

Incidence and Outcome of *BRCA* Mutations in Unselected Patients with Triple Receptor-Negative Breast Cancer

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Abstract

Purpose: To investigate the incidence of germline and somatic *BRCA1/2* mutations in unselected patients with triple-negative breast cancer (TNBC) and determine the prognostic significance of carrying a mutation.

Methods: DNA was obtained from 77 TNBC and normal tissues. *BRCA1/2* exons/flanking regions were sequenced from tumor and patients classified as mutant or wild type (WT). Sequencing was repeated from normal tissue to identify germline and somatic mutations. Patient characteristics were compared with chi-square. Survival was estimated by Kaplan–Meier method and compared with log-rank. Cox proportional hazards models were fit to determine the independent association of mutation status with outcome.

Results: Median age was 51 years (27–83 years). Fifteen patients (19.5%) had *BRCA* mutations: 12 (15.6%) in *BRCA1* (one somatic), and 3 (3.9%) in *BRCA2*. Patients with *BRCA* mutations tended to be younger than WT, ($P = 0.005$). Grade, histology, and stage were not associated with mutation status. At a median follow-up of 43 months (7–214 months), there were 33 (42.9%) recurrences and 35 (45.5%) deaths. Five-year recurrence-free survival estimates were 51.7% for WT versus 86.2% for patients with mutations, ($P = 0.031$); and 5-year overall survival estimates were 52.8% for WT versus 73.3% for patients with mutations ($P = 0.225$). After adjustment, patients with *BRCA* mutations had a significantly better RFS (HR: 0.19, 95% CI: 0.045–0.79, $P = 0.016$) compared with WT.

Conclusions: In this unselected cohort of TNBC, we found a 19.5% incidence of *BRCA* mutations. Genetic testing should be discussed with patients with TNBC. Patients with TNBC with *BRCA* mutations had a significantly lower risk of relapse. *Clin Cancer Res*; 17(5); 1082–9. ©2011 AACR.

Introduction

Triple-negative breast cancer (TNBC), defined as estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and human epidermal growth factor receptor 2 (HER2)-negative breast cancer currently represents a major challenge to physicians and patients. Although it accounts for 15% to 20% of breast cancer cases, TNBC is the cause of a disproportionate number of breast cancer deaths. Recent developments in gene expression arrays have categorized breast cancer into distinct subgroups. One of these subgroups defined by genetic clustering is the basal-like (1,2). Among the features of this subgroup is low expression of

hormone receptor, and HER2-related genes, making most of these tumors TNBC.

There is an interesting association of basal-like breast cancer with germ-line *BRCA1* mutations (3,4). At least three quarters of *BRCA1*-related breast cancers are basal-like by microarray (3) or by immunohistochemistry (4). In studies with selected patients referred for *BRCA* genetic testing, the frequency of TNBC has been reported to be 57% in *BRCA1* mutation carriers and 23% in *BRCA2* mutation carriers (5). The clinical outcomes for women with sporadic breast cancer compared with those with *BRCA*-related cancers have been reported to be similar (6). Aberrant DNA repair pathways by homologous recombination and genomic instability appear to be important characteristic of both *BRCA*-related and basal-like breast cancers (7,8), and agents targeting these aberrations, such as PARP inhibitors are emerging as promising therapeutic interventions. Thus, determining the prevalence of *BRCA* mutations in TNBCs and expected outcomes in *BRCA*-associated and non-*BRCA*-associated TNBC is critical for the design of future clinical trials with novel therapeutics.

The purpose of this study was to investigate the incidence of germline and somatic *BRCA1/2* deleterious mutations in an unselected group of patients with TNBC, and to

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Translational Relevance

In studies with selected patients referred for *BRCA* genetic testing, the frequency of TNBC has been reported to be 57% in *BRCA1* mutation carriers and 23% in *BRCA2* mutation carriers. Aberrant DNA repair pathways by homologous recombination and genomic instability appear to be important characteristic of both *BRCA*-related and basal-like breast cancers, and agents targeting these aberrations are emerging as promising therapeutic interventions. In this unselected cohort of triple-negative breast cancer (TNBC), we found a 19.5% incidence of *BRCA* mutations and that patients with TNBC with *BRCA* mutations had a significantly lower risk of relapse. Determining the prevalence of *BRCA* mutations in TNBCs and expected outcomes in *BRCA*-associated and non-*BRCA*-associated TNBC is critical for the design of future clinical trials with novel therapeutics.

determine the prognostic significance of carrying a mutation by assessing relapse-free survival (RFS) and overall survival (OS).

Methods

Patients and treatment

As part of a TNBC molecular characterization project the Breast Cancer Management System Database at The University of Texas M.D. Anderson Cancer Center (MDACC) was searched to identify patients with invasive TNBC who had definitive surgery and from whom tumor and normal tissue was available from the MDACC Breast Cancer Tumor Bank. Ninety-six primary frozen tumors were identified. Normal tissues were available in 77 cases diagnosed between 1997 and 2006. No germline DNA was extracted from blood.

All specimens and clinical information were collected under Institutional Review Board (IRB)-approved protocols.

Pathology and mutation analysis

Dedicated breast pathologists at MDACC reviewed all pathologic specimens. Diagnosis of invasive TNBC cancer was made by core-needle biopsy of the breast tumor. Clinical stage was defined by the sixth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. The histologic type of all tumors was defined according to the World Health Organization's classification system. Tumor grade was defined according to the modified Black's nuclear grading system. TNBC was defined as negative ER, PR, and HER2 status. Immunohistochemical analysis to determine ER and PR status was performed using standard immunohistochemistry (IHC) procedures with monoclonal antibodies. Nuclear staining less than or equal to 5% was considered a negative result. HER2 status was evaluated by IHC or by fluorescence *in situ* hybridization (FISH). HER2-negative tumors were defined as 0 or 1+

receptor overexpression on IHC staining and/or lack of gene amplification found on FISH testing (ratio equal or greater than 2.0).

DNA Extraction from frozen tissues was performed using sections in Tissue-Tek OCT (QIAGEN), which were homogenized using a TissueRuptor (QIAGEN) after adding QIAzol lysis reagent. A QIAamp DNA MiniKit (QIAGEN) was used to isolate DNA per manufacturer's protocol with overnight incubation (56°C) and RNaseA treatment.

BRCA sequencing was performed at Myriad Genetics research laboratory. For mutation screening, PCR was performed on 2 ng DNA in a 3 μ L reaction using the primers flanking the exons of *BRCA1/BRCA2* that are used in the *BRCA*Analysis (Myriad Genetics,) clinical test with the following cycling conditions: 95°C for 10 minutes, 35 cycles of 95°C for 30 seconds, 62°C for 30 seconds, and 72°C for 1 minute, finishing with 72°C for 1 minute. Each PCR product was treated with 0.1 U Shrimp Alkaline Phosphatase (Sigma-Aldrich Inc.) The PCR product was diluted 1:9 and 0.8 μ L was used for cycle sequencing with Big Dye Sequencing Chemistry and Taq FS (Applied Biosystems). Cycle conditions were 95°C for 3 minutes, 32 cycles of 95°C for 30 seconds, 50°C for 30 seconds, 60°C for 3 minutes, 72°C for 10 minutes. Sequence products were run on a Megabace 4500 automated sequencer (GE) per manufacturer's protocol.

BRCA1/BRCA2 mutations were only included in the analyses described in the following text, if classified as deleterious or suspected deleterious based on established criteria (9). In patients in whom *BRCA1/BRCA2* mutations were identified, germline DNA (from blood or normal breast) was used to test for *BRCA1/BRCA2* mutations. Patients with mutations in tumor and normal tissue were classified as having germline mutations, patients with mutations in the tumor but not normal tissue were classified as having somatic mutations.

Statistical methods

Patient characteristics have been tabulated and described by their medians or ranges, and compared between groups (mutation carriers vs. wild type) by a chi-square test or Wilcoxon's rank-sum test, as appropriate. Time to recurrence was measured from the date of diagnosis to the date of local or systemic recurrence or the last follow-up. Patients who died before experiencing a disease recurrence were considered censored at their date of death in the analysis of RFS. Survival time was measured from the date of diagnosis to the date of death, or the last follow-up. Median survival time was calculated as the median observation time among all patients.

Survival outcomes were estimated according to the Kaplan-Meier product limit method and compared between groups by the log-rank statistic. Cox proportional hazard model was employed to determine the association of breast cancer subtype with the risk of recurrence after adjustment for other significant patient and disease characteristics. All terms that were significantly associated with

Table 1. Patient and tumor characteristics

Characteristic	Total		BRCA		BRCA		P
	n	%	Mutant n	Wild type %	n	%	
Age at Diagnosis	77	100%	15	19.5%	62	80.5%	–
Median	51	(27–83)	45	(27–61)	53	(28–83)	0.0051
Race							
Black	18	23.37%	2	13.33%	16	25.81%	
Hispanic	8	10.38%	3	20.00%	5	8.06%	
White	50	64.93%	10	66.67%	40	64.52%	
Other	1	1.29%	0	0.00%	1	1.61%	0.4385
Menopausal Status							
Premenopausal	29	37.66%	8	53.33%	21	33.87%	
Postmenopausal	48	62.33%	7	46.67%	41	66.13%	0.2718
Histology							
Ductal	64	83.11%	12	80.00%	52	83.87%	
Other	13	16.88%	3	20.00%	10	16.13%	0.7096
Pathological stage							
I and II	47	61.03%	8	53.33%	39	62.90%	
III	30	38.96%	7	46.67%	23	37.10%	0.6988
Nuclear grade							
2	5	6.49%	2	13.33%	3	4.84%	
3	70	90.90%	13	86.67%	57	91.94%	0.2598
Lymphovascular invasion							
Positive	18	23.37%	3	20.00%	15	24.19%	
Negative	57	74.02%	12	80.00%	45	72.58%	1.0
Adjuvant chemotherapy							
Anthracycline-based	1	1.3%	1	6.7%	0	0%	
Anthracycline/Taxane-based	75	97.4%	13	86.7%	62	100%	
None	1	1.3%	1	6.7%	0	0%	0.036
Adjuvant radiotherapy							
Yes	42	54.5%	8	53.3%	34	54.8%	
No	35	45.5%	7	64.7%	28	45.2%	0.91
Surgery type							
Breast Conservation	25	32.5%	3	20%	22	35.5%	
Mastectomy	52	67.5%	12	80%	40	64.5%	0.36
Contralateral prophylactic							
Mastectomy	10	13%					
Yes	67	87%	5	33.3%	5	8.1%	
No			10	66.7%	57	91.9%	0.02

recurrence-free survival (i.e., $P < 0.05$) were considered and included in a multivariable model. Final model was based on either statistical or clinical significance. All analyses were performed using R 2.10.1 (R Development Core Team <http://www.R-project.org>).

Results

As part of a TNBC molecular characterization project we identified and extracted 96 primary frozen tumors from the frozen tumor bank. Normal tissues were available in 77 cases. Looking at the current definition of TNBC with ER

and PR negativity as less than 1% nuclear staining (10), 3 patients in the cohort had ER staining more than 1% (2 had scant 1%, and 1 had 3%). The patients' characteristics are summarized in Table 1. Median age was 51 years (range 27–83 years). Of the 77 patients identified, 15 (19.5%) had BRCA mutations: 12 (15.6%) in BRCA1, one of them somatic, and 3 (3.9%) in BRCA2. Table 2 describes the complete list of deleterious mutations found in the cohort. Compared with wild type, patients with BRCA mutations tended to be younger, ($P = 0.005$). Nuclear grade, histology, and pathology stage were not significantly associated with mutation status.

Table 2. BRCA deleterious mutations

Germline	Somatic
<i>BRCA1</i> 187delAG (n = 3)	<i>BRCA1</i> S451X (1471C>G)
<i>BRCA1</i> 2795delAAAG	
<i>BRCA1</i> M1775R (5443T>G)	
<i>BRCA1</i> 3829delT	
<i>BRCA1</i> C61G (300T>G)	
<i>BRCA1</i> E29X (204G>T)	
<i>BRCA1</i> S451X (1471C>G)	
<i>BRCA1</i> E1134X (3519G>T)	
<i>BRCA1</i> Del Exon 17	
<i>BRCA2</i> 5804del4	
<i>BRCA2</i> 5578delAA	
<i>BRCA2</i> E3111X (9559G>T)	

In general, of 77 patients, 33 (43%) were referred to genetic counseling for evaluation. Twenty-two patients (30%) had a positive family history for breast and/or ovarian cancer. Twelve of these patients had at least one first-degree family member diagnosed with either malignancy. From these 22 patients, 12 were referred to genetic evaluation and 8 were tested, 5 of whom tested positive for a deleterious mutation in *BRCA1*. From the 33 patients referred to genetic counseling, genetic testing was recommended to 28 and completed on 17. Eleven patients declined testing, 1 patient declined counseling.

Six of the 14 germline mutation carriers and the patient who has the tumor with the somatic *BRCA1* mutation were not referred to genetic counseling. Nine out of the 14 germline mutation carriers had no first-degree family history of breast and/or ovarian cancer. Two patients refused testing, and testing was not recommended in 2 as they did not meet standard guidelines for testing.

Treatment information is summarized in Table 1. Twenty-five (37.8%) patients were treated with breast-conserving treatment and 52 with mastectomy. All 25 patients who underwent breast-conserving surgery received adjuvant radiation therapy. There were no significant differences in the type of primary surgery or the use of adjuvant radiotherapy. However, more patients with *BRCA* mutations underwent a contralateral prophylactic mastectomy. Contralateral prophylactic mastectomy was done in 5 patients with *BRCA* mutations. Two patients declined; 1 patient did not show up for genetics; 4 patients were not referred to genetics; and 1 patient had metastatic ovarian cancer.

All patients but one received adjuvant chemotherapy. Adjuvant chemotherapy consisted of FAC [5 fluorouracil 500 mg/m² intravenously (i.v.) on days 1 and 4, doxorubicin 50 mg/m² i.v. continuous infusion over 72 hours and cyclophosphamide 500 mg/m² i.v. on day 1, every 3 weeks] for 4 to 6 courses (1 patient), FEC (5 fluorouracil 500 mg/m² i.v., epirubicin 100 mg/m² i.v., and cyclophosphamide 500 mg/m² i.v. on day 1, every 3 weeks) for 4 cycles and taxane (paclitaxel 175–250 mg/m², or doc-

etaxel 100 mg/m² every 21 days for 4 cycles, or paclitaxel 80 mg/m² weekly for 12 weeks).

At a median follow-up of 43 months (range 7–214 months), there were 33 (42.9%) recurrences and 35 (45.5%) deaths. Three patients died without relapse and only 1 patient who had relapsed is still alive. Survival estimates are summarized in Table 3. Five-year RFS estimates were 51.7% for wild-type patients versus 86.2% for patients with *BRCA* mutations, ($P = 0.031$); and 5-year OS estimates were 52.8% for wild-type patients versus 73.3% for patients with *BRCA* mutations, ($P = 0.225$). The Kaplan–Meier plots for RFS and OS by mutational status are shown in Figure 1A and B.

Table 4 summarizes the results of the multivariable models for RFS and OS. After adjustment for other patient characteristics, patients with *BRCA* mutations had a significantly better RFS (HR: 0.19, 95% CI: 0.045–0.79, $P = 0.016$) compared with no mutation carriers.

Discussion

In this unselected cohort of patients with TNBC, we found a 19.5% incidence of *BRCA* mutations. The frequency of somatic and germline *BRCA* mutations in unselected TNBC has not been described before. In this unselected cohort of patients with TNBC, we found a 19.5% incidence of *BRCA* mutations. From all 77 patients, 35 were referred to genetic counseling for evaluation. Genetic testing was recommended to 30 and completed on 23. Six mutation carriers and the patient with a somatic *BRCA1* mutation were not referred to genetic counseling due to perceived low risk because they were older than 45 years or did not have a first-degree family member with breast or ovarian cancer (adequate family size).

Several studies, however, have reported the frequency of germline *BRCA1* mutations in small selected cohorts of ER-negative breast cancer as being between 24% and 29% (11–13). Liderau and colleagues examined 70 patients with ER-negative and high-grade breast cancer diagnosed before age 35 and found a 28.6% of *BRCA1* germline mutation rate compared with only 3.6% in their general tumor registry, odds ratio (OR): 10.8, 95% CI: 1.28–127.70, $P = 0.007$. Interestingly, only one of the patients with a *BRCA1* germline mutation had a significant family history (10). In a prospective, systematic study of 76 consecutive breast cancer patients younger than 45 years, 25% of patients with ER-negative and high-grade breast cancers were found to harbor germline mutations in *BRCA1*, 5.6% of *BRCA1*-associated breast cancers did not have this morphological profile compared with 94.4% patients without *BRCA1* mutations, OR: 5.67, 95% CI: 1.04–32, $P = 0.05$ (12). To test the hypothesis that germline *BRCA1*-related breast cancers were more likely than non-*BRCA1/2*-related breast cancers to express a basal epithelial phenotype, investigators reviewed 292 breast cancer specimens previously analyzed for ER, HER2, p53, and germline mutations in *BRCA1* and *BRCA2*. They identified 76 tumors from patients of Ashkenazi Jewish origin that did not

Table 3. Survival estimates

RFS estimates					
	n risk at	n events	5-year estimate	95% CI	P
All		33	57.8%	(47.3%, 0.6%)	
Race					
Black	18	10	38.7%	(20.4, 73.3%)	
Hispanic	8	2	75.0%	(50.3%, 100%)	
White	50	20	63.6%	(51.5, 78.6%)	
Other	1	1	-	-	0.237
Age					
≤ 50	36	13	65.3%	(50.2%, 85.0%)	
> 50	41	20	51.2%	(38.0%, 69.1%)	0.121
Menopausal status					
Premenopausal	29	12	62.8%	(46.5%, 84.7%)	
Postmenopausal	48	21	54.6%	(41.7%, 71.5%)	0.553
Histology					
Ductal	64	28	57.7%	(46.4%, 71.8%)	
Other	13	5	59.8%	(37.8%, 94.7%)	0.951
Pathological stage					
I and II	47	13	74.1%	(61.7%, 89.0%)	
III	30	20	32.3%	(19.1%, 54.7%)	<0.001.
Nuclear grade					
2	5	1	80.0%	(51.6%, 100%)	
3	70	32	54.9%	(43.9%, 68.8%)	0.264
Lymphovascular invasion					
Positive	18	10	44.4%	(26.5%, 74.5%)	
Negative	57	22	62.3%	(50.1%, 77.3%)	0.073
Mutation status					
Mutant	15	2	86.2%	(70.0%, 100%)	
Wild type	62	31	51.7%	(40.3%, 66.7%)	0.031
OS estimates					
	n risk at	n Events	5-year estimate	95% CII	P
All		35	55.9%	(44.7%, 70.0%)	
Race					
Black	18	10	30.8%	(11.8%, 80.5%)	
Spanish/Hispanic	8	2	75.0%	(50.3%, 100%)	
White	50	22	62.7%	(50.2%, 78.2%)	
Other	1	1	-	-	0.006
Age					
≤ 50	36	15	60.7%	(44.6%, 82.7%)	
> 50	41	20	53.4%	(40.1%, 71.2%)	0.279
Menopausal status					
Premenopausal	29	13	59.7%	(42.0%, 84.9%)	
Postmenopausal	48	22	54.8%	(41.9%, 71.6%)	0.626
Histology					
Ductal	64	29	57.0%	(44.8%, 72.6%)	
Other	13	6	51.3%	(29.6%, 88.8%)	0.681
Pathological stage					
I and II	47	14	73.3%	(59.4%, 90.6%)	
III	30	21	29.6%	(17.0%, 51.7%)	<0.001.

(Continued on the following page)

Table 3. Survival estimates (Cont'd)

	RFS estimates				
	<i>n</i> risk at	<i>n</i> events	5-year estimate	95% CI	<i>P</i>
Nuclear grade					
2	5	2	80.0%	(51.6%, 100%)	0.675
3	70	33	52.8%	(41.0%, 68.1%)	
Lymphovascular invasion					
Positive	18	10	44.4%	(26.5%, 74.5%)	0.246
Negative	57	24	59.5%	(46.2%, 76.7%)	
Mutation status					
Mutant	15	4	73.3%	(54.0%, 99.5%)	0.225
Wild type	62	31	52.8%	(40.7%, 68.5%)	

overexpress ER or HER2, 40 of which expressed epithelial cytokeratin 5 and/or 6. Germline *BRCA1* mutations were present in 17 (23.6%) of the 72 patients. In univariate analysis, the expression of cytokeratin 5/6 was associated with *BRCA1*-related breast cancers, OR: 9.0, 95% CI: 1.9 to 43, $P = 0.002$ (13).

Two studies have looked at the incidence of germline *BRCA1/2* mutations in selected patients with TNBC. The first one studied 54 women with high-grade TNBC at or before age 40. Patients were selected because they had little or no family history of breast or ovarian cancer and did not qualify for genetic testing using conventional family history criteria. All coding exons of *BRCA1* and the 2 large exons of *BRCA2* were screened. All mutations were confirmed with direct sequencing. Five deleterious germline *BRCA1* mutations and one deleterious *BRCA2* mutation (11% total)

were identified (14). The second study evaluated the prevalence of germline *BRCA1* mutations in 177 women with TNBC and compared the observed with the estimated prevalence according to an established risk calculation model. Observed and expected number of *BRCA1* mutations were compared by a Poisson test. *BRCA1* mutations were detected in 11.3%, and mutation prevalence was significantly higher than estimated by Myriad prevalence tables in the entire group (15). They also found that TNBC diagnosis improved identification of *BRCA1* mutation carriers when considered with age at diagnosis and family history. Diagnosis of TNBC was most informative for women younger than 50, without family history (15).

Information on *BRCA* status is now important not only to address the risk of breast and ovarian cancer, but also to select therapies. *BRCA1* and *BRCA2* play a critical role in

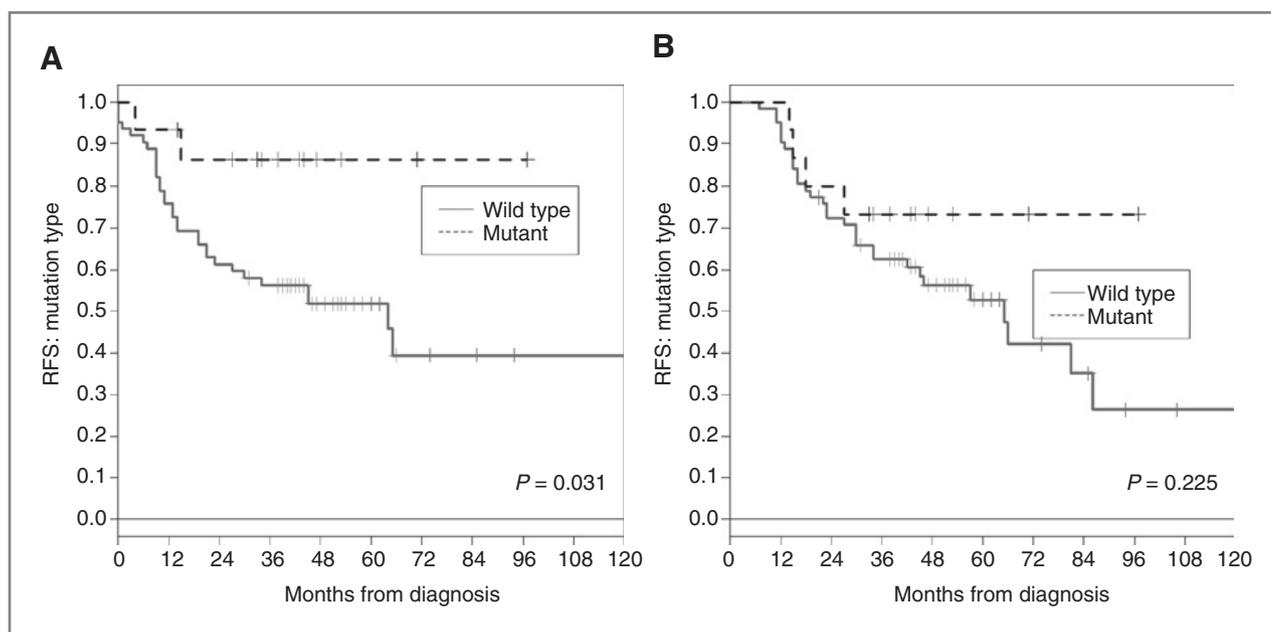


Figure 1. Kaplan-Meier survival plots for recurrence-free survival (A), and overall survival (B) by mutation status.

Table 4. Multivariable Cox proportional hazards models

RFS estimates			
	HR	95% CI	P
Mutation status			
Wild type	1.0	(0.041, 0.72)	0.016
Mutant	0.17		
Pathological stage			
I and II	1.0	(2.55, 11.10)	<0.0001
III	5.32		
Nuclear grade			
2	1.0	(0.16, 9.65)	0.830
3	1.25		
OS estimates			
	HR	95% CI	P
Mutation status			
Wild type	1.0	(0.16, 1.29)	0.138
Mutant	0.45		
Pathological stage			
I and II	1.0	(2.16, 9.12)	<0.0001
III	4.44		
Nuclear grade			
2	1.0	(0.14, 2.85)	0.550
3	0.63		

DNA repair by homologous recombination (16). PARP1 inhibitors demonstrated synthetic lethality with *BRCA1/BRCA2* dysfunction in homologous recombination deficient breast cancers and have shown efficacy as single agents in clinical trials in germline *BRCA* mutation carriers (17). The frequency of somatic *BRCA1/2* mutations and expression loss are sufficiently common in ovarian cancer to warrant assessment of tumors in addition to germline DNA for patient selection for clinical trials of PARP1 inhibitors (18–20). On the other hand, somatic mutations were rare in TNBC, with only 1 somatic mutation identified in 77 patients. However, our unselected patient cohort of TNBC shows a 19.5% incidence of *BRCA* deleterious mutations and almost half of the mutation carriers were not referred or tested mostly due to insufficient documented risk such as older age and lack of first-degree relatives or insurance difficulties. Further, in recent work from our institution to estimate the costs and benefits of different *BRCA* testing criteria for women with breast cancer under age 50, using a Markov Monte Carlo simulation comparing 6 reference criteria for *BRCA* testing showed that testing women with triple-negative breast cancers under age 50 was the most cost-effective strategy and could reduce future breast and ovarian cancer cases by 26% and 45%, respectively, compared with the reference strategy (21). Although our cohort is small, our data and the aforementioned results should

prompt us to discuss genetic counseling with patients with TNBC.

Mutations of *BRCA1/2* in TNBC were associated with better RFS after surgery and anthracycline and taxane-based chemotherapy, ($P = 0.031$). However, this benefit did not reach statistical significance for OS, ($P = 0.225$). After adjustment for other patient characteristics, patients with *BRCA* mutations had a significantly better RFS (HR: 0.19, 95% CI: 0.045–0.79, $P = 0.016$) compared with no mutation carriers. The prognosis of *BRCA*-associated breast cancer was elegantly summarized on a meta-analysis of the literature last year (22). They reviewed the clinical studies relevant to the prognostic associations of *BRCA1*- and *BRCA2*-associated breast cancers. Due to the methodologic limitations of earlier studies, they divided their analysis into early and more recent studies. Early studies published in the 1990s provided inconclusive results. However, more recent studies using improved methodology to ascertain prognosis failed, for the most part, to demonstrate a significant overall survival difference between *BRCA*-associated breast cancer and sporadic breast cancer. In one study, *BRCA1* mutation carriers had increased breast cancer mortality, but only if they did not receive chemotherapy (22). In a recent report, investigators studied the 10-year overall survival in a Caucasian population with high probability of hereditary breast cancer. They classified 5,923 patients registered into 3 different mutation risk categories: No family history of breast cancer slightly increased to intermediate risk and high risk. A total of 1,011 patients at high risk and increased to intermediate risk were tested for *BRCA1/2* mutations with a 22.8% (73/320) and 1.0% (7/691) mutation rate, respectively. In total, 80 patients were *BRCA1* carriers. OS was significantly better for patients in the high-risk category compared with patients in the intermediate risk category or who had sporadic breast cancer (82% vs.75% vs.73%, respectively; $P < 0.0001$). Comparing *BRCA1* mutation carriers with *BRCA*-negative and tested, and sporadic breast cancer patients, the OS estimates were 77% versus 77% versus 73%, respectively; $P < 0.001$. After adjustment for other patient characteristics, patients with *BRCA1* mutations had a significantly better OS (HR: 0.29, 95% CI: 0.13–0.62, $P = 0.02$) compared with patients with sporadic breast cancer (23). These data are intriguing and should direct us to study if the biology of TNBC with *BRCA* mutations is different compared with other TNBC, and if these tumors are more sensitive to standard adjuvant chemotherapy agents for breast cancer.

Although small, our unselected patient cohort of TNBC shows an important incidence of deleterious *BRCA* mutations, suggesting that genetic testing should be discussed with patients with TNBC. Also, it agrees with previous studies that show no difference or improved outcomes in mutation carriers. Further study is needed to determine whether *BRCA* status is indeed prognostic in patients with TNBC, or whether it is predictive of benefit from the systemic therapy regimens used in this patient cohort. It also suggests that testing either tumor or germline DNA of patients with TNBC is likely to identify a number of

patients that could potentially benefit from PARP inhibitor therapy that would not be selected based on current BRCA mutation testing approaches based on family history.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interests were disclosed.

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