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ORIGINAL REPORT

Clinical and Pathologic Characteristics of Patients With *BRCA*-Positive and *BRCA*-Negative Breast Cancer

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ABSTRACT

Purpose
Mutations in the *BRCA1* and *BRCA2* genes confer greater risk of developing breast cancer. We determined whether tumor pathologic features and clinical features differ in patients with and without *BRCA* mutations.

Patients and Methods
Tumor pathologic features and clinical characteristics were examined in 491 women with breast cancer who underwent genetic testing for *BRCA* mutations between 1997 and 2006. A retrospective review of medical records was conducted to determine clinical characteristics including ethnicity, age and clinical stage at diagnosis, age at parity, number of full-term pregnancies, use of oral contraceptives and hormone replacement therapy, and *BRCA* mutation status. Tumor pathology was reviewed to determine histologic type, tumor grade, and estrogen receptor, progesterone receptor, and HER-2/*neu* status.

Results
Of the 491 patients with identified breast cancers, 391 patients were *BRCA* negative, and 86 patients were *BRCA* positive. Triple-negative breast cancer (ie, those with negative estrogen receptor, progesterone receptor, and HER-2/*neu* status) was diagnosed in 57.1% of the *BRCA1*-positive patients, 23.3% of the *BRCA2*-positive patients, and 13.8% of the *BRCA*-negative patients. *BRCA1* mutation carriers had higher nuclear grade tumors than the other two groups ($P < .001$). Of the triple-negative cancer patients, *BRCA2* mutation carriers were older when diagnosed than *BRCA1* mutation carriers and noncarriers ($P < .01$).

Conclusion
These results suggest that tumors associated with *BRCA1* mutations may be divided into two distinct groups, triple-negative and non–triple-negative groups. Future studies should seek to determine whether patients with *BRCA1* mutations and triple-negative breast cancer respond to treatment better than BRCA-negative patients with similar tumor pathology.

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INTRODUCTION

Mutations in the tumor suppressor genes *BRCA1* and *BRCA2* are believed to be responsible for the majority of hereditary breast cancer cases. It is estimated that women with *BRCA1* and *BRCA2* mutations have a lifetime risk of developing breast cancer as high as 87%.[1,2] However, evidence indicating whether overall prognosis is poorer for women who have *BRCA*-related cancers has not been conclusive.[3,4] Currently, treatment recommendations for BRCA-related cancers are similar to those for sporadic breast cancers. It is possible that as treatment regimens become more tumor specific, future patients with *BRCA* mutations will be treated differently. Thus, it is important to determine clinical characteristics and tumor pathologic features in *BRCA* carriers that may affect treatment recommendations.

Breast cancer patients display diverse pathologic and clinical features, some of which have prognostic significance. Recent research has defined distinct subtypes of breast cancer using gene expression patterns.[5-7] Based on the molecular profiling of tumors, breast cancers have been divided into those with high expression of the estrogen receptor (ER) gene (luminal A and luminal B subtypes), and those that do not express ER.[5] Within the ER-negative group, tumors that overexpress the *HER2/neu* oncogene are named the HER-2/*neu*–positive subtype.[5] ER-negative tumors that express genes found in basal epithelial cells and can be stained with antibodies to keratin 5/6 have been identified as basal-like tumors.[5] A majority of these basal-like tumors are

believed to consist of tumors that do not express ER, progesterone receptor (PR), or HER-2/*neu* (ie, triple-negative tumors).[8] Several studies have demonstrated that *BRCA1*-mutation carriers are more likely to be diagnosed with triple-negative breast cancer than noncarriers.[9-11] In contrast, carriers of *BRCA2* mutations seem to share similar pathologic characteristics with noncarriers.[12,13] However, previous studies have been limited by relatively small sample sizes. In addition, important clinical information that may influence tumor development has been largely ignored by previous studies. Thus, the purpose of this study is to determine the pathologic characteristics of breast cancers in patients with and without a *BRCA* mutation, and to describe the clinical features of this population.

PATIENTS AND METHODS

Study Population

Between 1997 and 2006, 1,510 women were seen at the Department of Clinical Cancer Genetics at The University of Texas M. D. Anderson Cancer Center, and underwent *BRCA* genetic testing; 913 of these women were diagnosed with breast cancer. Of these, 491 women had pathology reports with complete ER, PR, and HER-2/*neu* status available for review and were thus included in the study. For these 491 women, electronic medical records were reviewed to extract data on clinical characteristics, including ethnicity, age, and clinical stage at diagnosis; age at parity; number of full-term pregnancies; use of oral contraceptive pills and hormone replacement therapy; and genetic-test results for mutations in the *BRCA1* and *BRCA2* genes. This retrospective study was approved by The University of Texas M. D. Anderson Cancer Center review board.

Tumor Pathology

Tumor pathology for 491 patients with breast cancer was reviewed by one of our designated breast pathologists. Information regarding the histologic type of breast cancer; tumor grade using the modified Black's nuclear grading system; and ER, PR, and HER-2/*neu* status of breast cancer samples were obtained from the patients' institutional pathology reports. All invasive breast cancer specimens were routinely evaluated for ER, PR, and HER-2/*neu* status using immunohistochemistry (IHC). Cases with HER-2/*neu* staining of 1+, 2+ or 3+ on IHC analysis were further evaluated by fluorescent in situ hybridization for amplification of the *HER2/neu* gene.

Statistical Analysis

The Kruskal-Wallis exact test was used to compare the number of full-term pregnancies and the median age at diagnosis, menarche, and first full-term pregnancy across the three patient groups (BRCA-negative, *BRCA1* mutation carriers, and *BRCA2* mutation carriers). A *P* value less than .05 was considered significant for accepting the hypothesis that at least two of the medians were significantly different from each other. A Wilcoxon rank sum test was used to compare median age at diagnosis, median age at menarche, median age at parity, and number of full-term pregnancies with receptor status in the *BRCA1* mutation group.

Fisher's exact test was used to assess the association between type of receptor (ER, PR, or HER-2/*neu*), fluorescent in situ hybridization for HER-2/*neu*, nuclear grade, and clinical stage across the BRCA groups. The same test was used when menopause status, use of birth control, use of hormone replacement therapy, and ethnicity were compared across the *BRCA* groups and by receptor status in the *BRCA1* group. A *P* value less than .05 using the

Table 1. Association Between Receptor, ER, PR, HER-2/*neu*, HER-2/*neu* (FISH), Nuclear Grade, and Clinical Stage and *BRCA* Status

	BRCA Status						
	Noncarriers (n = 391)		*BRCA1* Mutation Carriers (n = 56)		*BRCA2* Mutation Carriers (n = 30)		
Covariate	No. of Patients	%	No. of Patients	%	No. of Patients	%	*P**
Receptor							
Nontriple negative	337	86.2	24	42.9	23	76.7	< .001
Triple negative	54	13.8	32	57.1	7	23.33	
ER							
Negative	90	23.0	38	69.1	8	27.6	< .001
Positive	301	76.9	17	30.9	21	72.4	
PR							
Negative	143	37.2	37	71.2	10	34.5	< .001
Positive	241	62.7	15	28.9	19	65.5	
HER-2/*neu* (IHC)							
Negative	229	85.8	37	97.4	23	95.8	.06
Positive	38	14.2	1	2.6	1	4.2	
HER-2/*neu* (FISH)							
Negative	152	74.5	22	88.0	15	88.2	.23
Positive	52	25.5	3	12.0	2	11.8	
Nuclear grade							
1	43	12.6	2	4.2	1	4.4	< .001
2	167	49.0	5	10.4	9	39.1	
3	131	38.4	41	85.4	13	56.5	
Clinical stage							
1	85	28.4	16	34.0	12	44.5	.58
2	137	45.8	18	38.3	11	44.7	
3	74	24.8	13	27.7	4	14.8	
4	3	1.0	0	0	0	0	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor 2; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization.
*Using Fisher's exact test.

two-tailed Fisher's exact test was considered statistically significant. All of the statistical analyses were performed using SAS version 9.1 for Windows (SAS Institute, Cary, NC).

RESULTS

Of the 491 women included in this study, 391 women (79.6%) tested negative for mutations in the *BRCA1* or *BRCA2* genes, 56 women (11.4%) had a *BRCA1* mutation, 30 women (6.1%) had a *BRCA2* mutation, 13 women (2.6%) had variants of uncertain significance in *BRCA1* or *BRCA2*, and one woman (0.2%) had mutations in both *BRCA1* and *BRCA2*. Because the number of women who had variants of uncertain significance or mutations in both genes was too small to produce statistically valid results, these women were excluded from further analysis.

Triple-negative breast cancer was detected in 93 women. Of the women diagnosed with triple-negative breast cancer, 54 women (58.1%) were *BRCA* negative, 32 women (34.4%) were *BRCA1* positive, and seven women (7.5%) were *BRCA2* positive. The remainder of the study population was positive for the expression of at least one hormone receptor, or had HER-2/*neu*–positive disease. *BRCA1* carriers were more likely to be diagnosed with triple-negative breast cancer than noncarriers or *BRCA2* carriers (Table 1; $P < .001$). When each receptor was examined alone, *BRCA1*-associated cancers were more frequently ER and PR negative than were *BRCA*-negative and *BRCA2*-associated cancers ($P < .001$). HER-2/*neu* expression, as detected by either IHC or fluorescent in situ hybridization, did not differ significantly between mutation carriers and noncarriers ($P = .06$ and .23, respectively). *BRCA1* mutation carriers had higher nuclear grade tumors than did *BRCA*-negative women or *BRCA2* mutation carriers ($P < .001$). The ER, PR, and HER-2/*neu* status and nuclear grade of *BRCA2*-associated cancers were similar to those of *BRCA*-negative cancers (Table 1). The clinical stages at diagnosis of mutation carriers and noncarriers were similar ($P = .58$).

Within the *BRCA1* mutation carriers, 32 carriers (57.1%) had triple-negative breast cancer and 24 carriers (42.9%) had non–triple-negative breast cancer. There was a trend for *BRCA1* carriers with triple-negative disease to have higher nuclear grade tumors than non–triple-negative *BRCA1* carriers (Table 2; $P = .06$). However, the age at diagnosis and clinical stage did not differ between the two groups ($P = .44$ and .80, respectively).

Breast cancer risk factors did not differ between women with or without *BRCA* mutations. Ethnic background was similar in mutation carriers and noncarriers ($P = .78$). Although there was a trend for *BRCA1* carriers to be diagnosed at a younger age, this did not reach statistical significance (Table 3; $P = .07$). The median age of menarche ranged from 12 to 13 years and was similar between groups ($P = .43$). The median age of first full-term pregnancy and number of full-term pregnancies did not differ significantly between *BRCA*-positive and *BRCA*-negative women ($P = .31$ and .87, respectively). Women in the three mutation status groups were equally likely to have a history of using oral contraceptive pills (Table 3; $P = .94$). Menopause status at the time of diagnosis did not differ between *BRCA* mutation carriers and noncarriers. In contrast, the history of hormone replacement therapy differed between the three groups ($P < .05$); more women who were BRCA negative or who were *BRCA2* mutation carriers had received hormone replacement therapy than women who were *BRCA1* mutation carriers.

Table 2. Association Between Age of Diagnosis, Nuclear Grade, and Clinical Stage, and Triple-Negative Status in *BRCA1* Mutation Carriers

	Receptor Status				
	Triple Negative (n = 32)		Nontriple Negative (n = 24)		
Covariate	No. of Patients	%	No. of Patients	%	*P*
Age at diagnosis, years					
No. of observations	32		24		
Median	41.5		42.5		.44*
Range	27-71		25-61		
Nuclear grade					
1	0	0.0	2	10.0	.06†
2	2	6.5	3	15.0	
3	29	93.5	15	75.0	
Clinical stage					
1	9	30.0	7	41.2	.80†
2	12	40.0	6	35.3	
3	9	30.0	4	23.5	
4	0	0.0	0	0.0	

*Using Wilcoxon rank sum test.
†Using Fisher's exact test.

The breast cancer risk factors in triple-negative carriers and noncarriers of *BRCA1* and *BRCA2* mutations were also compared. Among the patients with triple-negative breast cancer, *BRCA2*-associated cancers were diagnosed at a later age than were *BRCA1*- and *BRCA*-negative cancers (Table 4; $P < .01$). As in the general study population, age of menarche, age at parity, number of full-term pregnancies, and use of oral contraception were similar between *BRCA* carriers and noncarriers (Table 4). Although *BRCA2* mutation carriers were more likely than noncarriers to be diagnosed postmenopausal and to have a higher frequency of prior hormone replacement therapy, these did not reach statistical significance.

Within the *BRCA1* carriers, the majority of clinical characteristics were similar between women with triple-negative cancer and women with non–triple-negative cancer. Although age at menarche was younger in women with triple-negative cancer (Table 5; $P < .05$), age at parity, number of full-term pregnancies, menopause status, history of oral contraceptive use, and history of hormone replacement therapy use was similar between the two groups.

DISCUSSION

In this study, we identified clinical and pathologic characteristics of tumors in a cohort of women with *BRCA*-positive and *BRCA*-negative breast cancer. Significantly more of the *BRCA1*-related breast cancers were triple negative than were the BRCA-negative and *BRCA2*-related breast cancers. In addition, significantly more *BRCA1*-related cancers were poorly differentiated and had a higher modified Black's nuclear grade. Although the median age at diagnosis was similar in *BRCA1* mutation carriers, *BRCA2* mutation carriers, and *BRCA*-negative women when receptor status was not considered, women with triple-negative breast cancer who were *BRCA2* mutation carriers were diagnosed at a later age than were *BRCA1* mutation carriers and noncarriers. It is possible that referral bias reduced the ability to detect

Table 3. Association Between Age at Diagnosis, Age at Menarche, Age at Parity, Number of Full-Term Pregnancies, Menopause Status, Use of Oral Contraceptives, Hormone Replacement Therapy, Ethnicity, and *BRCA* Group

	BRCA						
	Noncarriers (n = 391)		*BRCA1* Mutation Carriers (n = 56)		*BRCA2* Mutation Carriers (n = 30)		
Variable	No. of Patients	%	No. of Patients	%	No. of Patients	%	*P*
Age at diagnosis, years							.07*
No. of observations	391		56		30		
Median	44		42		43		
Range	21-75		25-71		30-67		
Age at menarche, years							.43*
No. of observations	367		54		30		
Median	12		13		13		
Range	8-18		9-18		11-15		
Age at parity, years							.31*
No. of observations	303		45		27		
Median	26		25		25		
Range	15-42		16-40		19-43		
No. of full-term pregnancies							.87*
No. of observations	383		55		30		
Median, years	2		2		2		
Range, years	0-9		0-10		0-4		
Menopause status							
Premenopausal	226	60.7	39	69.6	14	46.7	.12†
Postmenopausal	146	39.3	17	30.4	16	53.3	
History of oral contraceptive use							
No	69	18.9	11	20.4	5	16.7	.94†
Yes	296	81.1	43	79.6	25	83.3	
History of hormone replacement therapy use							
No	285	78.1	49	90.7	21	70.0	.04†
Yes	80	21.9	5	9.3	9	30.0	
Ethnicity							
White	280	71.9	41	73.2	20	66.7	.78†
Hispanic	49	12.6	5	8.9	4	13.3	
Black	16	4.1	4	7.1	1	3.3	
Asian	9	2.3	1	1.83	2	6.7	
Ashkenazi Jew	35	9.0	5	8.9	3	10.0	

*P value from Kruskall-Wallis exact test.
†P value from Fisher's exact test.

differences in age and menopausal status between *BRCA* mutation carriers and noncarriers. Within our institution, physicians are likely to refer patients to genetic counseling and testing if they are younger than age 50 years when diagnosed with breast cancer, but only refer women diagnosed at an older age if they have a substantial family history of breast or ovarian cancer. Ideally, it would be beneficial to compare *BRCA1* and *BRCA2* mutation carriers with the general breast cancer population; however, this is difficult because family history information is often incomplete and not always accurate in patients who have not been seen by a genetic counselor.

Several studies have evaluated hormone receptor status in *BRCA1* mutation carriers. In 39 women, those with a *BRCA1* mutation or a known familial *BRCA1* mutation more frequently had ER- and PR-negative tumors than control participants.[14] Studies of women in several different ethnic groups, including Ashkenazi Jew, Japanese, and Swede, have demonstrated that *BRCA1* mutation carriers were more likely to have ER-negative breast cancer.[12,13,15,16] PR-negative breast cancer also has been associated with *BRCA1* mutation carriers.[12,15,16] However, the relationship between BRCA mutation status and HER-2/*neu* positivity has been inconsistent. In one study of six *BRCA1* mutation carriers, no association between HER-2/*neu* status and *BRCA1* status was found, although there was a trend for *BRCA1* carriers to have ER- or PR-negative disease more frequently than noncarriers.[17] However, in other studies, *BRCA1* status was associated with HER-2/*neu*–negative tumors.[13,16] Here, 38 of 56 *BRCA1*-related tumors were ER negative and 37 of 56 *BRCA1*-related tumors were PR negative, which is consistent with previous reports. In addition, we provide evidence from a larger cohort that HER-2/*neu* expression status was similar between *BRCA1* mutation carriers and noncarriers.

Previous reports describing the distribution of ER, PR, and HER-2/*neu* positivity in *BRCA* carriers have been inconclusive mainly because, in these studies, *BRCA1*- and *BRCA2*-mutation carriers were grouped together instead of being examined as two distinct groups.[18,19] In 58 Ashkenazi Jewish women, significantly fewer *BRCA1* and *BRCA2* mutation carriers had ER-, PR-, or HER-2/*neu*–positive disease than noncarriers.[18] In another study,[19] ER-positive disease was less common in 39 *BRCA1* and *BRCA2* mutation carriers

Table 4. Association Between Age at Diagnosis, Age at Menarche, Age at Parity, Number of Full-Term Pregnancies, Menopause, Oral Contraceptive and Hormone Replacement Therapy Use, and *BRCA* Group in the Triple-Negative Group of Patients Only

Variable	*BRCA* Status: No. of Noncarriers (n = 54)		No. of *BRCA1* Mutation Carriers (%), n = 32		No. of *BRCA2* Mutation Carriers (%), n = 7		*P*
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Age at diagnosis, years							.01*
No. of observations	54		32		7		
Median	42		41.5		52		
Range	24-69		27-71		50-54		
Age at menarche, years							.30*
No. of observations	49		32		7		
Median	12		13		13		
Range	8-16		10-17		11-14		
Age at parity, years							.36*
No. of observations	38		27		7		
Median	26		25		21		
Range	15-36		17-40		19-43		
No. of full-term pregnancies							.50*
No. of observations	54		32		7		
Median, years	2		2		2		
Range, years	0-9		0-10		1-3		
Menopause status							
Premenopausal	34	68.0	23	71.9	2	28.6	.10†
Postmenopausal	16	32.0	9	28.1	5	71.4	
History of oral contraceptive use							
No	6	11.8	7	22.6	1	14.3	.39†
Yes	45	88.2	24	77.4	6	85.7	
History of hormone replacement therapy use							
No	40	78.4	28	90.3	4	57.1	.09†
Yes	11	21.6	3	9.7	3	42.9	

*P value from Kruskall-Wallis exact test.
†P value from Fisher's exact test.

than noncarriers, but no differences were observed between the two groups in PR or HER-2/*neu* positivity. Although these authors reported finding no difference between *BRCA1* and *BRCA2* tumor pathology, the majority of participants (30 of 39) were *BRCA2* mutation carriers. Thus, it is possible that if more *BRCA1*-associated cancers had been examined, differences would have emerged.[19]

Several previous studies have examined the relationship between *BRCA* mutation status and triple-negative tumor pathology.[9-11,20] In these studies, 50% to 88% of *BRCA1* carriers were diagnosed with triple-negative breast cancer compared with 14.6% to 34% of *BRCA* noncarriers. In addition, because triple-negative tumors are believed to constitute a majority of the basal-like tumors reported,[8] it is relevant to note that in a series of studies by Foulkes et al,[21,22] *BRCA1*-related cancers were more likely to be basal-like than sporadic cancers. However, these studies have been limited by the number of *BRCA1*-related breast cancers examined. In this study, we expanded on these findings in a much larger cohort, in which we found 57.1% of *BRCA1* carriers (32 of 56) had triple-negative tumors, compared with 13.8% of *BRCA1* carriers in *BRCA* noncarriers. Together, this evidence indicates that a significant number of *BRCA1* patients are triple negative.

In our study, nuclear grade at diagnosis was higher for *BRCA1*-related breast cancers than for other breast cancers. This result is consistent with previous reports. In a study of Ashkenazi Jewish women, 76.5% of *BRCA1*-positive tumors had a high nuclear grade compared with only 27.3% of BRCA-negative tumors.[15] In a Swedish report, *BRCA1*-related tumors were more likely to have a nuclear grade of 3 than non-*BRCA* related tumors.[16] Several previous reports also have shown that *BRCA1*-related cancers were of a higher histologic grade.[9,10,13,16,18] Although another study[18] reported that nuclear grade did not differ in sporadic and *BRCA*-related tumors, this study analyzed *BRCA1* and *BRCA2* mutation carriers as one group. As our results have indicated, because *BRCA1*- and *BRCA2*-related tumors seem to have different pathologic characteristics, it is possible that combining these two groups obscured the differences in nuclear grade between *BRCA1* and sporadic cases.[18]

In this study, the pathology of *BRCA2*-related breast cancer was similar to that of *BRCA*-negative breast cancers. One previous study suggested that *BRCA2*-related cancers have tumor pathology that is between that of *BRCA1* and sporadic cancers; however, this study was limited by the small number of *BRCA2* patients available for examination.[14] Other research has demonstrated that *BRCA2*-associated breast cancers and sporadic breast cancers are equally likely to be triple negative[9] or to have tumor pathology similar to sporadic cases.[12,13]

Our study, like previous reports, suggests that *BRCA1* mutation carriers have tumor pathology that differs from BRCA-negative patients and *BRCA2* mutation carriers. Because of these differences, researchers have examined whether tumor biology can predict *BRCA*

Table 5. Association Between Age at Menarche, Age at Parity, Number of Full-Term Pregnancies, Menopause Status, History of Oral Contraceptive Use, and History of Hormone Replacement Therapy Use and Triple-Negative Status in *BRCA1* Mutation Carriers

Variable	Receptor Status				*P*
	Triple Negative (n = 32)		Nontriple Negative (n = 24)		
	No. of Patients	%	No. of Patients	%	
Age at menarche, years					
No. of observations	32		22		
Median	13		12		.04*
Range	10-17		9-18		
Age at parity, years					
No. of observations	27		17		
Median	25.5		25		.82*
Range	16-40		17-40		
No. of full-term pregnancies					
No. of observations	32		22		.13*
Median, years	2		2		
Range, years	0-10		0-3		
Menopause status					
Premenopausal	23	71.9	16	66.6	.77†
Postmenopausal	9	28.1	8	33.3	
History of oral contraceptive use					
No	7	22.6	4	17.4	.74†
Yes	24	77.4	19	82.6	
History of hormone replacement therapy use					
No	28	90.3	21	91.3	1.00†
Yes	3	9.6	2	8.7	

*Using Wilcoxon rank sum test.
†Using Fisher's exact test.

mutation status. In a study of 207 families, the sensitivity of *BRCA*-PRO, a traditional model of predicting mutations in the *BRCA* genes using family history information, was increased by including the ER and PR receptor status and pathologic grade of the tumor.[23] Additional pathologic variables that may predict *BRCA1* mutation status include Ki67 and epidermal growth factor receptor.[14] In young (age younger than 54 years) women with breast cancer, high levels of Ki67 expression predicted a chance of having a *BRCA1* mutation as high as 75%.[14] Based on these studies and an increasing amount of evidence suggesting that *BRCA1* tumors have unique pathologic features, clinicians should perhaps consider using pathology results along with family history information when deciding whether a patient is at an increased risk for hereditary breast cancer. This may be particularly useful when family history information results in an intermediate concern for hereditary cancer.[14] However, because it appears that *BRCA2*-related cancers have pathology similar to that of non-*BRCA* carriers, it is currently unclear whether pathologic results may be used in predicting *BRCA2* mutation status. Additional research should be conducted to determine how much emphasis should be placed on tumor pathology and how this information can be included in already established models.

Our study demonstrated that *BRCA2* mutation carriers with triple-negative breast cancer were older at diagnosis than *BRCA1* carriers and noncarriers with triple-negative cancer. However, the general study population of *BRCA2* mutation carriers showed no significant difference in the age at diagnosis compared with *BRCA1* mutation carriers and noncarriers. Why *BRCA2* carriers develop triple-negative cancer at a later age than the other groups has yet to be determined. Referral bias and the small number of *BRCA2* mutation carriers may have influenced these results. In our study, we found that more *BRCA2* carriers had triple-negative cancer diagnosed postmenopausal, and that more of these carriers had undergone hormone replacement therapy than *BRCA1* carriers. Therefore, it is possible that menopausal status or the use of hormone replacement therapy may be involved. Additional research with a larger number of *BRCA2* carriers with triple-negative disease should be conducted to test this hypothesis.

One limitation of this study was the small number of women who were *BRCA2* mutation carriers and had triple-negative breast cancer. Because this combination of mutation status and tumor pathology appears to be uncommon, it would be interesting to examine this group in further detail. Future studies that explore this population should be conducted. Another limitation of our study was the possible referral bias in our study population. Because the *BRCA*-negative women were referred to our genetics program, they may not fully represent sporadic breast cancer cases, resulting in a bias in our control group. However, *BRCA* status and family history information is often unknown in unselected breast cancer patients, thus making comparisons between *BRCA*-positive and unselected breast cancer patients difficult. Future studies that screen prospectively for *BRCA* mutations in an unselected breast cancer population should be conducted to examine differences in tumor pathologic features and clinical characteristics in *BRCA*-positive and *BRCA*-negative patients in the general breast cancer population.

In conclusion, our results suggest that *BRCA1*-related breast cancers may be divided into two subgroups: one group consisting of

triple-negative, high-grade tumors, and the other group consisting of pathology more consistent with breast cancer observed in *BRCA* noncarriers. Future studies should determine whether treatment outcomes differ for *BRCA1* mutation carriers depending on different tumor pathology (ie, triple negative *v* non–triple negative). With the identification of novel targets for *BRCA1*- and *BRCA2*-related tumors, such as the poly(adenosine diphosphate-ribose) polymerase-1 pathway,[24] the efficacy of agents that target these pathways, such as poly(adenosine diphosphate-ribose) polymerase-1 inhibitors, should be examined.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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