately 30 different mutation types, whereas AJ and non-AJ patients had a higher frequency of the 3 main *BRCA* founder mutations 185delAG,

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TABLE 1. Clinical Characteristics of the Cohort

	***BRCA* Carriers n (%)**	***BRCA* NCs n (%)**	**Total n (%)**
Number of patients ***BRCA1*** ***BRCA2***	132 (22.5) 98 (16.8) 34 (5.8)	453 (77.4)	**585 (100.0)**
Median age at diagnosis (range), years	55 (33-76)	62 (37-86)	**58 (33-86)**
Stage I	15 (11.3)	41 (9.1)	**56 (9.6)**
II	8 (6.06)	40 (8.8)	**48 (8.2)**
III	96 (72.7)	307 (67.8)	**403 (68.9)**
IV	13 (9.85)	65 (14.4)	**78 (13.3)**
Histology Papillary serous	87 (65.9)	125 (27.6)	**212 (36.2)**
Endometrioid	6 (4.5)	40 (8.8)	**46 (7.8)**
Undifferentiated	39 (29.5)	288 (63.6)	**327 (55.9)**

NC indicates noncarrier.

TABLE 2. Mutation Types by Ethnicity

	Mutation Type	AJ	Non-AJ	Caucasian	Hispanic	Unknown
BRCA1	185delAG	49	13	3	1	
	1294del40	1				
	1720delAF>stop536	1				
	3731delA					1
	K1702X(5223A>T)					1
	5382insC	8		1		
	3829delIT			1		
	IVS11+1G>A			1		
	1806C\T-Igu536			1		
	2567delC, P163L			3		
	5083del19>stop1670			1		
	5181delGTT(Val1688del)			1		
	5663G7A;Trp1815stop			1		
	E1737X			1		
	E1737X			1		
	A1708E		2			
	tyr978x		2			
	cod1486ex14:4575delAstop1504			1		
BRCA2	6174delIT	16	3	2		
	6174delAG	1				
	5301insA			1		
	7408A/T;Arg2394stop			2		
	802delAT			1		
	A1708E	1				
	Dup exon13			1		
	cod2960ex22:9106C/t			1		
	cod68ex3:432delAstop79			1		
	2576delC, P163L			1		
	p.2411k t	1				
	274ideit		1			

AJ indicates Ashkenazi Jewish.

6174delT, and 5382insC.

The results of the present work affirm that *BRCA* carriers have increased PFS and OS compared with NCs in EOC, as had been published previously.[12] Our analysis showed statistically improved OS and a tendency toward improved first PFS for mutation carriers across all *BRCA* mutation subtypes. The prognostic significance of what were considered unclassified *BRCA* mutation variants (VUS) is unclear.[13-15] Our results show a trend for VUS in this multiethnic cohort to have better OS than those testing negative for *BRCA* mutations, although not to the extent of those with known deleterious mutations. Overall, these findings suggest that some patients with EOC testing positive for variants, and/or who are at high risk for *BRCA* mutations based on family history may benefit from early genetic testing and subsequent interventions with DNA damaging agents or inhibitors of DNA repair (ie, PARP inhibitors).

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FIGURE 1. Overall Survival Compared Between *BRCA1/2* Mutation Carriers and non-*BRCA* Carriers.

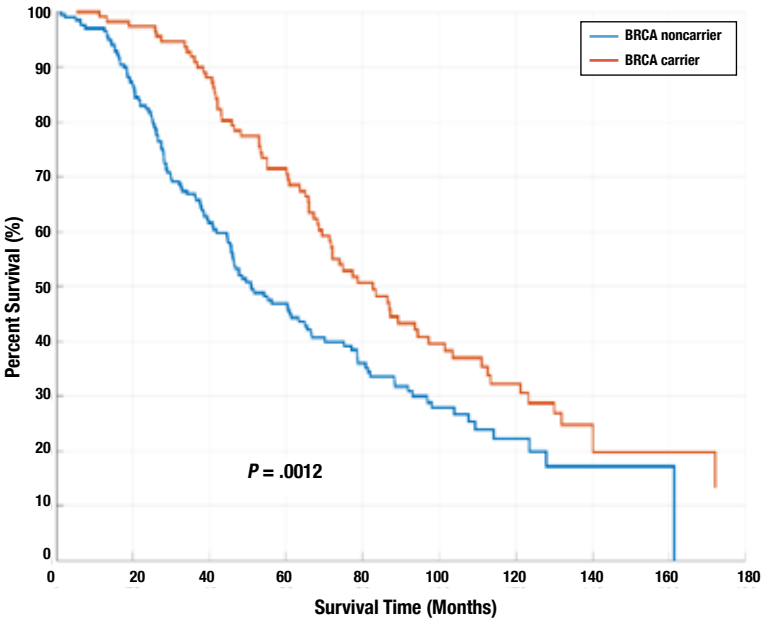

FIGURE 2. Median OS of *BRCA* Carriers by Mutation Types.

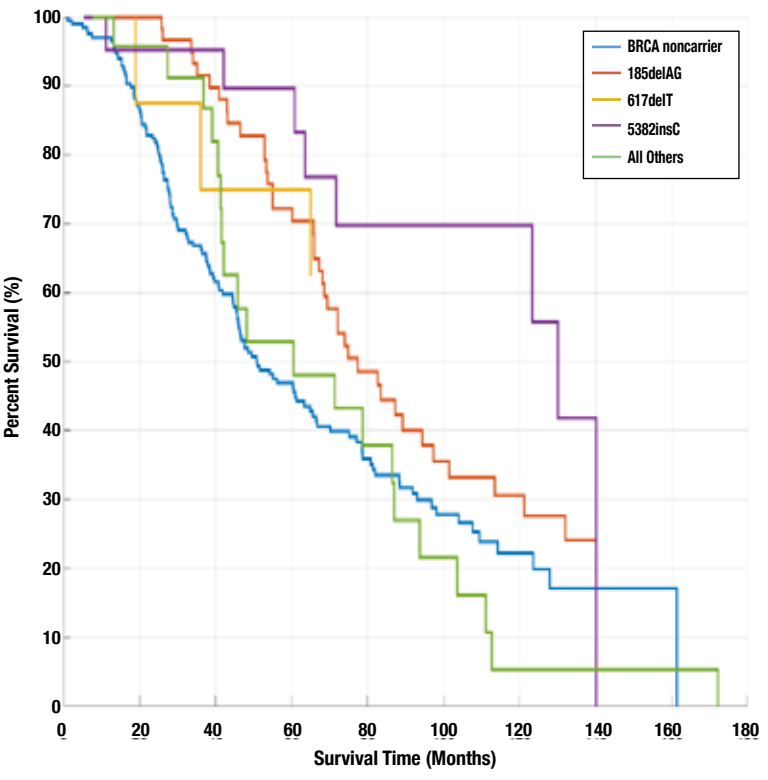

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FIGURE 3. Progression-free Survival Comparison by Mutation Type Between *BRCA* Carriers and non-*BRCA* Carriers.