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Research Article

Impact of Genetic Testing on Breast Cancer Surgery: Are the Variants Significant?

Danielle Henry[1], Marie Lee[2], Deanna Almanza[2], Weihong Sun[2], David Boulware[3], and Christine Laronga[2]*

[1]*Department of Breast Surgical Oncology, Orlando Health UF Health Cancer Center, USA*

[2]*Department of Breast Oncology, H. Lee Moffitt Cancer Center and Research Institute, USA*

[3]*Department of Biostatistics, H. Lee Moffitt Cancer Center and Research Institute, USA*

***Corresponding author**

Christine Laronga, Department of Breast Oncology, H. Lee Moffitt Cancer Center and Research Institute, 10920 N. McKinley Drive, Tampa, FL 33612, USA, Tel: 1-813-745-2480; Fax: 1-813-745-728; Email: Christine.Laronga@Moffitt.org

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Abstract

Background: With increasing variant of unknown significance (VUS) genetic testing (GT) results, we evaluated the significance on surgical management for breast cancer patients.

Methods: Patients from an IRB-approved database recruited from November 2000 to January 2017 with a VUS and history of breast cancer were identified. Self-reported questionnaire data was collected. Groups were compared using Chi-square, Fisher's Exact or Kruskal-Wallis test by surgical type and timing of GT.

Results: Seventy-nine VUS patients with breast cancer and questionnaire data were identified and studied. Initial surgical management was: 35 (44%) lumpectomies, 15 (19%) unilateral mastectomies and 29 (37%) bilateral mastectomies. Fifteen (19%) patients with bilateral breast cancer were excluded from analyses. Patients with VUS diagnosis before surgery, chose contralateral prophylactic mastectomy (CPM) more than diagnosis after surgery, but it was not statistically significant (50% vs 32%, p=0.215).

Conclusions: A VUS influences, but not statistically significantly, surgical decision making. Appropriateness for CPM should not rely on a VUS result.

ABBREVIATIONS

NCCN: National Comprehensive Cancer Network; VUS: Variant of Unknown Significance; ASCO: American Society of Clinical Oncology; RRM: Risk Reducing Mastectomy; ICARE: Inherited Cancer Registry; TM: Therapeutic Mastectomy; CPM: Contralateral Prophylactic Mastectomy

INTRODUCTION

A hereditary cause of breast cancer is suggested when multiple family members have developed breast and/or other cancers with an autosomal dominant inheritance pattern [1]. The recognition of an autosomal dominant pattern of breast cancer in families led to the discovery of the breast cancer susceptibility genes, BRCA1 and later BRCA2, in the 1990s [2-5]. When BRCA testing became commercially available in 1996, the American Society of Clinical Oncology released a consensus statement that genetic testing is recommended when three criteria are met: a personal or family history suggesting genetic cancer susceptibility, adequate interpretation of the test results, and the results will aid in the diagnosis or influence medical or surgical management of the patient or family members at risk for cancer [1,6].

Since that time, due to the end of the BRCA testing patent and advancements in genomic sequencing, we are able to offer more affordable and timelier testing. Although hereditary breast cancer still only accounts for approximately 5-10% of all breast cancers, within this minority we are now able to test for additional heritable genes that portend an increased risk for breast cancer when altered (pathogenic mutations) [1,7]. The use of multigene panel tests is increasing and the genetic testing landscape continues to evolve [8]. Based on the National Comprehensive Cancer Network (NCCN) guidelines, the most clinically relevant genes for an increased risk of breast cancer include: BRCA1, BRCA2, PTEN, TP53, ATM, CDH1, CHEK2, NBN, NF1, PALB2 and STK11 [9]. With more genes identified and varied implications of each mutation, American Society of Clinical Oncology (ASCO) updated the guidelines in 2010 to include the addition of genetic counseling with genetic testing [10].

Genetic counseling is essential for accurate interpretation of genetic testing results. This is especially important when testing for multiple genes, since there is a higher chance of getting a variant of unknown significance (VUS) [9,11]. A VUS is a mutation identified in a gene that has an unknown effect on protein function [12]. Currently not much is known about a VUS in regards to

clinical significance, which creates a counseling dilemma. As a result, a VUS is treated as a negative result. Overtime, a VUS can be reclassified definitely as a benign polymorphism (negative result) that is unrelated to an increased breast cancer risk. A VUS can also later be reclassified as a pathogenic mutation and indicate higher risk. Most reclassifications represent the former, with only 1-6% of VUS being reclassified as pathogenic [13,14]. Given the aforementioned, other factors that may make a person at an increased risk for the development of breast cancer should be considered in addition to a VUS result, such as a personal and/or family cancer history. These things may be more consistent with an familial cancer syndrome, and not simply the genetic testing results [15]. It is important to note that validated risk stratification models, such as the Gail Model and Tyrer-Cuzick, are not applicable to patients who have already been diagnosed with breast cancer, as they are intended for unaffected patients with multiple risk factors for breast cancer [16,17].

A patient may undergo genetic testing at one of three different time points in their lifetime: unaffected, after diagnosis of breast cancer but before definitive treatment, or after diagnosis and definitive treatment. The most immediate implications are among those who undergo testing after diagnosis but before definitive treatment [2]. When testing yields a positive (pathogenic) result, these results are associated with causing cancer. Risk-reducing surgery, such as risk-reducing mastectomy (RRM), has been shown to significantly reduce the risk of developing a contralateral breast cancer and improve overall survival in carriers of BRCA1 and BRCA 2 pathogenic mutations [1]. However, these risk reducing surgical benefits have not been proven for patients with a VUS.

A number of factors contribute to a patient's surgical decision making. Current trends suggest genetic testing makes a significant impact in surgical decision making, and not always appropriately. Kurian et al., showed that up to 50% of surgeons treated a patient with a BRCA1/2 VUS the same as a patient with a pathogenic mutation. What is more, bilateral mastectomy rates range from 25-51% in patients with a VUS for BRCA1/2, which could represent overtreatment [13,18]. Given the increasing number of VUS results and variation in treatment patterns, we sought to evaluate the significance of a VUS genetic testing result on primary index breast cancer management.

MATERIAL AND METHODS

The study population was derived from the Inherited Care Registry (ICARE), which is an IRB-approved international database of volunteer subjects recruited from November 2000 to January 2017 interested in participating in studies about inherited cancer. Participants were recruited from the institutional genetics clinic, internal and external providers, and social media outlets and genetics conferences.

After consent was obtained, participants were mailed a comprehensive questionnaire which ascertained self-reported demographic, clinical and family history. Within this questionnaire, knowledge about inherited cancer was assessed with a series of statements and the options for response were "TRUE", "FALSE" or "DON'T KNOW". Specific to this study, the statement "All individuals who have an altered inherited cancer gene get cancer" was chosen for analysis. The Cancer Worry Scale was also included in the questionnaire, for which the question "How worried are you about getting breast cancer someday?" was specifically chosen for analysis in this study. The options for response to the aforementioned question were" Not at all", "Rarely", "Sometimes", "Often", "Almost all the time". All patient responses were coded into a secured database.

All participants within the ICARE database with a documented variant of unknown significance for 1 or more of the 11 high and moderate penetrant genes for breast cancer per the 2017 NCCN guidelines were identified. Participants who had a documented concurrent deleterious mutation for any gene were then excluded. Participants with a reported history of breast cancer were selected for analysis. Self-reported demographic, clinical and questionnaire variables were collected. Results were reported as frequencies for the categorical variables and medians (ranges) for continuous variables. Comparisons between groups were performed using either the Chi-square test or Fisher's Exact test for categorical variables and the non-parametric Kruskal-Wallis test for continuous variables. A separate analysis was performed excluding patients who had surgery before 1996, prior to when genetic testing was commercially available, to adjust for any potential differences between groups. Ultimately, these patients were included in the final analysis, as their exclusion did not change the results. All analyses were performed in SAS version 9.4. Tests are deemed significant at the 0.05 significance level (and no corrections were made for multiple testing).

RESULTS

From the 2,252 participants in the ICARE registry, 1,568 participants with a VUS were identified. After excluding participants with a concurrent deleterious mutation, 181 (8%) participants with only a VUS remained. Of the 181 participants, 84 (46%) had a personal history of breast cancer and comprise our study cohort. Self-reported data was available for 79/84 subjects (94% response rate). The cohort was 100% female, 70% white, and 77% had some college education or higher (Table 1). All participants were from the United States, except one participant from the Bahamas. Median age of breast cancer diagnosis was 49, while median age of being diagnosed with a VUS was 59. A VUS of ATM, BRCA1 and BRCA2 were the most frequent. Initial surgical cancer management was as follows: 35 (44%) lumpectomies, 15 (19%) unilateral mastectomies and 29 (37%) bilateral mastectomies. In our cohort, there were 15 (19%) participants with bilateral breast cancer at diagnosis which were excluded from further analyses. Of note, 21/79 (27%) of participants self-reported a second cancer occurrence; the questionnaire responses were not able to classify whether a second occurrence represented a second primary tumor, a recurrent lesion, or a metastatic lesion.

There were 50 (78%) participants who received genetic testing results post-operatively. The median time of postoperative genetic testing was 3 years (range: 0-33 years). Among the postoperative genetic testing group, 16 (32%) had a therapeutic mastectomy plus contralateral prophylactic mastectomy (TM + CPM), 9 (18%) had a unilateral mastectomy and 25 (50%) had a lumpectomy (Figure 1). Of the initial lumpectomy participants, 5/25 (20%) had an in-breast recurrence and opted for therapeutic

Table 1: Demographic and Clinical Characteristics of Patients with breast cancer + VUS, (n=79).

Median age at cancer diagnosis, years (range)	49(27-78)
Median age at VUS diagnosis, years (range)	59(31-79)
Median age at questionnaire, years (range)	59(32-82)
Gene with VUS, *n* (%)	
ATM	16 (20%)
BRCA1	16 (20%)
BRCA2	16 (20%)
BRCA NOS	1(1%)
CDH1	3(4%)
CHEK2	9(11%)
NBN	2(3%)
NF1	3(4%)
PALB2	8(10%)
PTEN	3(4%)
STK11	1(1%)
TP53	1(1%)
Female gender, *n* (%)	79(100%)
Ethnicity, *n* (%)	
White	55(70%)
Hispanic	5(6%)
Black	12(15%)
Asian	4(5%)
Other	3(4%)
Marital Status, *n* (%)	
Married	38
Single	8
Divorced	7
Widowed	23
Cohabitating	3
Some College Education or Higher, *n* (%)	
Yes	61
No	18
Personal History of cancer excluding ovarian cancer, *n* (%)	12
Personal History of Ovarian cancer, *n* (%)	2
First Degree relative with breast cancer *n* (%)	27
Bilateral Breast Cancer, *n* (%)	15
Menopausal Status, *n* (%)	
Premenopausal	26
Postmenopausal	51
Unknown	2
Surgical Management, *n* (%)	
Lumpectomy	35 (44%)
Mastectomy	15 (19%)
Bilateral Mastectomy	29 (37%)
Received Genetic Counseling, *n* (%)	
Yes	68 (86%)
No	3 (4%)
Unknown	8 (10%)
Genetic Testing Timing, *n* (%)	
Pre-operative	16 (20%)
Post-operative	63 (80%)
VUS = Variant of Unknown Significance	

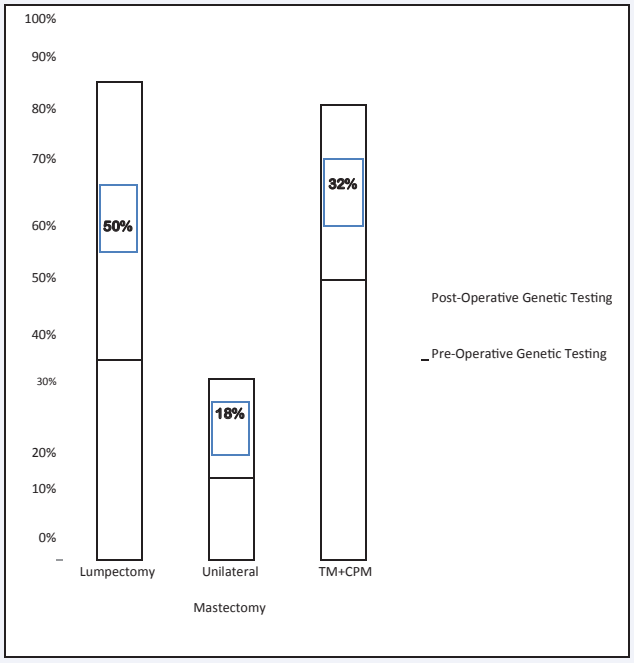

Figure 1 Surgical Distribution (%) by Timing of Genetic Testing. The breakdown of surgical management by genetic testing pre- or post-operatively. There was no significant difference in surgery type by timing of genetic testing (p=0.520). (TM + CPM = Therapeutic Mastectomy + Contralateral Prophylactic Mastectomy).

mastectomy + contralateral prophylactic mastectomy. Of these participants, 3/5 (60%) had genetic testing prior to their conversion to bilateral mastectomy. One mastectomy participant opted for a contralateral prophylactic mastectomy after delayed genetic testing.

There were 14 (22%) participants who received genetic testing results pre-operatively, of which 7 (50%) had a TM + CPM, 2 (14%) had unilateral mastectomy, and 5 (36%) had a lumpectomy.

There were no significant differences between participants who had genetic testing pre- or post-operatively for age at diagnosis of breast cancer, ethnicity, marital status, education level, personal history of ovarian or other cancer, or first degree relative with breast cancer (Table 2). However, the median age at which participants were diagnosed with a VUS was significantly younger for those who had testing pre-operatively compared to those who had testing post-operatively (46 vs 60 years, p=0.013).

Participants who had genetic testing post-operatively were more likely to be postmenopausal at breast cancer diagnosis (71% vs 43%, p=0.048). When comparing only participants that underwent TM + CPM by timing of genetic testing (pre-operatively vs post-operatively), participants who had genetic testing post-operatively were more likely to be post-menopausal at breast cancer diagnosis as well (29% v 88%, p=0.01). When evaluating participants who had genetic testing pre-operatively by surgery type (lumpectomy/ unilateral mastectomy vs TM +CPM), there were no significant differences for age at diagnosis of breast cancer, age at VUS diagnosis, menopausal status, ethnicity, marital status, education level, personal history of ovarian or other cancer, or first degree relative with breast cancer.

Table 2: Comparison of Pre - and Post-Operative Genetic Testing Groups (Excluding Bilateral Breast Cancer) n=64.

	Post-Operative Genetic Testing n=50	Pre-Operative Genetic Testing n=14	p- value*
Median age at cancer diagnosis, years (range)	50 (27-73)	45(39-78)	0.51
Median age at VUS diagnosis, years (range)	60 (31-79)	46(40-79)	0.013
Menopausal Status, *n* (%)			0.048
Premenopausal	14 (29%)		
Postmenopausal	35(71%)	6 (43%)	
Ethnicity, *n* (%)			0.313
White	34(68%)	7 (50%)	
Hispanic	4(8%)	1 (7%)	
Black	8\(16%)	3 (21%)	
Asian	3(6%)	1 (7%)	
Other	1(2%)	2 (14%)	
Marital Status, *n* (%)			0.679
Married	25(50%)	7 (50%)	
Single	4(8%)	3 (21%)	
Divorced	4(8%)	1 (7%)	
Widowed	15(30%)	3 (21%)	
Cohabitating	2(4%)	-	
Some College Education or Higher, *n* (%)	38(76%)	11 (79%)	1
Personal History of cancer excluding Ovarian cancer, *n* (%)	8 (16%)	-	0.183
Personal History of Ovarian cancer, *n* (%)	2 (4%)	-	1
First Degree relative with breast cancer *n* (%)	19 (38%)	4 (29%)	0.754
Surgical Management, *n* (%)			0.52
Lumpectomy	25 (50%)	5 (36%)	
Mastectomy	9 (18%)	2 (14%)	
TM + CPM	16 (32%)	7 (50%)	
Received Genetic Counseling, *n* (%)	46 (100%)	10 (83%)	0.04
Answered FALSE to "All individuals who have an altered inherited cancer gene get cancer", *n* (%)	37 (74%)	7 (50%)	0.115

*For categorical variables, either the Chi-Square test or Fisher's exact test was used, as appropriate. For the continuous variables, the Kruskal-Wallis test was used. TM + CPM = Therapeutic Mastectomy + Contralateral Prophylactic Mastectomy.
Abbreviations: TM + CPM: Therapeutic Mastectomy + Contralateral Prophylactic Mastectomy

A total of 56 (88%) of participants, reported having genetic counseling. Participants who had genetic testing post-operatively were more likely to have received genetic counseling (100% vs 83%, p=0.040). Forty-four (72%) participants answered "FALSE" to "All individuals who have an altered inherited cancer gene get cancer", regardless of having received counseling. Of all participants who ultimately had bilateral mastectomies at the time of questionnaire completion (n=39, 49%), they were significantly more likely to answer "not at all" or "rarely" worried about getting cancer (67% vs 33%, p=0.011).

DISCUSSION

An advantage to patients appropriately tested for a genetic mutation after breast cancer diagnosis is identifying those who will benefit from risk reducing surgery, such as CPM, as population-based risk stratification is no longer applicable. However, one pitfall of genetic testing is when the results are not completely informative, as is the case with a VUS. Ultimately, patients may be more likely to act upon the diagnosis of a VUS when tested before surgery. These patients are more likely to be younger and pre-menopausal, as seen in our cohort who underwent testing pre-operatively. Based on NCCN guidelines for genetic risk evaluation, any patient with a personal diagnosis of cancer ≤ 50 years old (previously ≤ 45 years old) is recommended to undergo genetic testing [9]. This is the rationale for the aforesaid study findings, and these patients should continue testing prior to surgery when available.

With the knowledge of a VUS diagnosis pre-operatively, more participants chose TM + CPM compared to those who tested positive for a VUS post-operatively, however, this was not statistically significant (50% vs 32%, p=0.215). Although this knowledge did not statistically significantly influence TM + CPM rate, a larger proportion of participants in the pre-operative genetic testing group suggests an influence that falls within the range of bilateral mastectomy rates for VUS cancer patients in previously published reports. Welsh at el showed that patients with a BRCA VUS had a prophylactic mastectomy of 22%. Kurian et al., reported that for a white female, ≤ 50 years of age with private insurance and a VUS diagnosis had a 43-51% chance of undergoing bilateral mastectomy.

Genetic counseling is imperative in helping both patients and surgeons decipher the rapidly growing body of knowledge in the genetic testing era. Although not much is known about a VUS, counselors can use other factors in context to help a patient understand their risk for future cancers based on personal and family history that can in turn be used for surgical decision making. Participants in our cohort who had genetic testing pre-operatively were less likely to have genetic counseling. Limited availability of certified genetic counselors and apprehension to delay definitive surgical management are often cited reason for this gap in counseling [19]. Interestingly, with the suggestive influence of a VUS in uptake of contralateral prophylactic mastectomy in this highly educated and counseled cohort, most patients were aware that not "All individuals who have an altered inherited cancer gene get cancer". One explanation for the aforementioned is participants might have felt that statement did not personally apply after already being diagnosed with cancer.

Studies have shown a higher distress rate in BRCA VUS patients compared to negative or pathogenic variants [13]. In our cohort, participants who ultimately had bilateral mastectomies at the time of completing the study questionnaire were significantly less concerned about getting cancer. Although this represents mood after final treatments for cancer, it suggests that fear of future cancer may be one of the driving forces of choosing bilateral mastectomy.

There are some limitations to this study that deserve mention. This is a retrospective study spanning 17 years based solely on self-reported data. Information from participants' medical records, most importantly staging data, was not available for analysis. As a result, exact information regarding staging could not be used to evaluate surgical decision making ability other than in the context of a contralateral prophylactic mastectomy. The time frame of this dataset, which is a strength and limitation, predates commercially available genetic testing and risk stratification models. When adjusting for the year of surgery, this did not change the overall study findings. Even though the diagnosis of a VUS is increasing, it still represents a fairly small number of patients. As a result, our sample size may be too small to reflect a real difference in surgical decision making. Furthermore, the limited self-reported follow-up data regarding second cancer occurrences is insufficient to determine whether second cancer events affected further surgical decision making. Lastly, without case matched controls, no conclusions can be drawn regarding the self-reported second event rate of 27% being above reported recurrence rates in the general population.

Future directions include studying a larger cohort of VUS participants with longer follow-up data to include more clinical data like recurrences, if any. What is more, in follow-up surveys, inclusion of questions aimed at identifying specific reasons for bilateral mastectomy.

CONCLUSION

In this VUS cohort, a VUS was associated with a higher contralateral prophylactic mastectomy rate, though not statistically significant. Although it is not the only factor in surgical decision making, it is imperative that surgeons are aware that a VUS does not have data to support that it confers the same risk as a pathogenic mutation. In the setting of a VUS diagnosis, appropriateness for prophylactic surgery should not rely primarily on genetic testing results. Until further data is available to determine appropriateness of risk reducing strategies, patients with a VUS mutation should be treated as having a negative result and encouraged to join clinical trials to help determine the pathogenicity, if any, of their variant. Additionally, they should be followed in a registry or high-risk clinic to allow for follow-up on their personal and family health.

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