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Differences among a modern cohort of BRCA mutation carriers choosing bilateral prophylactic mastectomies compared to breast surveillance

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Abstract

Background—Women with a BRCA mutation have significantly elevated breast cancer risk which can be reduced by >90% with bilateral prophylactic mastectomies (BPMs). We sought to compare a cohort of BRCA mutation carriers choosing BPM versus breast surveillance to better elucidate factors that may impact decision making.

Methods—Women with a BRCA mutation were retrospectively identified from a prospectively maintained database. The surveillance cohort (n=313) consisted of women seen in a high-risk clinic between 2014–2016; the surgery cohort (n=142) consisted of women who underwent BPM between 2010–2016. Clinical and familial factors were compared between the groups.

Results—Women choosing BPM were more likely to have a BRCA1 than BRCA2 mutation compared to the surveillance group (57% vs 45%, p=0.02) and were less likely to have a personal history of ovarian cancer (10% vs 20%, p=0.01). Women undergoing BPM were more likely to be married (78% vs 62%, p=0.01), to have more children (median 2 vs 1, p<0.001), and to have undergone a prophylactic oophorectomy (61% vs 37%, p<0.001). Women choosing BPM had more first-degree relatives (63% vs 48%, p=0.01) or a sister (23% vs 14%, p=0.02) with a history of breast cancer and were more likely to have a family member with ovarian cancer under age 40 (9% vs 4%, p=0.03). There was no difference in the number of prior breast biopsies or history of atypia/LCIS.

Conclusion—The decision to undergo BPM appears multifactorial, with gene mutation, family history, and relationships appearing to have the strongest influence on decision making.

Keywords

BRCA; bilateral prophylactic mastectomy; breast cancer; breast cancer risk; surveillance

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INTRODUCTION

Genetic testing is increasingly utilized in asymptomatic individuals with a significant family history of cancer to identify those who may benefit either from increased surveillance or risk reduction options. Women found to carry a deleterious BRCA1 or BRCA2 mutation are predisposed to an increased breast cancer risk imparted by inherited chromosomal instability, with a lifetime risk of breast cancer ranging from approximately 40–80%.^{1–3} BRCA carriers also have a susceptibility to earlier onset breast cancer compared to non-BRCA carriers.⁴ The National Comprehensive Cancer Network (NCCN) management strategies for women with a deleterious BRCA mutation include increased breast surveillance and counseling regarding the option for risk-reducing surgery.⁵ Standard recommendations for breast surveillance among BRCA carriers include annual mammogram, annual MRI, and routine clinical breast exam.^{6,7} Risk-reducing surgery refers to bilateral prophylactic mastectomies (BPMs), an effective risk-reducing procedure associated with >90% risk reduction among high-risk women undergoing this operation.⁸ Studies have reported variable uptake rates of BPM among BRCA mutation carriers, which differ by country and time period, ranging from 8% to 50%.^{9–13} Available data on patient characteristics vary, but suggest that age at genetic testing, parity, family history of ovarian cancer, cancer related distress, and education may impact a woman's decision to undergo BPM.^{14–16} We sought to compare a modern cohort of women with a BRCA mutation choosing BPM to a group choosing breast surveillance to better elucidate factors that may impact decision making among this high-risk group.

METHODS

Women with a known deleterious BRCA1 or BRCA2 mutation were retrospectively identified from a prospectively maintained database at Memorial Sloan Kettering Cancer Center (MSKCC). The surveillance group consisted of women seen at our high-risk breast clinic for a surveillance visit (physical exam and imaging) from 2014–2016, although many women were screened for a longer period of time, with a range of total length of screening from 0–232 months. The surgery cohort consisted of women who underwent BPM at MSKCC from 2010–2016. Women with a previous breast cancer diagnosis or a variant of unknown significance were excluded. Patient characteristics were reviewed, including personal demographics (age at genetic testing, age at BPM, personal history of ovarian cancer, personal history of bilateral salpingo-oophorectomy [BSO], parity, use of chemoprevention, age at first delivery, marital status, education level, tobacco use, and body mass index [BMI]) and breast imaging factors (MRI receipt, imaging recommendations for short-term follow-up and/or biopsy, history of prior benign breast biopsies, biopsy showing atypia or lobular carcinoma in situ [LCIS]). Detailed family histories, including number, gender, and age of first- and second-degree family members with breast and/or ovarian cancer diagnoses, were obtained.

Categorical variables were summarized with frequency and percent whereas continuous variables were summarized with median and range. To test for differences between groups, we used the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. A p-value < 0.05 was considered statistically significant. All statistical

analyses were conducted using R software version 3.2.5 (R Core Development Team, Vienna, Austria).

RESULTS

In total, 455 asymptomatic BRCA1 or BRCA2 carriers were identified, including 313 women in the surveillance cohort and 142 women in the BPM cohort. Of the 142 women who underwent BPM, 5 had occult malignancy identified on final pathology, including 1 invasive ductal carcinoma and 4 cases of ductal carcinoma in situ.

Personal Demographics

Table 1 compares BRCA mutations and personal demographics between the two groups. Women who underwent BPM were more likely to have a BRCA1 versus BRCA2 mutation compared to women in surveillance ($p=0.02$). There was no significant difference in age of genetic testing between the two groups (median 40 years versus 39 years, $p=0.64$). The average age at BPM was 43 years (range 21–67), and average age at the most recent surveillance visit for the screening cohort was 47 years (21–87). Women who underwent BPM were more likely to be married ($p=0.01$) and had more children (median 2 versus 1, $p=0.02$), although no significant difference in age at first delivery was observed (median 30 versus 29, $p=0.06$). Overall smoking rates were low; however, women who underwent BPM were more likely to be current smokers (5% versus 1%, $p=0.005$). Women in the BPM cohort were less likely to have a personal history of ovarian cancer (10% vs 20%, $p=0.01$) but were more likely to have undergone a prophylactic BSO (61% vs 37%, $p<0.001$).

Family History

The majority (90%–93%) of women in both cohorts had a positive family history of breast cancer. Detailed family history findings are summarized in Table 2. Women who underwent BPM were more likely to have a first-degree relative with breast cancer compared to the surveillance cohort (63% vs 49%, $p=0.01$) and, specifically, were more likely to have a sister with a history of breast cancer (23% vs 14%, $p=0.02$). The surgery cohort was also more likely to have a family member with ovarian cancer before the age of 40 years (9% versus 4%, $p=0.03$).

Breast Imaging

The majority of women in both cohorts had at least one prior breast MRI (96% of the BPM group and 97% of the surveillance group), with 88% of women in surveillance having undergone a breast MRI within the previous 18 months of their most recent visit to the high-risk clinic. Women who underwent BPM were more likely to have had imaging recommending additional radiographic work-up ($p=0.002$), but women undergoing surveillance were more likely to have had imaging recommending short-term follow-up ($p=0.005$). There was no difference between the groups in history of imaging recommendations for breast biopsy, number of prior breast biopsies, or history of a high-risk lesion identified on breast biopsy (atypia or LCIS) (Table 3). Among the 5 women found to have an occult malignancy identified at the time of BPM, all had a prior breast MRI (ranging from 1–9 months prior to surgery). Two women had preoperative imaging recommending

biopsies; pathology in both women was benign, one showed LCIS and atypical lobular hyperplasia.

DISCUSSION

Asymptomatic women with a deleterious BRCA mutation have significantly elevated breast cancer risk and therefore warrant consideration of both increased screening and risk reduction options. Current NCCN guidelines recommend increased breast surveillance, including screening with both mammogram and MRI, and consideration of BPM for risk reduction.⁵ Better understanding of factors associated with BPM decision making may allow improved counseling for women faced with this decision. Here we report on a modern cohort of women with a deleterious BRCA mutation and find that the decision to undergo risk-reducing BPM appears to be multi-factorial, incorporating both higher risk factors, extent of family history, and personal relationships.

BPM has been shown to be very effective in reducing breast cancer risk among high-risk women, with >90% risk reduction following prophylactic surgery.^{8,17,18} Rebbeck et al and Meijers-Heijboer et al specifically looked at BRCA carriers undergoing either BPM or surveillance and reported significant reductions in breast cancer incidence among the BPM groups.^{19,20} The PROSE study reported on 483 BRCA carriers, 105 in the BPM group and 378 in the surveillance cohort. At 6.5 years follow-up, 2% of the surgery group compared to nearly 50% of the surveillance cohort developed breast cancer (hazard ratio 0.05).¹⁹ Over time, groups have reported variable uptake of BPM ranging from 8% among unaffected Austrian BRCA carriers to an estimated uptake of 50% among Dutch women.^{9,11–13} Published series suggest that country of origin impacts uptake of BPM, with Holland and the United States having higher use of BPM than Poland and Norway.¹⁰ Interestingly, a physician's specialty also impacts the likelihood that she or he would recommend BPM for risk reduction among BRCA carriers²¹, with surgeons and oncologists most likely to recommend consideration of BPM, and family practitioners and internists least likely to recommend BPM to unaffected BRCA carriers. Our current population consists of women seen by surgeons and breast specialists at a cancer center, which also may bias treatment recommendations.

Intuitively, it would seem that women with the highest breast cancer risk should be those most likely to consider BPM. BRCA1 mutations confer a higher breast cancer risk than BRCA2 mutations⁷, and we did find a higher percentage of BRCA1 carriers in the BPM cohort compared to the surveillance group. These findings are in contrast to a number of small reports showing no difference in the proportion of BRCA1 to BRCA2 gene carriers opting for BPM.^{3,6,22} We also found that women in the BPM group were more likely to have a sister or any first-degree relative with a history of breast cancer, similar to what others have reported.^{3,5} Singh and colleagues evaluated motivators for BPM among a cohort of 136 unaffected BRCA carriers. Overall uptake of BPM in their study was 42%, with the most significant factor predicting the likelihood of BPM being a first- and second-degree relative deceased from breast cancer (odds ratio 11.0; $p=0.005$).¹¹ The association between family history and choice for risk-reducing surgery is likely complex. A stronger family history does confer a higher lifetime risk among gene carriers^{23,24} which may impact objective

decision making, but watching family members go through cancer treatment or die from breast cancer may also impact emotional decision making. Haroun et al surveyed BRCA mutation carriers and found that those women who estimated their breast cancer risk to be greater than 50% were more likely to opt for risk-reducing surgery compared to those who estimated a lower risk. Overall fear of cancer was the most common reason cited for choosing BPM, indicated by 38% of respondents.²⁵

In addition to family history of cancer, additional familial factors differed among the BPM and surveillance groups. Women in the BPM group were more likely to be married and had more children than those in the surveillance cohort. When a small cohort of women with BRCA mutation were interviewed regarding factors impacting BPM decision making, Lodder et al found that a significant factor in their decision to undergo surgery was fear of leaving young children behind⁴, and Haroun et al also reported that concern over children was a reason that 16% of BRCA carriers chose risk-reducing surgery.²⁵

In regards to ovarian history, we found that a higher proportion of women with a prior prophylactic BSO opted for BPM. Interestingly, studies show a significant reduction in breast cancer risk among premenopausal women who undergo BSO, although there is variability in the data on whether BSO is protective for both BRCA1 and BRCA2 carriers^{8,17,26,27}, suggesting that although this population may already be at lower breast cancer risk, women who have successfully undergone prophylactic BSO may have a greater willingness to accept additional breast prophylaxis, regardless of the absolute benefit. Friebe et al also reported that more women with a BRCA mutation underwent both BPM and BSO than BPM alone.³ Conversely, women with a personal history of ovarian cancer were less likely to undergo BPM in our cohort, likely secondary to competing mortality risk and knowledge that metachronous breast cancer risk is lower following treatment for ovarian cancer among BRCA carriers.²⁸

Together these findings suggest reliance on personal history, family members' history as well as personal relationships and support when balancing decision making for a risk-reducing operation that carries surgical risks and alterations in physical appearance. Gopie et al surveyed BRCA carriers preoperatively, and at two time points postoperatively. While 37% reported that their breasts felt unpleasant, 29% were not satisfied with their breasts' appearance, and 21% felt embarrassed for their naked body, overall sexual and partner relationships did not change significantly over time.²⁹ A systematic review including 22 studies assessing quality of life among women following BPM found that overall patients are satisfied with surgical outcomes and report high psychosocial well-being and positive body image, but that sexual well-being and somatosensory function are most negatively affected by the procedure.³⁰ Together, these reports highlight a complex interaction between family history, personal history, fear of cancer and anxiety, sexuality, and acceptance of psychosocial changes from the operation that may impact decision making for BPM. Physicians who advise women on risk reduction should be aware of the complexity of risk-reducing surgery decision making to better counsel those faced with this decision.

In accordance with screening guidelines, the majority of women in this study (96%) underwent MRI as part of their breast screening. While use of MRI and need for subsequent

biopsies has been shown to increase utilization of contralateral prophylactic mastectomy among women with a unilateral index breast cancer^{31,32}, need for breast biopsies or history of a high-risk breast lesion were not more prevalent in the BPM cohort. Women choosing BPM were more likely to have prior imaging that recommended additional work-up, but the surveillance cohort was more likely to have imaging recommending short-term follow-up, suggesting that the overall impact of abnormal imaging findings on BPM decision making among this population appears minimal.

While this study is limited by the retrospective nature, detailed data regarding family history, breast imaging, and personal demographics were available for review. Of note, this population constitutes an educated group of overall healthy women with low smoking rates and with a relatively high (35%) proportion of women with Ashkenazi Jewish background and therefore may not be generalizable to the entire population. Data on comorbidities and performance status were not available and may impact appropriateness for BPM consideration.

Conclusion

Overall, asymptomatic women with BRCA mutations choosing BPM were more likely to carry a BRCA 1 mutation, to be married or have more children, to have a personal history of prophylactic BSO, and to have a first-degree relative and/or sister with a history of breast cancer or a young family member with ovarian cancer. These data highlight factors that may be important in BPM decision making among a modern cohort of BRCA mutation carriers and may aid in counseling women faced with this decision.

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Synopsis

In this comparison of a cohort of BRCA mutation carriers choosing BPM versus breast surveillance, we find that the decision to undergo BPM appears multifactorial. Family history, emotional experiences, and relationships are the strongest drivers of decision making.

Table 1

Personal demographics

	BPM Group (n=142)	Surveillance Group (n=313)	p-value
BRCA mutation			.02
BRCA1	81 (57%)	140 (45%)	
BRCA2	61 (43%)	173 (55%)	
Age at genetic testing *, median (range)	40 (20, 66)	39 (18, 76)	.64
Parity, median (range)	2 (1,2)	1 (0,2)	<.001
Age at first delivery, median (range)	30 (27, 33)	29 (25, 32)	.06
Ashkenazi Jewish **	42 (30%)	119 (38%)	.59
Race			.23
Caucasian	62 (44%)	188 (60%)	
Other	6 (4%)	33 (11%)	
Unknown	74 (52%)	92 (29%)	
Marital Status			.01
Married	111 (78%)	194 (62%)	
Single	25 (18%)	83 (27%)	
Divorced/separated/widowed	5 (4%)	23 (7%)	
Unknown	1 (1%)	13 (4%)	
Education Level			.72
High school/vocational school	8 (6%)	20 (6%)	
Some college/college degree	50 (35%)	92 (29%)	
Graduate degree	47 (33%)	104 (33%)	
Unknown	37 (26%)	97 (31%)	
Current smoker †	7 (5%)	2 (1%)	.005
Former smoker ‡	43 (30%)	81 (26%)	.21
Body mass index ††, median (range)	24.97 (18.1, 47.4)	23.81 (16.3, 48.5)	.02

* Unknown for 9 in BPM group and 28 in surveillance group

** Unknown for 69 in BPM group and 89 in surveillance group

† Unknown for 1 in surveillance group

‡ Unknown for 8 in BPM group and 3 in surveillance group

†† Unknown for 50 in surveillance group

Table 2

Genetic factors and family history

	BPM Group (n=142)	Surveillance Group (n=313)	p-value
Family history of breast cancer	132 (93%)	280 (90%)	.3
1 st degree relative with breast cancer *			.01
0	52 (37%)	161 (51%)	
1	79 (56%)	130 (42%)	
>1	10 (7%)	21 (7%)	
Mother with breast cancer *	65 (46%)	121 (39%)	.15
Sister with breast cancer *	33 (23%)	45 (14%)	.02
2 nd degree relative with breast cancer **			.27
0	61 (43%)	132 (42%)	
1	47 (33%)	125 (40%)	
>1	32 (23%)	54 (17%)	
Number of family members with breast cancer under age 40 ***			.33
0	94 (66%)	228 (73%)	
1	38 (27%)	65 (21%)	
>1	9 (6%)	20 (6%)	
Male family member with breast cancer †	5 (4%)	12 (4%)	1
Family history of ovarian cancer ‡	74 (52%)	158 (51%)	.76
1 st degree relative with ovarian cancer *			.21
0	109 (77%)	224 (72%)	
1	29 (20%)	85 (27%)	
>1	3 (2%)	3 (1%)	
Mother with ovarian cancer *	26 (18%)	67 (21%)	.53
Sister with ovarian cancer *	8 (6%)	21 (7%)	.84
2 nd degree relative with ovarian cancer ††			.83
0	104 (73%)	235 (75%)	
1	30 (21%)	67 (21%)	
>1	5 (4%)	8 (3%)	
Family member with ovarian cancer ††† under age 40			.03
0	126 (89%)	302 (97%)	
1	7 (5%)	9 (3%)	

	BPM Group (n=142)	Surveillance Group (n=313)	p-value
>1	5 (4%)	2 (1%)	

* Unknown for 1 in BPM group and 1 in surveillance group

** Unknown for 2 in BPM group and 2 in surveillance group

*** Unknown for 1 in surveillance group

[†] Unknown for 2 in BPM group and 1 in surveillance group

[‡] Unknown for 2 in BPM group and 2 in surveillance group

^{††} Unknown for 3 in BPM group and 3 in surveillance group

^{†††} Unknown for 4 in BPM group

Table 3

Breast and imaging factors

	BPM Group (n=142)	Surveillance Group (n=313)	p-value
Age at BPM, median (range)	43 (21, 67)	N/A	N/A
Prior use of chemoprevention	2 (1%)	4 (1%)	.1
Current use of chemoprevention	2 (1%)	15 (5%)	.11
Imaging recommending breast biopsy *	34 (24%)	86 (28%)	.36
Imaging recommending short-term follow-up *	28 (20%)	99 (32%)	.005
Imaging recommending additional work-up *	13 (9%)	6 (2%)	.002
History of prior breast biopsies			.24
0	105 (74%)	207 (66%)	
1	34 (24%)	68 (22%)	
>1	15 (11%)	38 (12%)	
Abnormal pathology on biopsy (ADH, ALH, LCIS)	2 (1%)	10 (3%)	.73
Personal history of prophylactic bilateral salpingo-oophorectomy	86 (61%)	115 (37%)	<.001
Age at prophylactic bilateral salpingo-oophorectomy, median (range) **	43 (31,65)	49 (32,69)	.001
Personal history of ovarian cancer	14 (10%)	62 (20%)	.01
Age at ovarian cancer diagnosis	49 (43,58)	54 (36,73)	.24

* Unknown for 11 in surveillance group

** Unknown for 1 in BPM group and 4 in surveillance group