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High Prevalence of Pre-invasive Lesions Adjacent to BRCA1/2-Associated Breast Cancers

Banu Arun[*], **Kristen J. Vogel**[◊], **Adriana Lopez**[**], **Mike Hernandez**[**], **Deann Atchley**[*], **Kristine R. Broglio**[**], **Christopher I. Amos**[‡], **Funda Meric-Bernstam**[†], **Henry Kuerer**[†], **Gabriel N. Hortobagyi**[*], and **Constance T. Albarracin**[§]

[*]Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030

[**]Department of Biostatistics, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030

[‡]Department of Epidemiology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030

[†]Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030

[§]Department of Pathology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030

[◊]Center for Medical Genetics, Evanston Northwestern Healthcare, 1000 Central Street, Evanston, Illinois 60201

Abstract

Purpose—Mutations in BRCA1 and BRCA2 increase a woman's lifetime risk of developing breast cancer to 43%-84%. It was originally postulated that BRCA1/2-associated breast cancers develop more rapidly than sporadic cancers and may lack pre-invasive lesions. More recent studies have found pre-invasive lesions in prophylactic mastectomy specimens from mutation carriers; however, there is little information on the presence of pre-invasive lesions in tissue adjacent to breast cancers. Our aim is to investigate the role of pre-invasive lesions in BRCA-associated breast carcinogenesis.

Methods—We retrospectively compared BRCA1/2-associated breast cancers and sporadic breast cancers for the prevalence of pre-invasive lesions (ductal carcinoma in situ [DCIS], lobular carcinoma in situ [LCIS], and atypical lobular hyperplasia [ALH]) in tissue adjacent to invasive breast cancers.

Correspondence to: Banu Arun, M.D., Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1354, Houston, Texas 77030, USA. Telephone: 713-792-2817; Facsimile: 713-794-4385; barun@mdanderson.org.

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Results—Pathology was reviewed for 73 BRCA1/2-associated tumors from breast cancer patients. We selected 146 mutation-negative breast cancer patients as age-matched controls. Of BRCA1/2-associated breast cancers, 59% had at least one associated pre-invasive lesion compared with 75% of controls. Pre-invasive lesions were more prevalent in BRCA2 mutation carriers than in BRCA1 mutation carriers (70% vs. 52%, respectively). The most common pre-invasive lesion in both groups was DCIS; 56% of BRCA1/2-associated breast cancers and 71% of the sporadic breast cancers had adjacent intraductal disease, respectively.

Conclusions—Pre-invasive lesions, most notably DCIS, are common in BRCA1/2-associated breast cancers. These findings suggest that BRCA1/2-associated breast cancers progress through the same intermediate steps as sporadic breast cancers, and that DCIS should be considered as a part of the BRCA1/2 tumor spectrum.

Approximately 7%-10% of early-onset breast cancers and 10%-15% of ovarian cancers are thought to be hereditary (1-5). The majority of these cancers result from germline mutations in the BRCA1 and BRCA2 genes (6, 7). Risk factors to carry a mutation in BRCA1 or BRCA2 include diagnosis of breast cancer at an early age (<50 years), diagnosis of ovarian cancer at any age, diagnosis of bilateral breast cancer, diagnosis of breast and ovarian cancer, diagnosis of male breast cancer, family history positive for breast and/or ovarian cancer, and Ashkenazi Jewish ancestry (2, 8-10). Women who carry a germline mutation in BRCA1 or BRCA2 have a 43%-84% risk of developing breast cancer and a 22%-39% risk of developing ovarian cancer by age 70 years (6), (11), (12).

Studies have demonstrated significant differences in the histopathologic features of BRCA1/2-associated breast cancers as compared to sporadic breast cancers (13-17). BRCA1/2-related tumors are more likely to be of higher grade and poorly differentiated than sporadic breast tumors (13-17). BRCA1-associated tumors are also more likely to be negative for estrogen receptor (ER) and progesterone receptor (PR) as compared to sporadic breast cancers. The ER/PR status of BRCA2-associated tumors and of sporadic controls does not appear to differ, as noted in several reports. (13, 15, 16). While the pathologic characteristics of BRCA1/2-related breast cancers have been described, much less is known about the progression process of BRCA1/2-associated versus sporadic breast cancers.

Fifty percent of BRCA-associated breast cancers are interval cancers that occur between two screening mammograms, and the diagnosis is often made in the absence of prior mammographic and pathologic findings (18), (19), (20). As such, high-risk or pre-invasive histopathologic lesions (i.e., atypias or in situ carcinomas) have not been considered to be part of the BRCA1/2-related disease spectrum. Moreover, it was previously proposed that BRCA1/2-related tumors may have a different natural history and may progress more quickly (particularly in the case of BRCA1) than sporadic tumors (21), (22). The Breast Cancer Linkage Consortium study for example, showed a lower prevalence of DCIS, among BRCA mutation carriers (17), (23) whereas another study did not (14). Currently, most of the BRCA risk assessment models do not take the presence of pre-invasive lesions, including DCIS, into consideration when calculating the risk of carrying a BRCA mutation (24, 25). However, recent studies have indeed reported the presence of high-risk pre-invasive lesions in tissue obtained during prophylactic mastectomies of BRCA1/2 mutation

carriers (22), (26), (27),(28), (29) (22, 28-30). None of the studies evaluated the presence of these lesions within the context of a breast cancer progression model in patients who are BRCA mutation carriers.

To further advance the understanding of the role that high-risk pre-invasive lesions play in BRCA-associated breast carcinogenesis, we retrospectively evaluated the presence and prevalence of pre-invasive high-risk lesions adjacent to invasive breast cancers from BRCA1/2 mutation carriers, as compared to BRCA1/2-negative sporadic breast cancers.

Subjects and Methods

Patients

Between 1997 and 2006, approximately 900 individuals received genetic counseling and testing for BRCA1/2 at the University of Texas M. D. Anderson Cancer Center and 209 were found to be carriers for a deleterious mutation either in the BRCA 1 or BRCA 2 gene. Ninety-eight of 209 individuals had a personal history of invasive breast cancer. We reviewed the electronic medical records of those 98 patients for pathology reports related to their breast cancer diagnoses; 73 patients had available pathology at M.D. Anderson Cancer Center. 146 patients with invasive breast cancer who had tested negative for mutations in BRCA1 and BRCA2 were selected as controls and matched to mutation carriers by age ± 2 years at a ratio of 2:1. This study was approved by the institutional review board.

Tumor Characteristics and Histology

Invasive Breast Cancers—Breast tumor pathology from 146 sporadic cases and 73 BRCA1/2 mutation carriers were evaluated for histologic tumor type, modified Black's nuclear grade, estrogen receptor (ER) status and progesterone receptor (PR) status by immunohistochemistry (IHC), HER-2/neu by IHC, HER-2/neu gene amplification by fluorescent in situ hybridization (FISH), and the presence of adjacent pre-invasive lesions. At our institution all outside breast cases are re-reviewed in a standardized fashion by designated breast pathologists and a new report is issued

Pre-invasive Lesions—Adjacent preinvasive lesions included the presence of ductal carcinoma in situ, lobular carcinoma in situ and atypical lobular hyperplasia that occur in the same quadrant or same area as the invasive carcinoma. These lesions were evaluated for in each case at our Institution and their presence was reported as part of the report. Reports also indicate the presence of in situ carcinoma when it is away from the area of the invasive carcinoma since this can represent a multifocal process.

Statistical Analyses and Methods

Patient and disease characteristics were tabulated according to BRCA1/2 group: BRCA1+ versus BRCA2+ versus BRCA- (sporadic controls). Fisher's exact test was used to assess the association between pre-invasive lesions and other prognostic factors among the groups. Multiple comparisons were performed; thus, the *P*-value required to declare statistical significance was adjusted to account for the increase in the probability of finding false-positive results. The significance level was divided by three relating to the three pair-wise

comparisons of interest (BRCA1/2+ versus BRCA1/2-, BRCA1+ versus BRCA1/2-, and BRCA2+ versus BRCA1/2-) considering each disease characteristic independently. The Bonferroni correction method resulted in a *P* value <0.05/3=0.0167 to be considered statistically significant. All statistical analyses were performed using SAS 9.1 (SAS, Cary, NC).

Results

Patients

Seventy-three patients with breast cancer who were BRCA mutation carriers (46 BRCA1 and 27 BRCA2) were included in the study. The control group consisted of 146 patients with sporadic breast cancer who were negative for the BRCA1/2 mutation. The median age at diagnosis was 42 years of age (21y-71y) for patients with BRCA mutations, and 42 years of age (22y-70y) for sporadic controls. Twenty-five % of the BRCA mutation carriers 36 % of the controls underwent segmental mastectomy, respectively.

Invasive Breast Cancers

The invasive carcinomas (n=219: 73 BRCA1/2+ and 146 BRCA1/2- [controls]) were of various histologic types and included ductal (n=195), lobular (n=7), medullary (n=1), sarcomatoid (n=1), and mixed ductal and lobular (n=15) types. The histologic types of the invasive cancers were not statistically significantly different in BRCA1 versus BRCA2 mutation carriers.

In general, BRCA1/2 associated breast cancers tended to be higher grade tumors than sporadic breast cancers. This difference was significant when comparing sporadic tumors to BRCA1/2-positive tumors (*P*=<.0001). However, when tumors were compared with BRCA1- and BRCA2-positive tumors separately, the tumor grade difference remained significant for BRCA1 positive tumors (*P*=<.0001) but did not reach statistical significance for BRCA2 positive tumors (*P*=.0330) (Table 1).

Tumor expression of ER, PR, and HER-2-neu was compared among the mutation status categories of invasive breast carcinomas. BRCA1-positive tumors were significantly more likely to be ER-negative (76.92%, 30 of 39; P=<.0001) and PR-negative (73.68%, 28 of 38; P= 0.0029) (Table 1). In contrast, BRCA2-positive tumors showed neither a significant correlation with, nor a trend toward, any ER or PR status. No significant differences in tumor expression of HER-2/neu were noted among tumors in the various mutation status categories regardless of whether HER-2/neu expression was obtained by IHC or FISH.

Pre-invasive Lesions

A wide spectrum of pre-invasive lesions, including atypical lesions and in situ carcinoma, was found in tissue adjacent to invasive breast carcinomas, both in BRCA1/2 mutation carriers and in BRCA1/2-negative controls. Among BRCA1/2-positive tumors, 59% (43 of 73) had one or more separate histologic types of pre-invasive lesion(s) adjacent to invasive tumor tissue compared with 75% (109 of 146) of BRCA1/2-negative tumors. When BRCA1-positive and BRCA2-positive tumors were evaluated separately, there appeared to

be a trend toward fewer pathologic pre-invasive lesions adjacent to BRCA1-positive tumors (52%, 24 of 46) than were adjacent to BRCA1/2-negative tumors (75%, 109 of 146). There was no difference between BRCA2-positive tumors and BRCA1/2-negative tumors in the number of adjacent pre-invasive lesions present (70%, 19 of 27 vs. 75%, 109 of 146) (Table 2).

DCIS was by far the most commonly occurring type of pre-invasive lesion and was found adjacent to invasive breast cancer in 48% (22 of 46) of BRCA1-positive tumors, 70% (19 of 27) of BRCA2-positive tumors, and 71% (103 of 146) of sporadic (BRCA1/2-negative control) tumors (Table 2). The percentage of adjacent DCIS was similar for BRCA1/2-positive tumors and sporadic control tumors (P=0.049). It was noted that BRCA1-positive invasive breast cancers had a smaller percentage of adjacent pre-invasive DCIS tumors than BRCA1/2-negative tumors had (*P*=.0074) and that the percentage of adjacent DCIS was similar for BRCA2-positive tumors and sporadic control tumors (P=1). DCIS adjacent to BRCA1/2-positive breast cancers tended to be higher grade than DCIS adjacent to sporadically occurring control tumors (*P*=.0045).

Discussion

In this study, we evaluated invasive tumor characteristics and presence and frequency of pre-invasive lesions adjacent to BRCA1- and BRCA2-positive invasive breast cancers and compared the findings with those for age-matched BRCA1/2-negative control tumors. BRCA1 positive tumors were higher grade and were significantly more likely to be ER and PR-negative. Interestingly, no significant differences in tumor expression of HER-2/neu were noted among tumors in the various mutation status categories, which was most probably due to the small number of cases because of missing data.

We found that pre-invasive lesions occurred with considerable frequency in BRCA1/2-negative controls as well as in carriers of the BRCA1/2 mutation. In particular, the frequency of pre-invasive lesions in sporadic and BRCA2-associateed tumors were similar (75% vs 70%). BRCA1-associated tumors also contained a considerable number, albeit a lower frequency, of pre-invasive lesions (59%) compared to BRCA2-associated or sporadic tumors.

Pre-invasive lesions, including DCIS, were not always considered to be part of the spectrum of BRCA1/2-positive breast cancers. Sun et al reviewed a database of BRCA1 mutation carriers and their families and found 200 cases of invasive breast cancer but only 4 cases of DCIS. It was even suggested that perhaps BRCA1/2-positive tumors had a different pattern of tumor progression than sporadically occurring tumors(21). Similarly, Frank et al evaluated BRCA mutations from 10,000 individuals tested at Myriad Genetic Laboratories (10). The prevalence of BRCA mutations was significantly lower in patients ages 50 years and less with DCIS, than in patients with invasive breast cancer. However, subsequent studies in prophylactic mastectomy specimens from BRCA1/2 positive carriers have demonstrated incidental findings of DCIS (18, 22, 26, 27). Comparison of prophylactic specimens from BRCA1/2 mutation carriers and BRCA negative individuals showed no significant difference in the prevalence of DCIS, atypical ductal hyperplasia or lobular

neoplasias with no BRCA1/2 mutation but who had a strong family history of breast cancer, and individuals with no family history of breast cancer(22).

Claus et al examined the prevalence of BRCA mutations in women with DCIS and reported mutation rates similar to those found for invasive breast cancer (26). The authors suggested that DCIS is a part of the BRCA cancer syndromes. A very recent study by Hwang et al evaluated breast cancer outcomes in a retrospective cohort of 129 BRCA-positive and 269 BRCA-negative women and reported that DCIS was equally prevalent in patients who have BRCA mutations as in BRCA non-carriers, suggesting that DCIS may be on the casual pathway to invasive disease (27). In our study, we likewise found no significant difference between mutation carriers and controls in the prevalence of these pre-invasive lesions.

In another study, Hoogerburgge et. al. reported that up to 57% of women with a hereditary risk for breast cancer who underwent prophylactic mastectomy were found to have one or more high-risk pre-invasive lesions (ADH, ALH, LCIS, DCIS) in excised tissue specimens, although that study had no control group for comparison (28). The investigators went on to perform a larger study in which they compared the pathology of prophylactic mastectomy tissue specimens from BRCA1/2 mutation carriers with the pathology of prophylactic specimens from individuals at high risk for breast cancer who did not carry the mutation. They found that high-risk pre-invasive lesions were more common in women who did not carry a BRCA1/2 mutation than in women who did carry the mutation (71% vs. 43%, respectively). These investigators also found no significant difference between BRCA1 carriers and BRCA2 carriers in the prevalence of high-risk pre-invasive lesions. This study reported ALH to be the most common pre-invasive lesion among both, BRCA carriers and BRCA non-carriers and found DCIS to be the least common lesion (29). Kauff et. al. reported that pre-invasive lesions were actually more common in prophylactic mastectomy tissue specimens from carriers of the BRCA1/2 mutation than in breast tissue obtained at autopsy in from unaffected women with no known hereditary predisposition to breast cancer (30).

In our study we have observed a similar incidence of DCIS in patients with BRCA 1/2 positive tumors compared to BRCA negative tumors. We also found that other preinvasive lesions, such as (ALH and LCIS) were seen frequently in BRCA1/2 positive tumors; however, DCIS was the most commonly occurring lesion.

A limitation to our study is that it is a retrospective review; however at our institution, all cases are reviewed and reported prospectively by designated breast pathologists using the same review and reporting standards so that there is a system in place to use this information in future studies, as this current one.

One other limitation of our study is that the controls had all received genetic testing. It is therefore possible, that there is some selection bias in terms of controls and that this group still might represent a high risk population.

Finally, we have used the Bonferroni correction to address the issues associated with comparisons across multiple groups of patients (BRCA-, BRCA1+, BRCA2+). From a practical perspective, the correction decreases the chances of making a Type I error (i.e.

rejecting the null hypothesis when it is in fact true) by lowering the p-value needed to declare statistical significance and increasing the standard of proof.

Nevertheless, our results provide support for a subsequent prospective analysis in which each specimen will be evaluated with the intention of determining the true prevalence of adjacent pre-invasive lesions in both BRCA1/2-associated breast cancers and BRCA1/2 negative controls.

The possible reasons for such large discrepancies in the literature most probably includes patient selection, incomplete pathology review, differences in pathological definitions, or simply small sample sizes and random variation. It needs to be acknowledged that with relatively small sample sizes, including this study, subset comparisons are problematic and the confidence intervals are potentially large.

In conclusion, it was originally thought that BRCA1/2-related breast cancers do not go through the same steps of tumorigenesis as sporadically occurring breast cancers do. However, the finding of DCIS with considerable frequency in prophylactic mastectomy tissue samples from carriers of the BRCA1/2 mutation supported the theory that BRCA1/2-associated breast cancers and sporadic breast cancers undergo similar tumor development, although no definitive conclusions could be reached.

We have supplied additional evidence to support this model, showing that pre-invasive lesions, particularly DCIS, are often found adjacent to BRCA1/2-associated invasive breast cancers. This finding also provides evidence that hereditary breast cancer progresses through the same intermediate steps as sporadic breast cancer does. Therefore, DCIS should be included in the clinical spectrum of hereditary breast cancers and genetic counseling and testing should be considered for patients who have these pre-invasive lesions.

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Table 1

Characteristics of Invasive Breast Cancers According to BRCA1/2 Status

Tumor Characteristic		Mutation Status										
		BRCA1/2-(Sporadic)		BRCA1/2+			BRCA1+			BRCA2+		
		N (146)	%	N (73)	%	P-value*	N (46)	%	P-value*	N (27)	%	P-value*
Grade	1	14	10.14	10	16.39		6	14.63		4	20.00	
	2	74	53.62	12	19.67	<.0001#	7	17.07	<.0001#	5	25.00	0.0330
	3	50	36.23	39	63.93		28	68.29		11	55.00	
	Data N/A	8	N/A	12	N/A		5	N/A		7	N/A	
ER	-	35	26.92	36	61.02		30	76.92		6	30.00	
	+	95	73.08	23	38.98	<.0001#	9	23.08	<.0001#	14	70.00	0.7905
	Data N/A	16	N/A	14	N/A		7	N/A		7	N/A	
PR	-	59	45.38	39	67.24		28	73.68		11	55.00	
	+	71	54.62	19	32.76	0.0071#	10	26.32	0.0029#	9	45.00	0.4759
	Data N/A	16		15			8			7		
HER2neu by FISH	-	46	69.70	23	85.19		14	82.35		9	90.00	
	+	20	30.30	4	14.81	0.1909	3	17.65	0.3746	1	10.00	0.2676
	Data N/A	80	N/A	46	N/A		29	N/A		17	N/A	
HER2neu by IHC	0	39	42.39	13	41.94		10	52.63		3	25.00	
	1+	23	25.00	11	35.48		7	36.84		4	33.33	
	2+	16	17.39	6	19.35	0.2888	2	10.53	0.2030	4	33.33	0.4140
	3+	14	15.22	1	3.23		0	0.00		1	8.33	
	Data N/A	54	N/A	42	N/A		27	N/A		15	N/A	
HER2neu expression IHC	0 – 1+	62	67.39	24	77.42		17	89.47		7	58.33	
	2+ - 3+	30	32.61	7	22.58	0.33680	2	10.53	0.0573	5	41.67	0.5321
	Data N/A	54	N/A	42	N/A		27	N/A		15	N/A	

*Based on comparison to sporadic BRCA1/2- controls, ER: Estrogen receptor, PR: Progesterone receptor.

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#comparison remained significant after Bonferroni correction

Table 2

All Pre-invasive lesions by BRCA Mutation Status

Pre-invasive Lesion		BRCA Mutation Status					
		BRCA1/2-		BRCA1+		BRCA2+	
		N	%	N	%	N	%
DCIS	no	43	29.45	24	52.17	8	29.63
	yes	103	70.55	22	47.83	19	70.37
DCIS grade	1	4	5.06	1	5.88	2	12.50
	2	45	56.96	4	23.53	4	25.00
	3	30	37.97	12	70.59	10	62.50
LCIS	no	132	90.41	44	95.65	25	92.59
	yes	14	9.59	2	4.35	2	7.41
ALH	no	134	91.78	45	97.83	26	96.30
	yes	12	8.22	1	2.17	1	3.70
Any pre-invasive lesion	no	37	25.34	22	47.83	8	29.63
	yes	109	74.66	24	52.17	19	70.37