# Risk-reducing Surgery and Cancer-related Distress Among Female BRCA1 and BRCA2 Mutation Carriers

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### INTRODUCTION

- The identification of a mutation in one of the two breast and ovarian cancer susceptibility genes, BRCA1 or BRCA2, is a seminal event in a woman's life and represents the single greatest cancer risk factor in the family.
- The risk of breast cancer has been reported to be between 56%<sup>1-2</sup> and 87%<sup>3-4</sup> for *BRCA1* carriers and between 33%<sup>5</sup> and 84%<sup>6</sup> for *BRCA2* carriers in early studies. The risk of ovarian cancer ranges from 10%<sup>1-2,5</sup> to 60%<sup>3-5</sup> by 70 years depending on the gene and mutation location. These high risks have been confirmed in prospective studies of unaffected BRCA carriers.<sup>2,7-9</sup>
- Cancer-related distress is heightened 1 year after genetic testing among BRCA mutation carriers<sup>10</sup> and resemble the distress levels reported among breast cancer patients. 11-15
- Risk-reducing bilateral mastectomy (BM) can decrease the risk of breast cancer by up to 95% and risk-reducing bilateral salpingo-oophorectomy (BSO) reduces the risk of ovarian cancer by approximately 90%, and the risk of breast cancer by approximately 50%. 17
- Unaffected women found to carry a BRCA mutation are faced with complex decisions about how to manage their cancer risk, and it is not known if uptake of risk-reducing surgery influences long-term cancer related distress or psycho-social functioning.

### STUDY OBJECTIVES

- To evaluate long-term cancer-related distress in women with BRCA mutations To determine predictors of cancer-related distress
- To assess the relationship between current cancer-related distress and the uptake of cancer risk-reducing surgeries
- These findings represent interim analyses of a larger international and multi-center patient preference study and discrete choice experiment of BRCA mutation carriers to assess women's willingness to adopt interventions (including hypothetical) that may prevent or reduce the risk of breast cancer
- Study designed to capture patient perspectives for drug development considerations

### METHODS

#### Inclusion criteria

- Female BRCA1 or BRCA2 mutation carriers
- Age 25-55 years
- No personal history of cancer

#### Study Sample

- These interim data are specific to women recruited through the FORCE (Facing Our Risk of Cancer Empowered) online advocacy organization, focused on women at familial/genetic risk of breast and ovarian cancer.
- Between January and August 2015, advertisement with a link to the survey was sent to more than 50,000 people in the United States in a monthly newsletter, as well as featured in Facebook and Twitter posts, and the FORCE research web page.

#### Survey Instrument

- Modified 15-item Impact of Events Scale (IES)-Revised<sup>18,19</sup>
- To measure extent to which traumatic events\* intrude upon the respondents thoughts and the extent to which respondents actively avoid thinking about the traumatic event.
- \* "Being at increased risk of cancer" because of a confirmed mutation in the BRCA1 or BRCA2 genes.
- Scores between 0 and 8 considered subclinical, between 9 and 25 indicate mild distress, between 26 and 43 indicate moderate distress, and scores greater than 43 indicate severe distress
- Detailed questions capture demographic, personal treatment history, and family history data Statistical Analysis
- Multivariate linear regression models were used to predict distress among women.
- Regression modeling conducted for all respondents as well as separately for women who have undergone risk-reducing surgery and those who had not undergone surgery.

### METHODS (Continued)

### Statistical Analysis (continued)

- Logistic regression model using moderate to severe distress showed similar results (not shown) Covariates included based on a priori understanding of cancer-related distress included: age, education level, time since gene identification, whether they have children, and history or type of surgery (prophylactic BM [PBM] vs. BSO vs. both vs. none). Family history included for analysis was the total number of relatives with breast cancer.
- Likelihood of PBM in the future was modeled for respondents who had not had surgery using logistic regression and the same covariates with the addition of a categorical variable indicating whether the respondents had moderate or severe distress based on their IES score.

### RESULTS

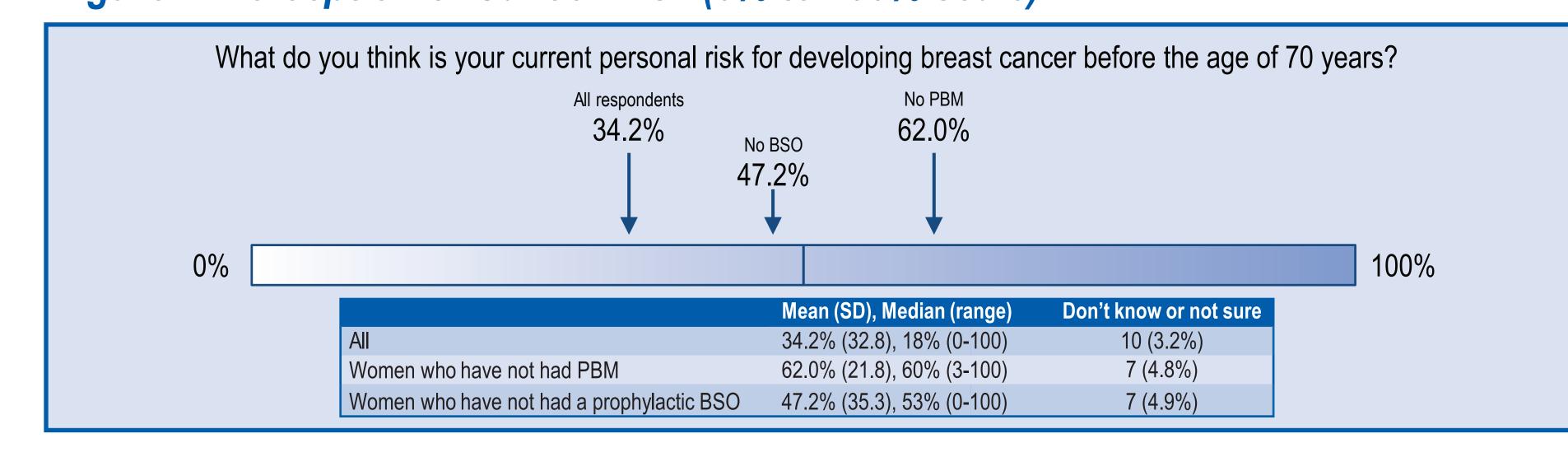
#### Study Sample

- We report results for 309 women who completed the survey as part of the online FORCE recruiting efforts (Table 1).
- Fifty-two (16.8%) women had undergone PBM only, 55 (17.8%) had undergone BSO only, 110 (35.6%) had undergone both PBM and BSO, and 92 (29.8%) had not pursued any risk-reducing surgeries.
- Mean age of respondents was 41.4 years, the majority were married or living as married (75.8%), employed full time (62.3%) and had completed at least a 4-year college degree (79.5%).
- Women who have not had PBM reported highest levels of perceived cancer risk, followed by those who have not had prophylactic BSO (Figure 1).

### Table 1. Demographics of FORCE Respondents (n = 309)

|   |  | All FORCE Respondents<br>(N = 309) |
|---|--|------------------------------------|
| Age (years)   | Mean (SD), Median (range)                                | 41.4 (8.3), 42 (25-55)             |
| Marital status  | Single / never married                                   | 43 (15.8%)                         |
|   | Married / living as married / civil partnership          | 207 (75.8%)                        |
|   | Divorced or separated                                    | 21 (7.7%)                          |
|   | Widowed / surviving partner                              | 1 (0.4%)                           |
|   | Other  | 1 (0.4%)                           |
|   | Missing  | 36                                 |
| Employment status   | Employed full time                                       | 170 (62.3%)                        |
|   | Other  | 103 (37.7%)                        |
|   | Missing  | 36                                 |
| Highest education   | Completed a 4-year college degree, some graduate school, |                                    |
|   | or earned a graduate or professional degree              | 217 (79.5%)                        |
|   | Did not complete a 4-year college degree                 | 56 (20.5%)                         |
|   | Missing  | 36                                 |
| Time since gene mutation identified (years)               | Mean (SD), Median (range)                                | 3.5 (3.5), 2 (0-18)                |
| Gene mutation   | BRCA1  | 165 (53.4%)                        |
|   | BRCA2  | 141 (45.6%)                        |
|   | BRCA1 and BRCA2  | 2 (0.6%)                           |
|   | Don't know or not sure                                   | 1 (0.3%)                           |
| Actions to reduce your risk for breast or ovarian cancer? | PBM  | 162 (52.4%)                        |
|   | BSO  | 165 (53.4%)                        |
|   | No prophylactic surgery                                  | 92 (29.8%)                         |

#### Figure 1. Perception of Cancer Risk (0% to 100% scale)



### RESULTS (Continued)

Table 2. Risk Modification and Family History Among FORCE Respondents

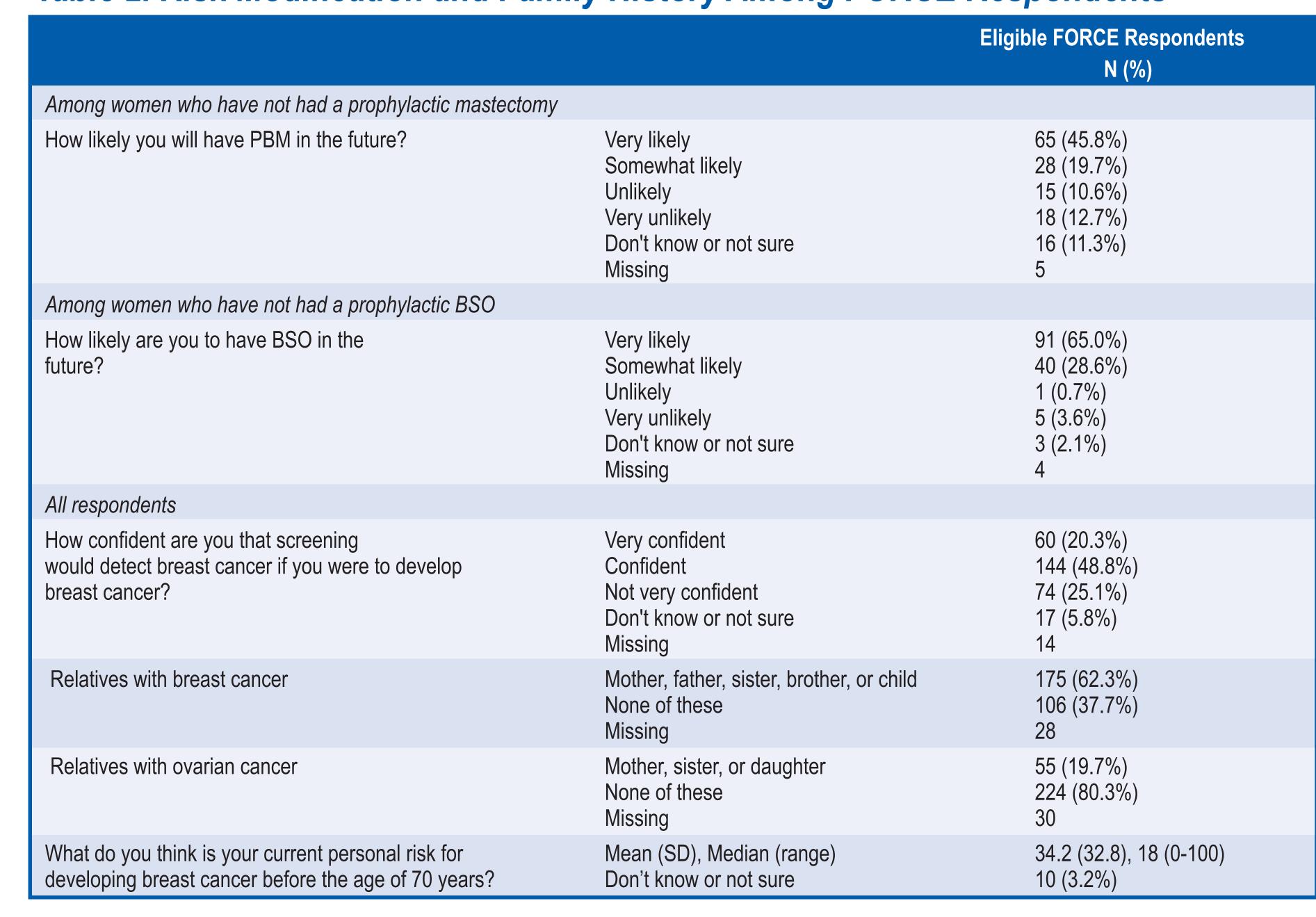
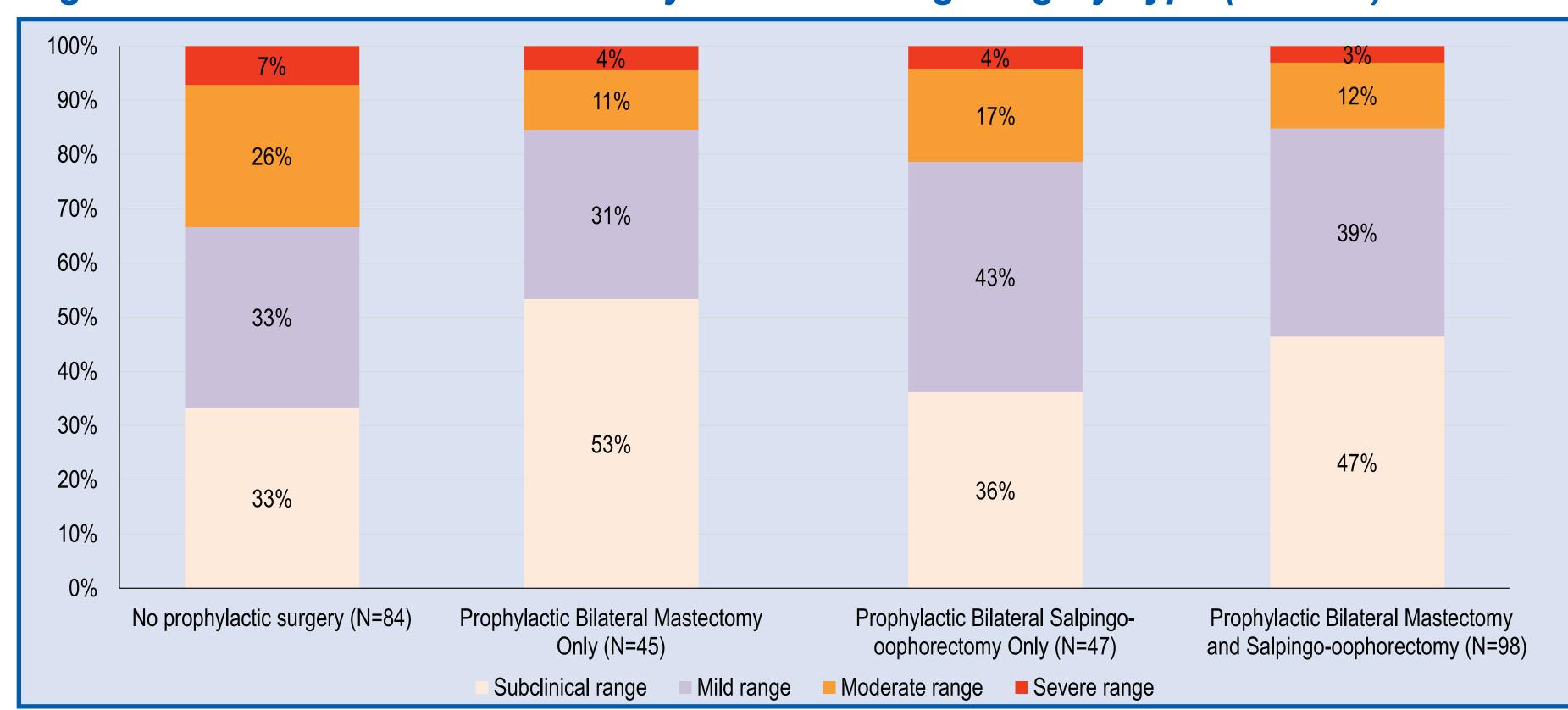


Figure 2. IES Score Distributions by Risk-reducing Surgery Type (N = 274)



#### IES Results

- 274 women answered the IES questions. Of 15 items in the IES intrusion and avoidance subscales, the items that were most frequently ranked at the highest level on the Likert scale included:
- "Any reminder brought back feelings about being at increased risk of breast cancer" (23.4%)
- "I had trouble staying asleep" (15.0%)
- "I had waves of strong feelings about being at increased risk of breast cancer" (11.3%)
- Overall, 59 (21.5%) women reported moderate or severe cancer-related distress. Women with no prophylactic surgery were more likely to report moderate to severe distress than women who had undergone at least one prophylactic surgery (Figure 2).
- Lower current IES levels were associated with higher education (beyond high school diploma), having PBM, and longer time since genetic test disclosure. BSO did not have a significant effect on distress levels in this population of BRCA mutation carriers (Table 3).
- For women with prior risk-reducing surgery, higher education, and longer time since genetic test disclosure were associated with lower IES scores. Statistically significant predictors of IES scores were not identified among the women who did not have preventive surgeries.

Table 3. Predictors of Psychological Distress Among BRCA-positive Women With and Without Risk-reducing Surgery

|                              | All respondents (n = 274)                     | Women with prior risk-<br>reducing surgery (n = 190) | Women with no risk-<br>reducing surgery (n = 84) |
|------------------------------|---|--|--|
|                              | 14.9 (SD 14.2)*                               | Mean IES Score<br>12.7 (SD 13.0)*                    | 19.7 (SD 15.5)*                                  |
|                              | Relative Risk (95% confidence limits) for IES |  |  |
| Age                          | -0.068 (-0.358, 0.222)                        | -0.124 (-0.463, 0.214)                               | -0.099 (-0.674, 0.476)                           |
| Relatives with breast cancer | 0.309 (-1.144, 1.761)                         | 1.192 (-0.344, 2.729)                                | -3.401 (-7.054, 0.251)                           |
| Post-secondary education     | -5.749 (-10.12, -1.377)*                      | -5.107 (-9.668, -0.546)*                             | -9.014 (-20.605, 2.577)                          |
| Income                       | 0.002 (-0.027, 0.031)                         | -0.014 (-0.047, 0.02)                                | 0.029 (-0.03, 0.088)                             |
| Time since genetic test      | -0.677 (-1.147, -0.207)*                      | -0.517 (-1.041, 0.007)*                              | -0.953 (-1.955, 0.05)                            |
| Have children                | 1.696 (-2.034, 5.427)                         | 0.951 (-3.42, 5.321)                                 | 4.198 (-3.101, 11.497)                           |
| PBM only                     | -7.913 (-12.949, -2.877)*                     | -1.759 (-8.034, 4.515)                               | n/a  |
| BSO only                     | -4.2 (-9.768, 1.368)                          | 3.678 (-0.869, 8.226)                                | n/a  |
| PBM and BSO                  | -7.944 (-13.187, -2.702)*                     | n/a  | n/a  |

shown to be statistically significant in multivariate linear regression mod

Table 4. Predictors of Intention to Pursue Risk-reducing PBM Among Women With No Risk-reducing Surgery (n = 84)

| Odds Ratio (95% control of the form of the |                     |
|--|---------------------|
| Moderate or severe IES   | 1.144 (.362, 3.613) |
| Age  | 0.916 (.840, .998)* |
| Relatives with breast cancer   | 1.003 (.559, 1.797) |
| Education  | 1.062 (.167, 6.745) |
| Income   | 1.001 (.992, 1.010) |
| Time since genetic test  | 0.941 (.817, 1.085) |
| Having children  | 2.629 (.847, 8.157) |

\*shown to be statistically significant in multivariate logistic regression model

- Among women who have not had any risk-reducing surgeries, only age had a significant effect (older women are less likely to say they will have PBM in the future), but the effect is small.
- Stated intentions to pursue surgery in the future was not significantly associated with distress as measured by the IES scores.

### CONCLUSIONS

- This study measured cancer-related distress in a large population of unaffected women with BRCA mutations who are participants in the FORCE online support community.
- Lower current reported levels of cancer-related distress were associated with higher education level, having PBM, and longer time since genetic test disclosure. BSO did not have a significant effect on distress levels in this population.
- A limitation of this study is that we measured IES levels at one time-point without the ability to compare to a baseline IES such as before women underwent genetic testing or before the decision to have risk-reducing surgeries.
- These findings are specific to a more informed community of women with high levels of education and understanding of cancer risk than may be seen in the clinical setting.
- These data will be combined and compared to a similar sample of BRCA-positive women tested at genetics clinics in the United States, Canada, United Kingdom, and Australia.

## ACKNOWLEDGEMENTS REFERENCES

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