Contralateral prophylactic mastectomy rate and predictive factors among patients with breast cancer who underwent multigene panel testing for hereditary cancer

Nisreen Elsayegh1, Rachel D. Webster2, Angelica M. Gutierrez Barrera1, Heather Lin3, Henry M. Kuerer4, Jennifer K. Litton5, Isabelle Bedrosian4 & Banu K. Arun1,2

1Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas
2Department of Clinical Cancer Genetics, The University of Texas MD Anderson Cancer Center, Houston, Texas
3Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas
4Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

Abstract

Although multigene panel testing is increasingly common in patients with cancer, the relationship between its use among breast cancer patients with non-BRCA mutations or variants of uncertain significance (VUS) and disease management decisions has not been well described. This study evaluated the rate and predictive factors of CPM patients who underwent multigene panel testing. Three hundred and fourteen patients with breast cancer who underwent multigene panel testing between 2014 and 2017 were included in the analysis. Of the 314 patients, 70 elected CPM. Election of CPM by gene status was as follows: BRCA carriers (42.3%), non-BRCA carriers (30.1%), and VUS (10.6%). CPM election rates did not differ between non-BRCA carriers and BRCA carriers (P = 0.6205). Among non-BRCA carriers, negative hormone receptor status was associated with CPM (P = 0.0115). For those with a VUS, hormone receptor status was not associated with CPM (P = 0.1879). Although the rate of CPM between BRCA carriers and non-BRCA carriers was not significantly different, the predictors of CPM were different in each group. Our analyses shed the light on the increasing use of CPM among patients who are non-BRCA carriers as well those with a VUS. Our study elucidates the differing predictive factors of CPM election among BRCA carriers, non-BRCA carriers, and those with a VUS. Our findings reveal the need for providers to be cognizant that non-BRCA genes and VUS drive women to elect CPM despite the lack of data for contralateral breast cancer risk associated with these genes.

Introduction

Although most breast cancers are sporadic, approximately 5–10% of breast cancers are hereditary, caused by a germline mutation in a myriad of genes implicated in carcinogenesis [1–3]. Mutations in the BRCA1 and BRCA2 genes account for 60–80% of inherited breast cancers [4]. Defining mutation carrier status is crucial because carriers have a 43–84% risk of developing breast cancer and up to a 65% risk of developing contralateral breast cancer (CBC) [4, 5]. Rarer, highly penetrant genes, such as CDH1, PTEN, STK11, and TP53, have similarly been shown to be associated with significantly increased risks of developing breast cancer and some potential association with an increased risk of developing CBC [6–9].

In the past decade, moderately penetrant genes associated with breast cancer, such as ATM, CHEK2, and PALB2, have also been shown to increase the risk of developing breast cancer (between 18.3% and 44%) [10, 11]. Studies on these more recently described genes have yet to definitively determine the likelihood of second primary breast cancers owing to the paucity of data. Multiple sources report a significant increase in CBC risk among CHEK2 mutation carriers, yet other studies did not show a significant association between CHEK2 and CBC [12–15]. The WECARE study showed that ATM mutations are associated with an elevated risk
of CBC, but that association is largely dependent on the use of radiotherapy during treatment of initial breast cancer [16–18]. Tischkowitz et al. also published data from the WECARE study showing a higher rate of PALB2 mutations in women with CBC compared with those with unilateral breast cancer [19]. Many of these studies had small sample sizes or presented conflicting data, suggesting that the risk of developing CBC in patients with moderately penetrant gene mutations is still up for debate.

Clinical guidelines developed over the past two decades, such as those presented by the National Comprehensive Cancer Network (NCCN), recommend additional breast cancer screening and consideration of contralateral prophylactic mastectomy (CPM) for breast cancer patients with BRCA1 and BRCA2 mutations to address the risk of developing a second primary cancer. The most recent iteration of these guidelines now addresses the appropriate screening considerations for individuals with deleterious mutations in moderately penetrant genes, like the guidelines for rarer, highly penetrant genes with a less established association with developing a second primary breast cancer. The National Comprehensive Cancer Network (NCCN) guidelines encourage consideration of family history for CPM decisions. In the absence of sufficient data and clear consensus guidelines, patients and their physicians are tasked with determining the appropriate course of treatment as the rate of CPM increases among all patients with breast cancer [20, 21].

While there has been an uptake in multigene panel testing in patients with cancer, the management trends of breast cancer patients with non-BRCA mutations or variants of uncertain significance (VUS) have not been well described. This study aimed to evaluate the rate and predictive factors of CPM in a cohort of individuals who underwent multigene panel testing. We also aimed to determine whether predictors of CPM differed by gene implicated or result type.

Methods

Three hundred and fifty patients diagnosed with ductal carcinoma in situ or invasive breast cancer who underwent genetic counseling and multigene panel testing between 2014 and 2017 were identified from a prospectively maintained research registry in the Department of Clinical Cancer Genetics at The University of Texas MD Anderson Cancer. The study was approved by the MD Anderson institutional review board. Each patient underwent genetic testing and received pretest genetic counseling per standard of care. The following genes were included in the multigene panel: APC (2), ATM (17), BARD1 (2), BRCA1 & BRCA2 (71), BRIP1 (4), CDH1 (5), CDKN2A (2), CHEK2 (19), MEN1 (1), MLH1 (1), MUTYH (2), NBN (1), PALB2 (17), PMS2 (2), PTEN (5), RAD51C (1), and TP53 (11). After the testing, all results were disclosed by a genetic counselor.

Patients with bilateral breast cancer and patients who had CPM before they underwent multigene panel testing were excluded from our analysis, as were patients with a negative genetic test result. After excluding the 36 patients who elected CPM before genetic testing, we were left with 314 patients who had a pathogenic or likely pathogenic mutation or VUS. For analysis simplicity and the very small number of non-BRCA genes included in the panel, we combined all the non-BRCA carriers together, all patients with VUS in either BRCA or non-BRCA genes together. Therefore, the analysis compared three groups: non-BRCA carriers (all other genes listed above), BRCA1 (BRCA1 or BRCA2) carriers, and those with a VUS.

We examined predictors of CPM that occurred between the date on which test results were disclosed and the time of CPM election. For patients who had not elected CPM by the time of data analysis, times were censored at the last contact at which the patient was known not to have elected CPM, alive, or dead. The median follow-up time was 8.6 months. The distribution of time to CPM election for each group was estimated using the Kaplan–Meier method [22]. The log-rank test was used to determine the differences in the distributions of time to CPM between groups [23].

Regression analyses of time to CPM were conducted using the Cox proportional hazards model [24]. Martingale residuals were used to check the function form of continuous variables, including age at diagnosis and at genetic testing, in the Cox proportional hazards models. A multivariable Cox proportional hazards model was obtained by first including a set of candidate predictor variables with a P value <0.10 in a univariate analysis. Because age at diagnosis and age at genetic testing were correlated, we chose age at genetic testing for the multivariable analysis because its association with time to CPM was more pertinent to answering our research question. Backward elimination was then performed using P < 0.05 for the significance level of the Wald chi-square for an effect to stay in the model. Once the list of variables in our final model was selected, we further assessed the interaction effect on time to CPM between gene status and other variables to determine whether the predictors of electing CPM after genetic testing differed by final gene status. SAS version 9.4 and S-Plus version 8.2 were used to carry out the computations for all analyses.

Results

Table 1 shows patient demographic and clinical characteristics. Of the 314 patients, 70 elected CPM and 244 did not. Election of CPM by gene status was as follows: 30 of
the 71 BRCA1/BRCA2 carriers (42.3%), 22 of the 73 non-BRCA carriers (30.1%), and 18 of the 170 with a VUS (10.6%). The mean age at genetic testing was 49.3 years.

Univariate analysis (Table 2) showed that patients aged 50 years or younger at the time of genetic testing were more likely to elect CPM ($P = 0.0006$). Educational status was also significantly associated with CPM such that those with advanced degree were likely to elect CPM than those lower educational level ($P = 0.03$).

After adjustment for age, the multivariable Cox proportional hazards regression model revealed that BRCA carriers and non-BRCA carriers were both more likely to elect CPM than those who had a VUS ($P < 0.0001$; Table 3). CPM election rates did not significantly differ between patients who were non-BRCA carriers and those who were BRCA carriers ($P = 0.6205$; Table 3), even after adjustment for age.

A cumulative incidence plot for election of CPM after genetic testing showed that the rate of CPM election among BRCA carriers over 6 months and non-BRCA carriers over 12 months was greater than the rate of CPM election among those who had a VUS ($P < 0.0001$; Table 3). CPM election rates did not significantly differ between patients who were non-BRCA carriers and those who were BRCA carriers ($P = 0.6205$; Table 3), even after adjustment for age.

Analysis of predictors of CPM election revealed an interaction between gene mutation status and hormone receptor status in predicting CPM election, after adjustment for age at genetic testing ($P = 0.0053$). As shown in Table 5, for

| Characteristic No. (%) |
|------------------------|
| Nuclear grade          |
| I                      | 29 (9.2)           |
| II                     | 112 (35.7)         |
| III                    | 136 (43.3)         |
| Unknown                | 37 (11.8)          |
| TNM stage              |
| 0                      | 31 (9.9)           |
| 1                      | 89 (28.3)          |
| 2                      | 106 (33.8)         |
| 3                      | 53 (16.9)          |
| 4                      | 18 (5.7)           |
| Unknown                | 17 (5.4)           |
| Gene status            |
| BRCA carrier           | 71 (22.6)          |
| BRCA variant of uncertain significance | 38 (12.1) |
| Non-BRCA carrier       | 73 (23.2)          |
| Non-BRCA variant of uncertain significance | 132 (42.0) |
| Hormone receptor status|
| Positive               | 223 (71.0)         |
| Negative               | 69 (22.0)          |
| Unknown                | 22 (7.0)           |
| Her2 status            |
| Positive               | 42 (13.4)          |
| Negative               | 216 (68.8)         |
| Unknown                | 56 (17.8)          |

Table 1. Demographic and clinical characteristics of patients with breast cancer who underwent multigene panel testing ($n = 314$).

| Characteristic No. (%) |
|------------------------|
| Contralateral prophylactic mastectomy |
| Yes 70 (22.3)           |
| No 244 (77.7)           |
| Personal history of ovarian cancer |
| Yes 55 (17.5)           |
| No 259 (82.5)           |
| Marital status          |
| Divorced 29 (9.2)       |
| Married 212 (67.5)      |
| Separated 5 (1.6)       |
| Single 39 (12.4)        |
| Widowed 11 (3.5)        |
| Unknown 18 (5.7)        |
| Race/ethnicity          |
| Hispanic 46 (14.6)      |
| White 203 (64.6)        |
| Black 34 (10.8)         |
| Other 29 (9.2)          |
| Unknown 2 (0.6)         |
| Education               |
| Advanced degree 45 (14.33) |
| Bachelor’s degree 71 (22.61) |
| High school 11 (3.50)   |
| Some college or technical school 14 (4.46) |
| Unknown 173 (55.10)     |
| First-degree family history of breast cancer |
| 0 215 (68.5)           |
| ≥1 97 (30.9)           |
| Unknown 2 (0.6)        |
| Total no. of relatives with a breast cancer diagnosis |
| 0 101 (32.2)           |
| ≥1 211 (67.2)          |
| Unknown 2 (0.6)        |
| First-degree family history of ovarian cancer |
| 0 297 (94.6)           |
| ≥1 15 (4.8)            |
| Unknown 2 (0.6)        |
| Total no. of relatives with an ovarian cancer diagnosis |
| 0 262 (83.4)           |
| ≥1 50 (15.9)           |
| Unknown 2 (0.6)        |
| Estrogen receptor status |
| Negative 69 (22.0)     |
| Positive 223 (71.0)    |
| Unknown 22 (7.0)       |
| Progesterone receptor status |
| Negative 103 (32.8)   |
| Positive 187 (59.6)    |
| Unknown 24 (7.6)       |

(Continued)
BRCA carriers, hormone receptor status was not associated with CPM election \( (P = 0.5657) \), but for non-BRCA carriers, negative hormone receptor status was associated with CPM election \( (P = 0.0115) \). For those with a VUS, hormone receptor status was not associated with CPM election \( (P = 0.1879) \). However, age \( \leq 50 \) years was associated with CPM election in this group \( (P = 0.0286) \).

**Discussion**

Our results showed that, overall, 23\% of patients with breast cancer who underwent multigene panel testing with a non-negative result, including BRCA carriers, non-BRCA carriers, and those with a VUS, opted for CPM, up from the average of 7\% among breast cancer patients [20]. Patients who had a pathogenic variant identified were more likely to elect CPM than those with a VUS, no matter which gene was implicated.

Moreover, patients aged 50 years or younger were more likely to elect CPM than older patients for all genes included in this cohort, and patients with an advanced educational level were also more likely to elect CPM that those with a lower educational level. Predictors and rates of CPM have already been established among patients...
carrying \textit{BRCA1} or \textit{BRCA2} pathogenic variants, but data are lacking regarding predictors and rates of CPM among patients who are carriers of non-\textit{BRCA} pathogenic variants or those with a VUS. Our study revealed that while the rate of CPM between \textit{BRCA} carriers and non-\textit{BRCA} carriers was not significantly different, the predictors of CPM were different in each group.

Few studies have examined the rate and predictors of CPM among non-\textit{BRCA} carriers, although one noteworthy study by Kurian et al. [25] showed a similar trend of self-reported CPM election to that of our study. Their study revealed that patients with a pathogenic variant in \textit{BRCA1}/\textit{BRCA2} or another gene associated with breast cancer were more likely to elect CPM than those with negative results or a VUS. Our study took this a step further to determine that there is no significant difference in CPM rate between \textit{BRCA} carriers and non-\textit{BRCA} carriers. While these groups are receiving CPM at similar rates, it is important to note that their surgical recommendations and risk profiles are significantly different due to the lack of data on CBC rates in non-\textit{BRCA} carriers. Despite the lack of data on CBC risk and the absence of consensus guidelines recommending CPM, both studies confirm a trend of more invasive surgical intervention

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**Table 3.** Multivariate Cox PH model of time to election of contralateral prophylactic mastectomy in patients with breast cancer who underwent multigene panel testing \((n = 314)\).

| Parameter                                      | Hazard ratio | 95% Hazard ratio confidence limits | \(P\)   | \(P\) for overall effect |
|------------------------------------------------|--------------|-----------------------------------|---------|--------------------------|
| Gene Status                                    |              |                                   |         |                          |
| BRCA carriers vs. VUS                          | 4.162        | 2.307–7.509                       | <.0001  | <.0001                   |
| Non-BRCA carriers vs. VUS                      | 3.618        | 1.932–6.775                       | <.0001  | <.0001                   |
| BRCA carriers vs. non-BRCA carriers            | 1.1504       | 0.6606–2.004                      | 0.6205  | <.0001                   |
| Age at genetic testing                         |              |                                   |         |                          |
| <50 vs. ≥50                                    | 2.321        | 1.321–4.080                       | 0.0034  | <.0001                   |

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**Table 4.** Rates of contralateral prophylactic mastectomy (CPM) election by age at genetic testing and test results among patients with breast cancer who underwent multigene panel testing \((n = 314)\).

| Variable                        | CPM/total | 6 months after genetic testing | 12 months after genetic testing |
|---------------------------------|-----------|-------------------------------|-------------------------------|
| Age at genetic testing          |           |                               |                               |
| <50 years                       | 54/182    | 26.0 (19.3–34.4)              | 40.3 (31.8–50.0)              |
| ≥50 years                       | 16/132    | 11.7 (6.9–19.6)               | 15.0 (9.1–24.3)               |
| Genetic test results            |           |                               |                               |
| \textit{BRCA} carrier           | 30/71     | 29.9 (19.5–44.2)              | 55.4 (41.1–70.8)              |
| Variant of uncertain significance | 18/170    | 9.2 (5.3–15.7)                | 13.4 (8.3–21.2)               |
| Non-\textit{BRCA} carrier       | 22/73     | 36.4 (24.7–51.4)              | 43 (29.7–59.1)                |

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**Table 5.** Predictors of contralateral prophylactic mastectomy election among patients with breast cancer who underwent multigene panel testing \((n = 314)\).

| Variable                        | \(P\)     | Hazard ratio | 95% Confidence interval |
|---------------------------------|-----------|--------------|-------------------------|
| Age <50 vs. ≥50 years           |           |              |                         |
| \textit{BRCA} carrier           | 0.5703    | 1.283        | 0.543–3.029             |
| Non-\textit{BRCA} carrier       | 0.0941    | 2.382        | 0.862–6.578             |
| Variant of uncertain significance | 0.0286   | 3.801        | 1.150–12.56             |
| Negative hormone receptor status |         |              |                         |
| \textit{BRCA} carrier           | 0.5657    | 0.796        | 0.366–1.732             |
| Non-\textit{BRCA} carrier       | 0.0115    | 3.278        | 1.305–8.230             |
| Variant of uncertain significance | 0.1879  | 0.316        | 0.057–1.756             |
for individuals with breast cancer and any hereditary predisposition to cancer.

The rate of CPM election among BRCA carriers has been well established given that bilateral prophylactic mastectomy (BPM) reduces the risk of developing breast cancer by more than 90% [26]. Among BRCA carriers, 65% of those with breast cancer and 15–60% of unaffected individuals elect prophylactic surgeries [27–30]. Factors associated with prophylactic surgery among BRCA carriers with breast cancer include age, type of initial breast cancer surgery, prophylactic oophorectomy, desire to have children, and family history of breast cancer [31–34]. Moreover, a study of CPM election rates among patients with ductal carcinoma in situ who were BRCA-positive, BRCA-negative, or untested showed that 27% opted for the surgery, and age, family history of ovarian cancer, and BRCA positivity predicted CPM election. The present study showed similar factors associated with CPM election in the cohort as a whole, including BRCA carriers, non-BRCA carriers, and those with a VUS. The predictors varied, though, when comparing each of these groups with one another.

Among non-BRCA carriers, negative hormone receptor status predicted CPM election. Moreover, previous studies without an emphasis on genetic testing results indicated that the risk of developing CBC in hormone receptor-negative breast cancers is 1.6-fold higher than in hormone receptor-positive breast cancers [35]. Given the increased risk, it stands to reason that patients with hormone receptor-negative breast cancer are more likely to elect CPM than those with hormone receptor-positive breast cancer [36]. Additionally, Brewster et al. [37] found that CPM was associated with improved disease-free survival in patients with hormone receptor-negative breast cancer. Although these factors could explain the CPM election rate in the general population, their application to our population is less clear because genetic results were not included in that analysis. Future studies are needed to determine whether the same factors are evident among patients who undergo multigene panel testing. It is important to note that the small sample size in the group of patients who were non-BRCA carriers makes it hard to reach a solid conclusion that hormone receptor-negative status is a significant factor for CPM among non-BRCA carriers. However, we think the magnitude of the hazard ratio associated with it is not negligible. This finding warrants further validation in future large studies. Additionally, the insignificant association between hormone receptor status and CPM for the BRCA carrier’s group in this study could be due to the small sample size. This finding also needs to be further explored with a larger sample size.

Finally, age ≤50 years predicted CPM election for those who had a VUS in our analysis. Age is a well-established significant predictor of CPM election among BRCA carriers [27–30]. Our study provided evidence that age also seems to affect the decision to elect CPM among those with a VUS. However, future studies with a larger sample are needed to confirm these findings further clarify how the VUS population differs from the general population of patients with breast cancer.

The decision-making process for the election of CPM is complex and entails several driving forces, including the possible anxiety of receiving a positive genetic testing result. Studies suggest that CPM election may also be influenced by biopsies, screening costs and fatigue, cosmetic considerations, psychological factors, and perceived emotional advantages of CPM, among others [38, 39]. Also, these patients had to make their decision about CPM on the basis of the treatment planned for their unilateral breast cancer, so their desire to avoid repeated treatment (CBC) could have influenced the decision.

Future prospective studies are needed to determine whether the same psychosocial factors influence the surgical decision making of individuals with hereditary cancer predispositions beyond BRCA1 and BRCA2.

Despite the rapid growth of next-generation sequencing allowing for simultaneous testing of multiple genes linked to cancer risk, the clinical impact of pathogenic variants in genes beyond BRCA1 and BRCA2, especially in terms of CBC risk, is still largely unknown. Therefore, physicians are faced with the dilemma of making surgical recommendations without CBC risk data for genes often included on multigene panel tests marketed for patients with breast cancer. Our study indicates that patients are still opting for CPM as a measure of prevention even though substantive data on the potential need for this surgery is unavailable. It is also important to note that there are potential harms associated with CPM, such as postsurgical complications and concerns with body image, femininity, and sexuality [39]. It is not clear that increased CPM in non-BRCA carriers will improve disease-specific or overall survival. While long-term prospective studies are needed to determine whether CPM is the ideal clinical intervention for non-BRCA carriers, our data suggest the need for additional provider and patient education on the known and unknown CBC risks to aid in treatment planning.

To the best of our knowledge, our study is the first to uniquely evaluate CPM election rates and predictors of CPM election among patients who are non-BRCA carriers and those with a VUS. Our findings suggest that predictors of CPM election may differ among non-BRCA carriers and those with a VUS from those who are BRCA carriers. Our findings also highlight the similarity in CPM election rates among BRCA carriers and non-BRCA carriers despite the lack of evidence concerning CBC risk.
among those with a non-BRCA mutation. This finding suggests that patients with a non-BRCA mutation may have similar perception of CBC risk as those with a BRCA mutation. The follow-up in this study time was less than a year from the time of genetic testing to date of CPM; it is important to highlight that the rate of CPM may increase with longer follow-up. Future studies are needed to track CPM rate in this cohort for longer follow-up period.

A few limitations of this study are worthy of consideration when interpreting the results. The authors recognize that is this a retrospective review in a cohort of patients who were referred for genetic counseling and testing at a large academic research hospital with genetic services integrated into the patient care team. Therefore, this population likely has a different level of post-test education on their genetic testing results than the average breast cancer patient.

The predictors of CPM and issues of patient education may differ in hospital settings without easy access to genetic counseling. Our findings may need to be replicated in a study with a larger sample size to allow for generalizability; subgroup analyses should be interpreted with caution given the small sample sizes. Moreover, previous research has found an association between preoperative MRI and CPM [40]. However, we did not collect information on the use of preoperative MRI in this cohort which posed another limitation to our findings. Future prospective studies need to address this association among individuals undergoing multigene panel testing. Finally, future prospective studies are needed to evaluate the complex decision-making processes and the potential implication of genetic test results leading to CPM for individuals who undergo multigene panel testing. The present study identified demographic and clinical predictors of CPM in individuals undergoing multigene panel testing, but further research into patient’s motivation to undergo CPM is needed.

Conclusion

The present study reports CPM election rates specifically among patients with breast cancer who underwent multigene panel testing. Our analyses shed the light on the increasing use of CPM among patients who are non-BRCA carriers as well those with a VUS. Our study elucidates the differing predictive factors of CPM election among BRCA carriers, non-BRCA carries, and those with a VUS. These differing predictors may need to be considered in clinical recommendations for potential preventive surgeries. Our findings reveal the need for providers to be cognizant that non-BRCA genes and VUS drive women to elect CPM despite the lack of data for CBC risk associated with these genes. Factors driving their decision need to be carefully addressed.

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Conflict of Interest

The manuscript has never been published and is not under consideration for publication elsewhere. The authors have no financial disclosures to declare.

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