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REVIEW

Trends in use of bilateral prophylactic mastectomy vs high-risk surveillance in unaffected carriers of inherited breast cancer syndromes in the Inherited Cancer Registry (ICARE)

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Abstract

Purpose Awareness of inherited breast cancer has increased bilateral prophylactic mastectomy (BPM) among unaffected genetic mutation carriers, yet many still choose surveillance. We aimed to identify differences among women electing BPM vs high-risk surveillance.

Methods Participants from an IRB-approved database recruited from 11/2000 to 01/2017 with a deleterious/pathogenic, variant suspected deleterious, or likely pathogenic mutation in ≥ 1 of 11 genes with increased risk for breast cancer (per 2017 NCCN guidelines) were identified. Participants with breast cancer and males were excluded. Sociodemographic and clinical data were collected. The BPM and high-risk surveillance groups were compared using Wilcoxon, Fisher's Exact, and Pearson's Chi-Square analyses.

Results A total of 304 unaffected genetic mutation carriers were identified; 22 men were excluded. 113/282 (40%) underwent BPM. There was no significant difference in age, race, marital status, high school graduates, family history of breast cancer, breast biopsies, chemoprevention use, or understanding implications of genetic mutation carriage. BPM participants were more likely to have a prior pregnancy ($p = 0.0005$), college education ($p = 0.04$), income > \$50,000/year ($p = 0.01$), first-degree relative with breast cancer ($p = 0.04$), higher total number of relatives with breast cancer ($p = 0.01$), and rate of risk-reducing salpingo-oophorectomy ($p = < 0.0001$). The high-risk surveillance group was more likely to have a history of ovarian cancer ($p = 0.009$) and cancer worry ($p = < 0.0001$).

Conclusions BPM is a common but not universal choice among unaffected genetic carriers of inherited breast cancer syndromes. Parity, education, income, ovarian cancer history, first-degree relatives with breast cancer, and cancer worry play significant roles in these decisions.

Keywords Prophylactic mastectomy · High-risk surveillance · Genetics · Inherited cancer · Bilateral mastectomy · Family history

Background

Breast cancer is the most common non-cutaneous cancer among women [1], with an estimated 330,080 new cases of invasive and non-invasive cancer cases in 2018 [2]. Identifying individuals who are at an increased risk for breast cancer begins with a thorough history and physical, in which the history includes a 3-generation family pedigree [3, 4]. Family history is integral in determining risk for future cancers, as individuals with one first-degree relative with breast cancer have a 2 times higher likelihood of developing breast cancer [2]. However, family history

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alone is not enough to assess risk for future cancers, as it can overestimate or underestimate risk [5].

A family in which multiple individuals are affected with breast and/or other cancers, across multiple generations in an autosomal dominant pattern of inheritance, at a particularly young age is suggestive of a hereditary breast cancer syndrome [4, 6]. Hereditary breast cancer syndromes result from a mutation in a gene known to cause breast cancer, accounting for 5–10% of all newly diagnosed breast cancers [6, 7], with more than half attributed to BRCA1 and BRCA2 mutations [8]. Since their discovery (BRCA1, BRCA2) in the 1990s, additional genes have been identified that portend an increased risk of breast cancer and confer varying degrees of cancer risk [3]. Based on the National Comprehensive Cancer Network (NCCN) guidelines, the most clinically relevant genes (high and moderate penetrant) contributing to risk of breast cancer development include BRCA1, BRCA2, PTEN, TP53, ATM, CDH1, CHEK2, NBN, NF1, PALB2, and STK11 [4].

When BRCA testing became commercially available in 1996, the American Society of Clinical Oncology released a consensus statement recommending genetic testing when three criteria are met: a personal or family history suggesting genetic cancer susceptibility, adequate interpretation of the test results can be made, and the results will aid in the diagnosis or influence medical or surgical management of the patient or family members at risk for cancer [6, 9]. With the end of the patent for BRCA testing in 2014 and the introduction of next-generation sequencing, we are now able to simultaneously and rapidly test for more genetic mutations that are associated with an increased risk of breast cancer [3, 10]. As such, the NCCN guidelines, which are updated annually, recommend referral for genetic counseling and testing based upon evidence-based criteria for the likelihood of carrying a genetic mutation [4].

Identification of high-risk individuals who are genetic mutation carriers offers practitioners the ability to institute early detection strategies with evidence-based screening and/or risk reduction procedures [3]. Surgical risk reduction with bilateral prophylactic mastectomy offers more than a 90% risk reduction for breast cancer [11–15], 80% reduction in breast cancer specific mortality [12, 16], and overall survival benefit in BRCA mutation carriers [12, 14, 15, 17]. There is less, but sufficient evidence to support discussions regarding risk reduction with bilateral prophylactic mastectomies in mutation carriers of CDH1, PALB2, TP53, and PTEN genes; however, the evidence is not yet clear for other lower penetrant mutations [4, 18]. What is clear is that high-risk surveillance with bi-annual clinical breast exams, yearly mammograms, and MRI markedly increase the likelihood of early cancer detection in high-risk individuals who carry a pathogenic genetic mutation [12, 19–22].

For maximal benefit of information obtained through genetic counseling and testing, high-risk surveillance must be employed and risk-reducing surgeries should be discussed as an option. The rate of bilateral prophylactic mastectomy in BRCA mutation carriers varies widely in reports from 11 to 50% [12, 23–25]. Risk reduction in the form of chemoprevention is significantly underutilized with only 15% of BRCA genetic carriers approached for a chemoprevention trial and a mere 8.5% of BRCA carriers starting chemoprevention within 4 years of genetic testing result [12, 26]. Adherence to high-risk surveillance varies but has been reported above 80% for MRI and mammogram in BRCA genetic mutation carriers [24, 27].

Factors related to the uptake of bilateral prophylactic mastectomy have included younger age, parity, white race, high anxiety, and a first-degree family member with breast cancer [12]. With the surgical setting being a common entry point for identification/management of high-risk patients, surgeons need to be aware of factors related to patients who choose certain treatment options to better help guide patient counseling and referral to relevant resources. Hence, we sought to identify what sociodemographic and clinical factors are associated with the uptake of bilateral prophylactic mastectomies compared with high-risk surveillance in pathogenic mutation carriers.

Materials and methods

The study population was derived from the Inherited Care Registry (ICARE), which is an IRB-approved international database of volunteers interested in participating in studies about inherited cancer. Participants were recruited from November 2000 to January 2017 from the institutional genetics clinic, internal and external providers, social media outlets, and genetics conferences. After consent was obtained, participants were mailed a comprehensive questionnaire and their responses were coded into a secured database.

All participants within the ICARE database with a documented positive genetic testing result (deleterious/pathogenic, variant suspected deleterious, or likely pathogenic) for 1 or more of the 11 high and moderate penetrant genes for breast cancer per the 2017 NCCN guidelines were identified. Women with a previous history of breast cancer and males were excluded. Self-reported demographic, clinical, and questionnaire variables were collected. Subjects who underwent bilateral prophylactic mastectomy were compared to those electing high-risk surveillance at the time of questionnaire completion. Results were reported as frequencies for the categorical variables and medians (ranges) for continuous variables. Comparisons between groups were performed using Wilcoxon Rank Sum, Fisher's Exact, or Pearson Chi-square analyses. All analyses were performed

in JMP Genomics 9. Tests are deemed significant at the 0.05 significance level (and no corrections were made for multiple testing).

Results

From the 2252 participants in the ICARE registry, 1351 participants with a confirmed positive genetic testing result were identified. After excluding participants with a history of breast cancer and male gender, 282 unaffected genetic mutation carriers remained which comprise our study cohort. The cohort was 100% female, 95% White, 57% married, 91% with some college education or higher, and 76% with an income > $50,000/year (Table 1). Of note, 14 (5%) of participants were from outside of the United States. The median age at which participants underwent genetic testing is 42 years (range 18–75 years). The median age at study entry and questionnaire completion is 43 years (range 18–76 years). A mutation in BRCA1 (47%) and BRCA 2 (46%) were the most frequent, followed by CHEK2 (4%).

Of the study cohort, 113 (40%) underwent bilateral prophylactic mastectomy. The median age at bilateral prophylactic mastectomy was 42 years (range 21–68). There was a high rate of breast reconstruction, with 94 (83%) of participants undergoing reconstruction. Seven (50%) of the non-US participants had bilateral prophylactic mastectomy. The median number of years from genetic testing to bilateral prophylactic mastectomy was 1 year (range 0–9 years). Sixty-five percent of bilateral prophylactic mastectomy patients also underwent risk-reducing salpingo-oophorectomy. Median age at risk-reducing salpingo-oophorectomy was 43 years (range 21–64 years).

A total of 169 (60%) of participants did not undergo bilateral prophylactic mastectomy; however, 126 (75%) had undergone high-risk surveillance with either MRI or mammogram within the year of participation of this study. Forty-five participants (45/169, 27%) elected to undergo risk-reducing salpingo-oophorectomy. Median age at risk-reducing salpingo-oophorectomy was 45 years (range 30–67 years).

When comparing women who underwent bilateral prophylactic mastectomy to those who did not, there was no significant difference in race, marital status, high school graduates, positive family history of breast cancer, history of breast biopsy, or history of taking chemoprevention (Table 2). However, women who chose bilateral prophylactic mastectomy were significantly more likely to have a higher income (>$50,000/year), some college education or higher, undergo risk-reducing salpingo-oophorectomy, and had a previous pregnancy, family history of first-degree relative with breast cancer, and total number of relatives with breast cancer. Women who chose high-risk surveillance were significantly more likely to have a personal history of ovarian cancer and to worry often about getting cancer. There was no significant difference in knowledge of implications of genetic mutations as evidenced by choosing false to the statement on the questionnaire, "All individuals who have an altered inherited cancer gene get cancer."

Table 1 Sociodemographic and clinical characteristics of high-risk genetic mutation carriers $n = 282$

Median age at genetic testing, years (range)	42 (18–75)
Median age at questionnaire, years (range)	43 (18–76)
Bilateral prophylactic mastectomy, *n* (%)	113 (40%)
Bilateral risk-reducing salpingo-oophorectomy, *n* (%)	118 (42%)
Gene mutation, *n* (%)	
ATM	2 (1%)
BRCA1	132 (47%)
BRCA2	131 (46%)
CHEK2	10 (4%)
PALB2	6 (2%)
TP53	1 (< 1%)
Race, *n* (%)	
White	263 (95%)
Black	5 (2%)
Asian	4 (1%)
Other	6 (2%)
Marital status, *n* (%)	
Married	160 (57%)
Single	38 (14%)
Divorced	22 (8%)
Widowed	40 (14%)
Cohabitating	20 (7%)
Some college education or higher, *n* (%)	
Yes	253 (91%)
No	25 (9%)
Income > $50,000/year	
Yes	191 (75%)
No	62 (25%)
Parous, *n* (%)	211 (75%)
Personal history of ovarian cancer, *n* (%)	32 (11%)
Family history of breast cancer, *n* (%)	249 (88%)
First-degree relative with breast cancer *n* (%)	164 (58%)
History of chemoprevention, *n* (%)	29 (10%)
History of breast biopsy	79 (28%)

Discussion

Advances in genetic testing have afforded the opportunity to specifically identify patients who are at increased risk for breast cancer and may benefit from risk-reducing surgery. Despite well-established oncologic benefits of bilateral prophylactic mastectomy in genetic mutation carriers, the

Table 2 Comparison of bilateral prophylactic mastectomy to high-risk surveillance cohort

	Bilateral prophylactic mastectomy $n=113$	Surveillance $n=169$	p value
Median age at genetic testing, years (range)	42 (20–67)	42 (18–75)	0.80
Median age at questionnaire, years (range)	44 (21–73)	43 (18–76)	0.25
Gene mutation, *n* (%)			**0.03**
ATM	–	2 (1%)	
BRCA1	61 (54%)	71 (42%)	
BRCA2	51 (45%)	80 (47%)	
CHEK2	–	10 (6%)	
PALB2	1 (1%)	5 (3%)	
TP53	–	1 (1%)	
Race, *n* (%)			0.18
White	105 (95%)	158 (94%)	
Black	1 (1%)	4 (2%)	
Asian	3 (3%)	1 (1%)	
Other	1(1%)	5 (3%)	
Marital status, *n* (%)			0.07
Married	66 (59%)	94 (56%)	
Single	8 (7%)	30 (18%)	
Divorced	11 (10%)	11 (7%)	
Widowed	20 (18%)	20 (12%)	
Cohabitating	7 (6%)	13 (8%)	
Some college education or higher, *n* (%)	104 (95%)	149 (88%)	**0.04**
Income >$50,000/year, *n* (%)	86 (84%)	105 (70%)	**0.01**
Parous, *n* (%)	97 (86%)	114 (67%)	**0.0005**
Personal history of ovarian cancer, *n* (%)	6 (5%)	26 (15%)	**0.009**
First-degree relative with breast cancer, *n* (%)	73 (65%)	91 (54%)	**0.04**
Median total number of relatives with breast cancer, *n* (range)	2 (0–7)	2 (0–7)	**0.01**
History of chemoprevention, *n* (%)	8 (7%)	21 (12%)	0.15
History of breast biopsy	45 (27%)	34 (31%)	0.47
Bilateral RRSO, *n* (%)	73 (65%)	45 (27%)	**<0.0001**
Worry of getting cancer often, *n* (%)	7 (6%)	50 (30%)	**<0.0001**
Answered FALSE to "All individuals who have an altered inherited cancer gene get cancer," *n* (%)	107 (96%)	154 (92%)	0.19

Bolded p-values meet significance level of .05 or below

RRSO Risk-Reducing salpingo-oophorectomy

decision to undergo bilateral prophylactic mastectomy is not universal and remains an area of clinical investigation. In high-risk genetic mutation carriers, bilateral prophylactic mastectomy was a decision made by 40% of our cohort. With a median of 1 year from the time of genetic testing to surgery, participants who underwent bilateral prophylactic mastectomy in this cohort were motivated to pursue surgery, compared to only a 3% uptake rate of surgery seen by Lerman et al at 1 year following BRCA1/2 testing [28]. However, Schwartz et al found that uptake of bilateral prophylactic mastectomy increases over time, with up to 80% having surgery by 5 years after testing [27].

Adherence to high-risk surveillance has been variable in the literature, from reported low adherence [28] to adherence as high as 88% for mammogram and MRI [24, 27]. Patients within our cohort who did not undergo bilateral prophylactic mastectomy but elected for high-risk surveillance also represented a highly motivated group, where 75% of this group had a mammogram or MRI within the year of study participation. The high-risk surveillance group was significantly more likely to worry about getting cancer in the future, which may reflect the higher rate of adherence to screening. Utilization of MRI for screening has been shown in BRCA carriers to decrease the risk of Stage II–Stage IV

breast cancer at 6 years to < 2% compared to 6.6% with routine screening [29].

Socioeconomic factors have not been well studied in regard to the choice of bilateral prophylactic mastectomy vs surveillance in unaffected high-risk mutation carriers. We found in this similarly aged cohort a significant association between income > $50,000/year (84% vs 70%, $p = 0.01$) and college education (95% vs 88%, $p = 0.04$) with bilateral prophylactic mastectomy. Those who underwent bilateral prophylactic mastectomy also utilized reconstruction 83% of the time. These findings appear to be reflective of socioeconomic status as knowledge of the implications of genetic mutation carriage. Majority in both groups, by questionnaire response, illustrated an understanding that not all individuals who have an inherited cancer gene get cancer, in addition to there being no significant difference in this understanding between surgery and surveillance groups (96% vs 85%, $p = 0.27$). This knowledge is valuable in increasing efforts to provide appropriate resources to those motivated to undergo surgery but may lack the resources or support to do so.

Having a first-degree family member with breast cancer is one of the most often cited factors in choice of bilateral prophylactic mastectomy. Metcalfe et al found that among BRCA 1/2 carriers, when a woman's sister was affected with breast cancer, she was significantly more likely to undergo prophylactic mastectomy than when her sister had not had breast cancer [30]. A first-degree relative with breast cancer was significantly associated with bilateral prophylactic mastectomy in our cohort (65% vs 54%, $p = 0.04$). What is more, the higher the number of relatives reported to be affected in the family, the more likely the patient was to undergo bilateral prophylactic mastectomy ($p = 0.01$).

Reproductive historical factors were significant in the choice of surgery over surveillance in this cohort, which is consistent with findings of similar studies [12, 24, 31]. Participants who had bilateral prophylactic mastectomy were significantly more likely to have undergone risk-reducing salpingo-oophorectomy (65% vs 27%, $p = 0.0001$). NCCN guidelines recommend risk-reducing salpingo-oophorectomy between ages 35 and 45 or after completion of child-bearing for BRCA mutation carriers. The observation of significantly higher rate of parity in the bilateral prophylactic mastectomy group suggests that after child-bearing, not only is risk-reducing salpingo-oophorectomy a consideration, but also bilateral prophylactic mastectomy. The combination of risk-reducing salpingo-oophorectomy and bilateral prophylactic mastectomy was shown by Ingham et al to provide a significant survival advantage [17]. Bilateral prophylactic mastectomy may not be appropriate for all high-risk genetic mutation carriers. Risk-reducing mastectomy has not shown to be of benefit in ovarian cancer patients unless the ovarian cancer is early stage or more than 10 years after diagnosis and treatment [32]. This may account for significantly more participants with a history of ovarian cancer being in the surveillance group (15% vs 5%, $p = 0.009$).

There are some limitations to our study. This study is retrospective in nature and questionnaire data does not explicitly address the reasons for bilateral prophylactic mastectomy uptake. What is more, the questionnaires were administered at a single time point, and fail to reflect subsequent decisions regarding surveillance or use of prophylactic surgery. Additionally, the participants are a self-selected and likely a highly motivated group of genetic carriers; thus, those who volunteer to participate in this study would be more likely to undergo risk-reducing surgery or comply with high-risk screening. Due to the aforementioned, this cohort cannot specifically address those who may be disadvantaged or overlooked for risk reduction and screening. Worth mentioning is 5% of the cohort is international, where screening guidelines and access to resources differ than in the United States, although this did not appear to affect the use of prophylactic surgery among our respondents. Lastly, although there is heterogeneity in mutation carrier types which can be seen as a strength of this cohort, the majority of participants were BRCA carriers.

Future directions include outreach to ethnic and socioeconomic groups not represented in this study with more directed questions to specifically address uptake of bilateral prophylactic mastectomy. Recruiting patients with genetic mutations other than BRCA 1/2 would help to increase knowledge of their decision-making factors and ultimately assessment of outcomes. In addition, it would be desirable to add questions to help determine whether choice of surgery is patient driven, practitioner driven, or shared decision making.

Conclusions

For high-risk genetic mutation carriers, the choice of bilateral prophylactic mastectomy over surveillance is significantly associated with higher income, higher education, first-degree relative with cancer, total number of relatives with breast cancer, parity, and uptake of risk-reducing salpingo-oophorectomy. History of ovarian cancer and increased worry were more likely to be seen in the high-risk surveillance group. In this group, comprehension of genetic test results appeared to be similar, but utilization of elective risk reductive procedures was highly skewed towards educated and higher income carriers. This suggests that uptake of prophylactic surgery may be a function of socioeconomic status and also likely reflective of both the elective nature of prophylactic surgery, as well as different cultural values.

Compliance with ethical standards

Conflict of interest Dr. C. Laronga is on the Speaker's Bureau at Genomic Health and receives royalties from Up-To-Date. Drs. D. Henry, M. Lee, K. Ahmed and W. Sun, Mr. Boulware, and Ms. Almanza have no disclosures.

Ethical approval This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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