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Predictors that influence Contralateral Prophylactic Mastectomy Election Among Women with Ductal Carcinoma In Situ who were evaluated for *BRCA* genetic testing

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Abstract

Background—Patients with ductal carcinoma in situ (DCIS) are at increased risk for developing contralateral breast cancer (CBC). Consequently, more women with DCIS are electing contralateral prophylactic mastectomy (CPM). We evaluated factors associated with CPM in patients with DCIS who underwent genetic counseling for *BRCA* testing.

Methods—This retrospective study involved 165 women with DCIS referred for genetic counseling between 2003 and 2011. Patient characteristics were age, marital and educational status, tumor markers, nuclear grade, family history of breast cancer (BC) and ovarian cancer (OC), race, Ashkenazi Jewish ancestry, and *BRCA* results. Univariate and multivariate logistic regression analyses were used to determine predictive factors associated with CPM election.

Results—Of 165 patients, 44 (27%) underwent CPM. Patients < 45 years were more likely to elect CPM ($P = .0098$). A *BRCA*+ mutation was found in 17 patients (10.3%), and BRCA+ women were more likely to elect CPM than BRCA- or untested women ($P = 0.0001$). Patients who had a family history of OC (57.7%) were more likely to choose CPM than those with no family history ($P = 0.0004$). Younger age, *BRCA*+, and an OC family history remained significant in the multivariate model ($P < 0.008$).

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Conclusion—The CPM rate among patients with DCIS who undergo genetic counseling is high. Factors associated with increased likelihood of CPM among this group were age, *BRCA*+, and a family history of OC. Further studies are needed to evaluate patients' perceptions of CBC risk and their role in the likelihood of CPM choice.

Keywords

Intraductal carcinoma; ductal carcinoma in situ (DCIS); genetics; contralateral prophylactic mastectomy; Gene, *BRCA1*; Gene, *BRCA2*

Introduction

Ductal carcinoma in situ (DCIS) increased 7.2-fold between 1980 and 2001 as a result of the increased use of screening mammography,[1] and the detection rate continued to increase during the last decade.[2] Although DCIS is not immediately life threatening, patients with DCIS in 1 breast are at increased risk for developing contralateral breast cancer (CBC)[3]. The risk for developing either invasive cancer or DCIS in the contralateral breast is 0.6% per year.[1,2] To reduce CBC risk, an increasing number of women with DCIS are electing to undergo contralateral prophylactic mastectomy (CPM).[1, 2,4]

One of the largest risk factors for breast cancer (BC) is hereditary predisposition. The *BRCA1* and *BRCA2* gene mutations have been shown to indicate a higher susceptibility to develop BC. Individuals who carry 1 of these mutations have a 43% to 84% risk of developing BC, and up to a 65% risk for CBC.[5-6] Prospective studies of *BRCA* mutation carriers have shown that bilateral prophylactic mastectomy (BPM) reduces BC risk by more than 90%.[7] It has been reported that among *BRCA* mutation carriers, up to 65% of women with BC and 15% to 60% of unaffected women undergo risk-reduction breast surgeries.[8-11] The election to undergo prophylactic surgery is dependent upon several factors such as age, the desire to have children, and family history.[17-20]

The prevalence of *BRCA* mutations in patients with DCIS has been reported.[1,12] Our previous study[1] indicated a 27% prevalence of deleterious *BRCA* mutations among 118 patients with DCIS who were referred for genetic counseling. This study indicated that women who had DCIS and a family history of ovarian cancer (OC) had higher rates of *BRCA* positivity. Hwang et al[12] retrospectively reviewed 129 *BRCA*-positive and 269 *BRCA*-negative women undergoing genetic testing, and found that 37% of *BRCA* carriers had DCIS. Several previous studies assessed the prevalence of *BRCA1* and *BRCA2* mutations among women with DCIS and reported rates between 3.3% and 13%.[1,13,14] The frequency and patterns regarding CPM choice among patients with DCIS and *BRCA* mutations have not been well reported. Although several retrospective studies have examined the increasing rate of CPM among patients with DCIS, these studies did not examine variables such as family history, *BRCA* mutation status, or tumor characteristics and their influence for CPM.[2]

The aim of this study was to determine the rate of CPM election and further identify predictive factors for CPM election among patients with DCIS and who were referred for genetic counseling and followed in our high-risk BC and OC clinics.

Methods

Patient Selection and Data

Between 2003 and 2011, 165 women who were diagnosed with DCIS were referred for genetic counseling and were invited to participate in a prospective registry study that was approved by the internal review board at The University of Texas MD Anderson Cancer Center (MD Anderson). The criteria used to refer patients to genetic counseling were based on the National Comprehensive Cancer Network guidelines.[15] We excluded patients who had micro-invasion, bilateral DCIS, OC, or a genetic test result indicating a *BRCA1* or *BRCA2* variant of uncertain significance.

Diagnoses were made based on pathologic evaluation by dedicated breast pathologists at UTMD Anderson. All patients underwent genetic counseling that included a detailed review of family history. Those who proceeded with genetic testing underwent comprehensive *BRCA* 1 and *BRCA* 2 gene sequencing and in some, large rearrangement test (BART) when indicated and patient agreed to testing. Patients' demographic and clinical characteristics were obtained from the medical record. The variables considered in our analysis were age at the time of diagnosis; race; ethnicity (Ashkenazi Jewish [AJ], or non-AJ ancestry); marital status; educational level completed; family history of BC and/or OC in at least 1 first-degree relative; total number of relatives who had had BC and/or OC; and, if available, patients' *BRCA1* and *BRCA2* genetic test results, tumor nuclear grade (as defined by the modified nuclear grade system), estrogen receptor (ER), and progesterone receptor (PR) status (as determined by immunohistochemical (IHC) analysis).

Statistical Analysis and Outcome Measures

Patients' demographic and clinical characteristics were compared between the two groups and defined according to CPM status (patients who did and did not elect to undergo CPM). Univariate analyses were performed to test the significance of each variable in relation to whether a patient had undergone CPM; chi-square tests were used for categorical variables, and *t*-tests/analysis of variance or the counterparts of the nonparametric approaches (Wilcoxon rank sum or Kruskal-Wallis tests) were used for continuous variables.[16] Logistic regression analyses were used to assess the multivariate relationship between patient demographics and clinical characteristics and the probability of electing CPM.[17] A logistic regression model was obtained by first including an initial set of candidate predictor variables for which *P* values (≤ 0.05) had been obtained in the univariate analysis. A stepwise backward elimination was then performed using $P \leq 0.05$ for the significance level of the Wald chi-square for an effect to stay in the model.

Results

Patient characteristics are shown in Table 1. Of the 165 patients with DCIS who were included in the analysis, 44 (27%) underwent CPM. Seventeen (10.3%) of 165 patients were found to have a deleterious *BRCA* mutation, 91 (55%) did not have a *BRCA* mutation, and 57 (35%) did not undergo genetic testing. CPM was elected in 12 (71%) of the 17 patients who tested positive for a *BRCA* mutation, 23 (25%) of patients who tested negative, and 9

(16%) of the 57 patients who did not undergo genetic testing. Eight patients did not undergo testing because test was cancelled/ insurance restrictions, 3 were not interested/ declined testing, 14 did not meet testing criteria, 24 were not seen, 2 indicated other family members will undergo testing, 1 did not show, and 5 did not test for unknown reasons. Rates of CPM by *BRCA* status are illustrated in Table 2.

Univariate analysis (Table 3) demonstrated that *BRCA*-positive patients were more likely to choose CPM than were *BRCA*-negative and untested patients ($P = 0.0001$). Younger (≤ 45 years old) patients were more likely than older patients to choose CPM ($P = 0.0098$). When analyzed by family (first-degree relative) history of BC, the difference was not statistically significant ($P = 0.221$). However, patients with a family history of OC were more likely to choose CPM than were patients without an OC family history ($P = 0.0004$).

The multivariate logistic regression model revealed an association between patient characteristics and CPM (Table 4). Age at diagnosis and having 1 or more family members with OC and positive *BRCA* mutation status remained independent significant predictors of having elected CPM. More specifically, younger patients (median of 45 years of age or younger) were more likely than older patients to choose CPM (odds ratio [OR] = 3.07; 95% confidence interval [CI], 1.33-7.09; $P = 0.0085$). Patients with relatives with OC were more likely to undergo CPM (OR = 4.34; 95%CI, 1.644-11.46; $P = 0.0030$). Results of *BRCA* genetic testing were significantly associated with the probability of having chosen to have CPM ($P = 0.0041$). Specifically, patients with positive *BRCA* results were more likely to undergo CPM than those who were not tested (OR = 8.64; 95%CI, 2.27-32.82; $P = 0.0009$) or those with negative test results (OR = 6.57; 95% CI, 1.94-22.20; $P = 0.0024$). Patients with negative *BRCA* results were more likely to undergo CPM than those who were not tested (OR = 1.32; 95% CI, 0.53-3.26). However, the difference in CPM rates between the two groups was only marginally significant ($P = 0.0609$).

The final multivariate logistic regression model revealed an association between patient characteristics and CPM among patients who were BRCA-negative (Table 5). Age at diagnosis and having 1 or more family members with OC remained independent significant predictors of having elected CPM among patients who tested negative for a *BRCA* mutation. The regression showed a marginally significant trend that revealed younger patients (median of 45 years of age or younger) were more likely than older patients to have chosen CPM (OR = 0.373; 95% CI, 0.125-1.118; $P = 0.0784$). Patients with relatives with OC were more likely to undergo CPM (OR = 4.906; 95% CI, 1.479-16.281; $P = 0.0094$).

Discussion

This study revealed a 27% CPM rate among patients with DCIS, supporting previous work demonstrating the increasing rate of CPM among patients with DCIS.[2] Our multivariate regression analysis revealed that age of 45 years or younger, *BRCA* positivity, and having 1 or more relatives with OC independently predicted the decision to undergo CPM. To our knowledge, our study is the first to report rates of CPM among patients with DCIS in light of family history and genetic test results. Few studies have examined the rate of CPM among patients with DCIS; the first to do so by Tuttle and associates analyzed the initial

treatment of patients with unilateral DCIS to determine the CPM rate between 1998 and 2005. [2] A 13.5% CPM rate was revealed among patients who had a mastectomy on the affected side; among all surgically treated patients, the rate had increased by 148% between 1998 and 2005. The study populations were different, however. The Tuttle population was analyzed using the Surveillance Epidemiology and End Results database, which allowed for a more population-based approach. Our study included patients who were analyzed based upon referral for genetic counseling and genetic testing.

It has been shown that age plays a role in the decision to pursue prophylactic mastectomy. Our data shows that younger DCIS patients are more likely than older patients to elect prophylactic mastectomies. Tuttle's findings also show that DCIS patients younger than 40 years were significantly associated with increased rates of CPM in their cohort. [2] Moreover, Heemskerk-Gerritsen and colleagues[18] found that prophylactic mastectomy was more prevalent among younger affected (with a history of BC) and/or unaffected women between 37 and 44 years of age.[18] Younger patients especially may benefit from CPM because of their potentially longer lifespan and increased risk for a subsequent BC.

It is also crucial to acknowledge and address the impact of genetic test results on patients' psychological adjustment. Receiving a positive genetic test result is an anxiety-provoking event that elicits psychological distress. Electing CPM can reduce anxiety and constant worry for certain patients[19]. Therefore, patients' perception of future (BC) risk and the psychosocial implications a positive genetic test result can trigger need to be addressed appropriately with care providers.

It has been well established that BPM in *BRCA* mutation carriers reduces BC risk by 90%.[9,7,21,23] In a prospective study, Meijers-Heijbor et al[20] evaluated the incidence of BC among 139 *BRCA1* and *BRCA2* mutation carriers who elected to undergo either BPM or close surveillance only. During an average follow-up interval of 3 years, 8 of the 63 women in the surveillance group developed BC, whereas none of the 76 women in the prophylactic-mastectomy group developed BC. However, in their updated paper,[18] only 1 previously unaffected woman developed metastatic BC almost 4 years after prophylactic mastectomy. Rebbeck et al.[7] evaluated 483 women with deleterious *BRCA1* and *BRCA2* mutations from the time of their ascertainment to time of surgery. BC was diagnosed in only 1.9% of women who had BPM, and 49% of women who did not have the procedure. Hartmann and associates[21] identified 26 women with an alteration in the *BRCA1* or *BRCA2* genes (18 had deleterious changes, and 8 had variants of uncertain clinical significance) who underwent prophylactic mastectomy. Of these women, 26 patients, none developed BC after 13.4 years of follow-up. These studies provide a plethora of evidence for the effectiveness of BPM in BC risk reduction among *BRCA* mutation carriers.

Our data show a substantial proportion (25%) of patients who tested negative for a *BRCA* mutation still elected CPM. Our results confirm that the presence of family history of OC and younger age (≤ 45) at diagnosis explain why these patients elected CPM despite their negative *BRCA* genetic test result. Few studies examined CPM among patients who tested negative for *BRCA* mutations; therefore we are currently analyzing a prospective cohort. Howard-McNatt et al [22] examined CPM among patients with invasive BC who tested

negative for a *BRCA* mutation. Among 110 women who received genetic testing, 37% of the *BRCA*-negative women chose CPM.

Goldflam and colleagues[23] found evidence that family history of BC was mostly associated with CPM. They retrospectively reviewed data for 239 patients with unilateral early-stage BC who elected to undergo CPM, and family history of BC was the most frequent reason given to undergo CPM in more than half of the patients. Contrary to this study, family history of BC did not predict CPM in our study. However, family history of OC was not evaluated in the Goldflam study. It has been shown that family history of OC is more suggestive of a *BRCA* mutation than a family history of BC.[1] In turn, *BRCA* positivity is associated with increased risk for primary BC and CBC, which explains why patients are concerned about risk for CBC and elect CPM. Our data indicated a relationship between *BRCA* positivity and family history of OC in CPM predictions.

It's noteworthy to mention the improvements in cosmetic outcomes related to skin and nipple sparing mastectomy and expertise in plastic surgical reconstruction has markedly influenced the use of CPM in patients with DCIS at MD Anderson. In our most recent overall experience among 2,037 patients treated for DCIS, the median pathologic size of the lesion was 1.3 cm and the use of CPM was highly significantly related to age (37% < 40 years, 17% 40-70 years, 6% > 70 years) as well as the use of immediate reconstruction (82% < 40 years, 66% 40-70 years, 16% > 70 years.[24]

Our results should be interpreted in light of study limitations; this was a retrospective review of clinical data from women who were referred to clinical cancer genetics for genetic counseling and thus a selected population.

Our results may not be generalizable to all patients with DCIS owing to selection bias. Future studies are needed to evaluate patients' perceptions of CBC and how these perceptions affect their decision to undergo CPM. The decision to undergo CPM is personal and individualized; consequently, patients need to have an accurate estimate of their CBC risk as well as potential risks and benefits of CPM. Montgomery and colleagues reported that 6% of patients who elected CPM regretted their decision for various reasons such as diminished sense of sexuality, poor cosmetic result, and lack of education regarding alternative methods. [25] Researchers need to explore whether the decision to undergo CPM is driven by physician recommendation or by a complete understanding of CBC risk. Considering the complexity of the decision to undergo CPM, genetic testing is a critical step that, if taken, can help patients interpret their risk and make informed decisions. New data may inform clinicians' recommendations and patients' decision making in weighing CBC risk against the short and long-term effects of prophylactic surgery. At present, CPM remains a highly desirable procedure among patients with DCIS who wish to reduce their CBC risk.

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Table 1

Patient Characteristics (n = 165)

Variable	Category	Total No. of Patients	Percentage of Total Patients
CPM	No	121	73.3
	Yes	44	26.7
Age at diagnosis	≤ 45 years	85	51.5
	> 45 years	80	48.5
AJ ethnicity	No	113	68.5
	Unknown	3	1.8
	Yes, maternal side	1	0.6
	Yes, paternal side	40	24.2
	Yes, both sides	8	4.9
Race	Non-AJ white	91	55.2
	AJ white	35	21.2
	Black	8	4.9
	Other	28	17.0
	Unknown	3	1.8
Marital status	Divorced	10	6.1
	Married, living together	127	77.0
	Separated	1	0.6
	Single (never married)	23	13.9
	Widowed	4	2.4
Education	Advanced degree	36	21.8
	College	52	31.5
	Some college/technical school	39	23.6
	High school	21	12.7
	Unknown	17	10.3
First-degree family history of breast cancer	0	99	60.0
	≥ 1	66	40.0
Total No. of relatives with a breast cancer diagnosis	0	40	24.2
	≥ 1	125	75.8
First-degree family history of ovarian cancer	0	157	95.1
	≥ 1	8	4.9
Total No. of relatives with an ovarian cancer diagnosis	0	139	84.2
	≥ 1	26	15.7
ER status	Negative	28	17.0
	Positive	108	65.5
	Unknown	29	17.6
PR status	Negative	40	24.2

Variable	Category	Total No. of Patients	Percentage of Total Patients
	Positive	94	57.0
	Unknown	31	18.8
Nuclear grade	I	14	8.5
	II	67	40.6
	III	73	44.2
	Unknown	11	6.7
BRCA result	Positive	17	10.3
	Negative	91	55.1
	Not tested	57	35.0

Abbreviations: CPM, contralateral prophylactic mastectomy; AJ, Ashkenazi Jewish; ER, estrogen receptor; PR, progesterone receptor.

Table 2

Contralateral Prophylactic Mastectomy Rates by *BRCA* Mutation Status (n = 165)

	CPM	No CPM
Positive for *BRCA* mutation	12 (70.6%)	5 (29.4%)
Negative for *BRCA* mutation	23 (25.3%)	68 (74.7%)
Not tested	9 (15.8%)	48 (84.2%)

Table 3

Association Between Patient Characteristics and Contralateral Prophylactic Mastectomy in the Univariate Analysis

Covariate	Variables	CPM (%)	No CPM (%)	*P*
Age at diagnosis	≤ 45 years	30 (35.3)	55 (64.7)	**0.0098**
	> 45 years	14 (17.5)	66 (82.5)	
Race	Non-AJ white	29 (31.9)	62 (68.1)	0.1770
	AJ white	7 (20)	28 (80)	
	Black	3 (37.5)	5 (62.5)	
	Others	4 (14.3)	24 (85.7)	
Marital status	Married, living together	34 (26.8)	93 (73.2)	0.9555
	Others	10 (26.3)	28 (73.7)	
Education	Advanced degree	10 (27.8)	26 (72.2)	0.6239
	College	14 (26.9)	38 (73.1)	
	Some college	9 (23.1)	30 (76.9)	
	High school	4 (19.0)	17 (81.0)	
	Unknown	7 (41.2)	10 (58.8)	
Family history (first-degree relatives)	BC + OC	3 (100)	0 (0)	**0.0008**
	BC only	18 (28.6)	45 (71.4)	
	OC only	4 (80.0)	1 (20.0)	
	Neither	19 (20.2)	75 (79.8)	
First-degree family history of breast cancer	0	23 (23.2)	76 (76.8)	0.2218
	≥ 1	21 (31.8)	45 (68.2)	
Total No. of relatives with a breast cancer diagnosis	0	9 (22.5)	31 (77.5)	0.4936
	≥ 1	35 (28.0)	90 (72.0)	
First-degree family history of ovarian cancer	0	*37 (23.6)*	*120 (76.4)*	**0.0004**
	≥ 1	7 (87.5)	1 (12.5)	
Total No. of relatives with an ovarian cancer diagnosis	0	29 (20.9)	110 (79.1)	**0.0001**
	≥ 1	15 (57.7)	11 (42.3)	
ER status	Negative	7 (25.0)	21 (75.0)	0.8382
	Positive	28 (25.9)	80 (74.1)	
	Missing/Unknown	9 (31.0)	20 (69.0)	
PR status	Negative	9 (22.5)	31 (77.5)	0.7822
	Positive	26 (27.7)	68 (72.3)	
	Missing/Unknown	9 (29.0)	22 (71.0)	
Nuclear grade	I	3 (21.4)	11 (78.6)	0.8953
	II	18 (26.9)	49 (73.1)	
	III	21 (28.8)	52 (71.2)	
BRCA mutation test result	Positive	12 (70.6)	5 (29.4)	**0.0001**
	Negative	23 (25.3)	68 (74.7)	

Covariate	Variables	CPM (%)	No CPM (%)	*P*
	Not tested	9 (15.8)	48 (84.2)	

Abbreviations: AJ, Ashkenazi Jewish; ER, estrogen receptor; PR, progesterone receptor.

Table 4

Association Between Patient Characteristics and Contralateral Prophylactic Mastectomy in the Multivariate Analysis

Parameter		Pr > ChiSq	Odds Ratio	95% CI of OR		*P* Value
				Lower Limit	Upper Limit	
Intercept		0.1386				
Age at diagnosis	≤ 45 yrs. vs> 45 yrs.	0.0085	3.067	1.332	7.092	0.0085
No. of relatives with an ovarian cancer diagnosis	= 0 vs ≥ 1	0.0030	4.340	1.644	11.456	0.0030
BRCA result	Positive vs not tested	0.0009	8.637	2.273	32.820	0.0041
	Positive vs Negative	0.0024	6.5702	1.9447	22.1972	
	Negative vs not tested	0.0609	1.315	0.530	3.259	

Abbreviations: OR, odds ratio; CI, confidence interval; Pr, probability

Table 5

Association Between Patient Characteristics and CPM in the Multivariate Analysis Among Patients Who are *BRCA*-Negative

Parameter		Odds Ratio	95% Wald Confidence Limits of Odds Ratio		*P* Value
			Lower limit	Upper limit	
Intercept	1				0.0014
Age at diagnosis	> 45 vs ≤ 45	0.373	0.125	1.118	0.0784
No. of relatives with ovarian cancer diagnosis	≥ 1 vs 0	4.906	1.479	16.281	0.0094