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Predictors of Contralateral Prophylactic Mastectomy in Genetically High Risk Newly Diagnosed Breast Cancer Patients

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Abstract

Purpose: Recent trends indicate increased use of contralateral prophylactic mastectomy (CPM) among newly diagnosed breast cancer patients, particularly those who test positive for a pathogenic variant in the *BRCA1/2* genes. However, the rate of CPM among patients who test negative or choose not to be tested is surprisingly high. We aimed to identify patient predictors of CPM following breast cancer diagnosis among such patients.

Methods: As part of a randomized controlled trial of rapid genetic counseling and testing vs. usual care, breast cancer patients completed a baseline survey within 6 weeks of diagnosis and before definitive surgery. Analyses focused on patients who opted against testing (n=136) or who

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Ethical Standards

This study was approved by the Institutional Review Boards of all participating sites. The study complies with all current laws of the United States of America.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Data Availability

The data that support the findings of this study are available upon reasonable request from the corresponding author [MDS]. The data are not publicly available due to the inclusion of information that could compromise research participant privacy/consent.

received negative *BRCA1/2* test results (n=149). We used multivariable logistic regression to assess the associations between sociodemographic, clinical and patient reported factors with use of CPM.

Results: Among patients who were untested or who received negative test results, having discussed CPM with one's surgeon at the time of diagnosis predicted subsequent CPM. Patients who were not candidates for breast conserving surgery and those with higher levels of cancer-specific intrusive thoughts were also more likely to obtain a CPM.

Conclusions: The strongest predictors of CPM in this population were objective clinical factors and discussion with providers. However, baseline psychosocial factors were also independently related to the receipt of CPM. Thus, although CPM decisions are largely guided by relevant clinical factors, it is important to attend to psychosocial factors when counseling newly diagnosed breast cancer patients about treatment options.

Keywords

Contralateral prophylactic mastectomy; Genetic testing; Breast cancer; Decision making

Women newly diagnosed with breast cancer face complex decisions about how to treat their cancer and manage their risk for future cancers. An increasingly common option to reduce the risk of a second breast cancer is contralateral prophylactic mastectomy (CPM) [1]. Recent trends indicate a significant increase in the use of CPM among newly diagnosed breast cancer patients [2–6]. Since 2002, the proportion of newly diagnosed breast cancer patients opting for CPM has more than tripled from 3.9% to 12.7% [3].

Some of the increase in CPM is likely due to increased use of genetic testing for pathogenic variants (PV) in the *BRCA1* and *BRCA2* (*BRCA1/2*) genes at the time of diagnosis. Studies document higher use of CPM among patients who have been tested compared to untested patients [7, 8]. Recent reports indicate that while nearly one quarter of all breast cancer patients obtain genetic testing, only 40% of patients at high risk for a PV are tested [9, 10]. Breast cancer patients found to carry a *BRCA1/2* PV face a 20% to 60% risk for developing a contralateral breast cancer [11, 12]. Given this high risk along with the 90% risk reduction associated with CPM [1, 13–15] and recent studies suggesting that CPM may be associated with increased overall survival in women with a *BRCA1/2* PV [16–18], it is not surprising that CPM is common in patients with a *BRCA1/2* PV [19–22].

However, as noted above, most breast cancer patients do not obtain genetic testing, and among those who are tested, most do not carry a PV. Despite having a much lower objective risk of developing a contralateral breast cancer, a substantial portion of women negative for a *BRCA1/2* choose to undergo CPM [22–25]. The use of CPM in untested patients and women negative for a *BRCA1/2* PV is poorly understood and few studies have prospectively investigated predictors of CPM in these groups. While limited prior reports suggest that marital status, family history of breast cancer, and physician recommendation may be associated with the use of CPM in women negative for a *BRCA1/2* PV [23–26], little is known about patient-level predictors (e.g. knowledge, cancer-specific distress) of CPM among patients who test negative or opt against testing.

In this study, we used data from a randomized controlled trial of proactive, rapid genetic counseling and testing (RGCT) vs. usual care (UC) to prospectively examine individual and psychosocial factors [20, 27] that predict CPM use in newly diagnosed breast cancer patients who received a *BRCA1/2* test result or opted against testing. In our previous report [20], we found that the RGCT intervention did not impact CPM uptake. Thus, in this report, we focus on identifying predictors of CPM uptake across both arms of the study. We assessed the following categories of predictors: clinical predictors, psychosocial predictors, knowledge/risk comprehension, and participation in genetic counseling and testing.

Methods

Participants

From 2006-2012, we recruited participants for a two-armed, randomized controlled trial comparing RGCT to UC. Participants were recruited from breast surgery clinics at Georgetown University Medical Center (Washington, DC), The Icahn School of Medicine at Mount Sinai (New York, NY), and Hackensack University Medical Center (Hackensack, NJ) as well as an affiliated private practice in Washington, DC. Eligible women were aged 18-75, diagnosed with TNM stage 0 to IIIa breast cancer within the previous 6 weeks and had not undergone definitive breast cancer surgical treatment (e.g., initiation of radiation therapy; unilateral or bilateral mastectomy). In addition, they had to be at increased risk for carrying a *BRCA1/2* mutation as defined as being diagnosed at <50 years of age or diagnosed between ages 50-75 with a family history of one or more first- or second-degree relatives diagnosed with breast cancer at < 50, ovarian cancer at any age or male breast cancer at any age. Women with a prior history of cancer (except non-melanoma skin cancer), bilateral, inflammatory, or metastatic breast cancer, or who had previously received *BRCA1/2* counseling or testing were ineligible. Women who were pregnant, lacked the cognitive capacity to provide informed consent or could not communicate in English were also excluded.

As displayed (Fig. 1), 330 eligible women completed a baseline interview and were randomly assigned to RGCT (n=222) vs. UC (n=108). For the current analysis, we excluded 26 participants for whom we could not determine final surgery status, yielding a final sample of n= 304. Overall, 12 participants received a positive test result, 7 received a variant of uncertain clinical significance (VUS) result, 149 received a negative test result and 136 opted against genetic testing. For analyses of predictors of CPM, we focused on the 285 participants who received negative test results or opted against testing. We eliminated mutation carriers from these analyses because of their extremely high uptake of CPM and we eliminated those with a VUS result because of their high CPM rate and the low overall number of participants with VUS results.

Randomization

Participants were randomized to RGCT or UC in a 2:1 ratio using a computer-generated random number and stratified by study site.

Procedure

The institutional review boards at all study sites approved this study. All new patients were asked to complete a family history form and provide consent for study contact. Research assistants (RA) reviewed appointment and pathology records to identify newly diagnosed patients. If a patient had not completed the family history form, we contacted the patient's surgeon to obtain permission to approach the patient. Potentially eligible patients were approached by an RA in clinic or by telephone shortly after the clinic visit. The RA introduced the study and obtained permission to contact patients by telephone to complete the baseline interview.

A RA then called interested patients to confirm eligibility, explain the study, obtain verbal consent and complete the baseline survey to collect demographic, cancer history and psychosocial information. If the baseline survey was not completed within 6 weeks of diagnosis, the participant was considered a study decliner. Immediately following the baseline survey, participants were randomized to RGCT or UC in a 2:1 ratio. After randomization, participants were sent (via priority mail) informed consent and medical records release forms. Participants were asked to mail back the consent and release forms in postage-paid envelopes.

RGCT participants were proactively contacted by telephone within 24-72 hours of randomization to schedule a genetic counseling session. To further expedite genetic counseling, RGCT participants had the option to schedule an in-person or telephone genetic counseling session. Ninety-three (49.5%) RGCT participants who received genetic counseling chose telephone counseling and 95 (50.5%) chose in-person counseling. UC participants were not proactively contacted but could contact the genetic counseling program for an in-person pre-test genetic counseling appointment. All study-related genetic counseling was provided at no cost and utilized a standard protocol and visual aids. *BRCA1/2* testing costs were billed to patients or insurers directly by the testing laboratory. All participants who opted for genetic testing could choose whether to have an in-person or telephone disclosure session when test results were available. In the current analysis the baseline survey served as our source for all patient reported predictors. We assessed participation in genetic counseling, genetic test results and definitive surgery from clinic records and patient reports on follow-up surveys.

Measures

Predictors

Sociodemographics and Family History.—We assessed the following sociodemographic variables: age, education level (college graduate vs. < college graduate), marital status, race (non-Hispanic white vs. racial/ethnic minority), employment status and Ashkenazi Jewish ancestry.

Family and Personal Cancer History.—We assessed personal and family cancer history and used this information to calculate an a priori risk score with the BRCAPRO model [28].

Clinical Variables.—From participants' medical records, we abstracted date of diagnosis, cancer stage, receptor status, receipt and timing of genetic counseling and testing, and genetic test result. As displayed in Table 1, incomplete abstraction of medical records led to missing data for ER/PR status (n=61) and cancer stage (n=54). On the baseline survey, we assessed whether the participant discussed CPM with her surgeon, whether the participant recalled being told that she was a candidate for breast conserving surgery (BCS), how the patient's current breast cancer was detected and the participant's perceived risk for carrying a *BRCA1/2* mutation.

Knowledge.—We measured knowledge with a scale created for this study. The scale was comprised of 10 true/false statements related to breast cancer and *BRCA1/2* mutations (Cronbach's Alpha = 0.68).

Distress.—We measured cancer-specific distress with the Likert-style 15-item Impact of Events Scale (IES) [29]. The IES measures distress associated with a specific life event, in this case, a new cancer diagnosis. The IES consists of two scales measuring avoidant thoughts and behavior and intrusive ideation. We measured general distress with the 12-item Brief Symptom Inventory (BSI) [30]. The BSI measures symptoms of depression and anxiety. Reliability for both measures was excellent (Cronbach's Alpha = 0.86 to 0.87).

Quality of Life.—We assessed general health-related quality of life with the 27-item Functional Assessment of Cancer Therapy-General (FACT-G) [31]. The FACT-G measures four primary quality of life domains: physical well-being, emotional well-being, functional well-being and social well-being. In this study, we used the total score. Higher scores represent better quality of life (Cronbach's Alpha = 0.86).

Outcome Variable

From medical records, we abstracted the final breast cancer surgery obtained by all participants within one year of randomization. Participants were categorized as having obtained a lumpectomy or unilateral mastectomy vs. bilateral mastectomy (i.e., mastectomy of the affected breast plus a CPM of the unaffected breast).

Statistical Analyses

All statistical analyses were conducted using SAS version 9.4 [32]. We confirmed the comparability of RGCT and UC at baseline using chi-square and t-tests. In intention-to-treat analyses, we compared RGCT to UC on uptake of CPM using chi-square tests. We evaluated the association between genetic test result and uptake of CPM using a chi-square test and the possibility of a group by genetic test result interaction via logistic regression. For surgery decisions, we compared uptake of CPM in RGCT compared to UC with chi-square analysis. We repeated this analysis stratified by test result using chi-square and Fisher Exact tests. To identify independent predictors of CPM uptake, we included all variables with a significant ($p < .05$) bivariate association with CPM in the first step of a multivariable logistic regression with backward variable selection. We controlled for group assignment by forcing it to remain in the final model.

Sample Characteristics—Among the 285 participants who received negative test results or opted against testing, 69% were non-Hispanic white and 31% were racial/ethnic minorities. The majority were college-educated (77%) and married (67%). Participants had a mean age of 46.3 years (SD = 8.5 years) and a mean a priori *BRCA1/2* mutation risk of 11.9% (SD=17.4%).

Group Assignment, Genetic Testing and CPM—In our previous report [20] the RGCT and UC groups did not differ in uptake of genetic testing or CPM. Given the exclusions described above, we repeated these analyses in the current sample and found comparable results. The RGCT and UC groups did not differ in genetic testing uptake (RGCT = 57.6%; UC = 50.5%; χ^2 (df=1, n=304) = 1.39, p=0.24) or use of CPM (26.7% in RGCT and 21.8% in UC; X^2 (df=1, n=304) = 0.84, p=0.36).

Genetic Test Results and CPM—Within the full sample (n=304), genetic test result significantly predicted CPM uptake with 75% (9/12) of participants who learned that they carried a *BRCA1/2* mutation opting for CPM compared to 42.9% (3/7) of those who learned that they carried a VUS, 28.9% (43/149) of those who tested negative and 15.4% (21/136) of those who opted not to be tested (χ^2 (df=3, n=304) = 25.0, p<0.0001).

Predictors of CPM—Because of the small number of positive and VUS results and the high use of CPM within these groups, we limited our subsequent analyses to women who received a negative test result and those who were not tested.

As displayed in Table 1, significant (p<.05) bivariate predictors of CPM were: younger age; non-Hispanic white race/ethnicity; higher a priori mutation risk; not a candidate for BCS; receipt of genetic counseling prior to surgery; receipt of genetic testing; perceived risk for second breast cancer; lower avoidant ideation; higher intrusive ideation; higher knowledge; and having discussed CPM with surgeon prior to baseline survey.

To identify independent predictors of CPM use, we conducted a multivariable logistic regression with backward variable selection in which we initially included all variables with significant (p<.05) bivariate associations with CPM along with group assignment (forced to remain in the model). In the final model (Table 2), the following variables independently predicted CPM: a priori mutation risk (OR: 1.24, 95% CI: 1.07-1.44); patient report of BCS eligibility (BCS candidate vs. not a candidate; OR: 0.27, 95% CI: 0.14-0.55); completing pre-surgical genetic counseling (OR: 2.40, 95% CI: 1.16-4.97), patient report of having discussed CPM with a surgeon (OR: 4.65, 95% CI: 2.33-9.30), avoidant ideation (OR: 0.72, 95% CI: 0.58-0.89) and intrusive ideation (OR: 1.35, 95% CI: 1.10-1.66). The odds of obtaining a CPM were about twice as high for women who completed a genetic counseling session prior to surgery, over four times as high for women who discussed CPM with their surgeon and only one quarter as high for women who were candidates for BCS. Each half standard deviation increase in a priori risk was associated with a 24% increase in the odds of obtaining a CPM and each half standard deviation increase in intrusive thoughts was associated with an 35% increase in odds of CPM while the same increase in avoidant thoughts was associated with a 38% decrease in the odds of CPM.

In exploratory analyses, we tested the following variables as potential moderators of the association between group assignment (RGCT vs. UC) and CPM uptake: race/ethnicity, knowledge, intrusion, avoidance, discussion of CPM with surgeon, objective risk and eligibility for BCS. We tested each moderator separately by adding their main effect term (if not already in the model) and the randomization group by moderator interaction term to the final main effect model described above. None of the interactions approached statistical significance ($p > .10$).

Discussion

As in prior studies, most (75%) patients who learned that they carry a *BRCA1/2* PV opted for CPM [19, 21, 22]. Among those who received a negative test result, the 28.9% CPM uptake rate is consistent with the 20% to 37% uptake reported in prior studies [19, 23, 24, 33, 34]. This consistency is striking considering the differences among these populations and the 15-year time span across these studies. In contrast, in 2004 we found that 4% of test decliners opted for CPM [19] while here we found that 15% chose CPM. In our multivariable analyses, CPM uptake did not differ between those who tested negative and those who declined testing. These results align with a recent study that also reported a 15% CPM rate among untested patients [34] and other reports documenting overall increases in CPM among newly diagnosed breast cancer patients [25, 35, 36].

Discussing CPM with a surgeon at the time of diagnosis (i.e., prior to the baseline survey) was the strongest predictor of subsequent CPM receipt. Surgeon's recommendation has consistently emerged as a key predictor of CPM [19, 37] including a recent retrospective study of patients with a negative test result [24]. We distinguished between discussion of CPM and CPM recommendation. At baseline, few patients reported an explicit CPM recommendation, but over one-third reported having discussed the option of CPM. Of the patients who reported discussing CPM with their surgeon, 42% obtained a CPM compared to only 11% of those who did not report a discussion. This aligns with a recent population-based report, which indicated that after mutation status, surgeon characteristics and preferences are key predictors of CPM decisions [9]. In our study, it is unclear whether these initial discussions were initiated by the surgeon or by patients who were already considering CPM. Nonetheless, it is striking that a discussion of CPM so soon after diagnosis served as a strong independent predictor of surgical choices that were implemented weeks to months in the future. Further research is needed to better understand the decision-making process prior to genetic testing since these data suggest that the groundwork for subsequent CPM decisions may be laid prior to genetic counseling referral.

Several other clinical variables also predicted CPM use. Patients who reported that they were not candidates for BCS were more likely to obtain a CPM. This is consistent with a recent study of young stage I to III breast cancer patients [38]. Beyond risk reduction, this likely reflects considerations related to reconstructive surgery [39, 40]. For example, these patients may be more likely to be referred to a plastic surgeon who might raise the topic of CPM. A priori mutation risk also independently predicted CPM. Patients at higher risk were more likely to opt for CPM – likely due to their higher risk for contralateral breast cancer. A priori

risk may be an especially important factor in patients who test negative or opt against testing. In contrast, a priori risk is less relevant for patients who learn that they carry a PV.

Participation in presurgical genetic counseling and baseline cancer distress also predicted CPM use. Patients who participated in genetic counseling prior to surgery may have been motivated by their interest in CPM or by a surgeon's referral following a CPM discussion. Thus, the higher CPM rate in this group is not surprising. Patients who reported high cancer-specific intrusive thoughts at baseline were also more likely to obtain CPM. While higher intrusive thoughts may be a partial consequence of considering CPM, it is more likely that these intrusive thoughts reflect worries about the cancer diagnosis, which then motivated CPM uptake. Indeed, in prior studies, CPM intentions and uptake have been predicted by distress, fear of recurrence, anxiety, and lack of optimism [7, 27, 38]. These results contrast to a recent study by Hamilton and colleagues [24], which found no association between psychosocial factors and CPM uptake. Differences between the studies may explain this discrepancy. The Hamilton study focused exclusively on women with a negative genetic test result whereas we included women who opted against testing. It is possible that patients who proceeded with CPM without undergoing genetic testing were more motivated by psychosocial factors than those who opted to pursue genetic testing. The second difference is that we assessed psychosocial factors prior to the receipt of CPM. The receipt of CPM has been shown to yield reduced cancer worry [41]. Thus, the impact of psychosocial factors may be more apparent when data are collected prospectively.

The fact that objective risk and BCS eligibility predict uptake suggests that CPM decisions are being guided by objective factors associated with the potential benefits of CPM. Similarly, discussion with surgeon and the receipt of presurgical genetic counseling predicted CPM, suggesting that patient decisions are being made with the support of their providers. However, the finding that baseline psychosocial factors were related to receipt of CPM suggests that more attention should be paid to these issues when counseling newly diagnosed breast cancer patients about their treatment options.

This study predates the emergence of multigene panel testing (MPT). It is likely that MPT will alter the pattern of CPM usage among breast cancer patients. MPT's increased sensitivity and comprehensiveness identifies more PVs than single gene testing [42,43]. Thus, the broad use of MPT could lead to increased CPM among the greater number of patients receiving positive test results. On the other hand, a negative MPT may be more informative and reassuring than a negative single-gene result. This could reduce CPM use among patients who receive negative test results. Finally, MPT yields more VUS results. Although this study had few VUS results, it is worth noting that 42% CPM rate among those with VUS results. Other recent studies have found that 10% to 21% of breast cancer patients with VUS results opt for CPM [22, 33]. Going forward it will be crucial to ensure that patients and surgeons fully understand the implications of such results.

This study has several limitations. This was not a population-based study, the total number of surgeons and genetic counselors across sites was limited, and all participants were enrolled in a randomized controlled trial focused on genetic counseling. These factors could limit the generalizability of the study. However, the consistency between our CPM rates and

those of prior studies adds confidence to the generalizability of these findings. Second, this study predates the emergence of MPT as well as recent reductions in cost and time needed for genetic testing. Thus, we recommend caution in extrapolating these results to current practice. Third, although this was a prospective study, participant recall bias could have impacted the results. Patient reports of having discussed CPM with a surgeon may reflect biased recall such that these conversations were more salient to those who were considering CPM. Finally, although our sample was diverse, the overall number of minority participants was too low for subgroup analyses. This is an important consideration as previous work has identified disparities in the delivery of cancer genetic services [44].

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Fig 1.
Study Flow Chart

Table 1Bivariate predictors of CPM among *BRCA1/2* negative and untested

		No BLM (N=221)	BLM (N=64)
<i>Continuous Predictors</i>		Mean (SD)	Mean (SD)
Age		46.8 (8.5)	44.5 (8.5) *
BRCAPRO Probability (%)		9.5 (14.5)	20.2 (27.2) **
Perceived Risk Contralateral Breast Cancer		33.9 (23.3)	45.5 (27.4) ***
FACT-Total		90.2 (10.5)	90.7 (9.7)
IES – Avoidance		15.4 (9.6)	12.3 (8.5) *
IES - Intrusion		17.8 (10.3)	20.9 (9.4) *
BSI -Total		37.8 (13.7)	41.1 (13.9)
Knowledge		51.2 (21.7)	60.3 (17.7) **
Decisional Conflict		18.0 (23.9)	18.2 (22.5)
<i>Categorical Predictors</i>		N (%)	N (%)
Randomization Arm			
	Usual Care	74 (79.6)	19 (20.4)
	RGC	147 (76.6)	45 (23.4)
Education			
	< College Graduate	54 (81.8)	12 (18.2)
	College Graduate +	167 (76.3)	52 (23.7)
Marital Status			
	Not Married	72 (76.6)	22 (23.4)
	Married	149 (78.0)	42 (22.0)
Race [#]			
	Racial/Ethnic Minority	75 (85.2)	13 (14.8) *
	Non-Hispanic White	146 (74.1)	51 (25.9)
Employment			
	Not Employed	64 (80.0)	16 (20.0)
	Currently Employed	157 (76.6)	48 (23.4)
Jewish Ancestry			
	Non-Jewish	201 (78.5)	55 (21.5)
	Jewish	20 (69.0)	9 (31.0)
Discuss BLM with Physician			
	No	162 (88.5)	21 (11.5) ***
	Yes	59 (57.8)	43 (42.2)
Genetic Testing			
	No	115 (84.6)	21 (15.4) **
	Yes	106 (71.1)	43 (28.9)
Pre-Surgical Genetic Counseling			

		No BLM (N=221)	BLM (N=64)
<i>Continuous Predictors</i>		Mean (SD)	Mean (SD)
BCS Candidate	No	118 (87.4)	17 (12.6) ***
	Yes	103 (68.7)	47 (31.3)
Cancer Stage	Not candidate for BCS	47 (58.7)	33 (41.3) ***
	Candidate for BCS	171 (84.6)	31 (15.4)
	Missing	51 (83.6)	10 (16.4)
ER/PR Status	Negative	32 (69.6)	14 (30.4)
	Positive	145 (78.8)	39 (21.2)
	Missing	44 (80.0)	11 (20.0)
Breast Cancer Detected	Routine Mammogram	105 (81.4)	24 (18.6)
	Other	116 (74.4)	40 (25.6)

Legend:

*
p<.05;

**
p<.01;

p<.001

Table 2

Final Logistic Multivariable Regression Model Predicting Uptake of Contralateral Prophylactic Mastectomy

Variables	OR (95% CI)	P value
Randomization [#]	0.85 (0.40, 1.82)	0.68
UC (ref)	--	
RGCT	0.85 (0.40, 1.82)	0.68
Genetic Counseling Timing		
Post-surgery/not counseled (ref)	--	
Pre-Surgery	2.40 (1.16, 4.97)	0.018
A priori mutation risk [%]	1.24 (1.07, 1.44)	0.005
Breast Conservation Candidate		
No (ref)	--	
Yes	0.27 (0.14, 0.55)	<0.001
IES Avoidance [%]	0.72 (0.58, 0.89)	0.003
IES Intrusion [%]	1.35 (1.11, 1.66)	0.004
Discuss CPM With Surgeon		
No (ref)	--	
Yes	4.65 (2.32, 9.30)	<.001

[#] Forced to remain in final model;[%] OR and 95% CI for a change of half a standard deviation.