Dear Editor,

Introduction

Women who carry the BRCA1/2 gene mutation are at a substantially high lifetime risk for breast and/or ovarian cancer, estimated at 80% and up to 50%, respectively [1]. Being a BRCA1/BRCA2 mutation carrier may have profound implications on psychological well-being and personal relationships [2]. Few interventions were carried out for BRCA1/2 mutation carriers, mostly involving a counseling program with an informative or supportive focus [3,4]. One increasingly popular approach to alleviate psychological distress and promote mental health among cancer patients is mindfulness interventions [5]. Inquiry-Based-Stress-Reduction (IBSR), developed by Byron Katie in 1986, enables individuals to identify the thoughts that cause stress and suffering in a systematic and comprehensive way, and to mindfully ‘investigate’ them by a series of questions and turnarounds [6]. The effectiveness of IBSR in a variety of conditions was previously demonstrated [7,8], yet its effectiveness for individuals at high risk for developing cancer has not been methodically evaluated to the best of our knowledge. The primary aim of the current study was to test the notion that the IBSR intervention may improve the Quality of Life (QOL) parameters and psychological scales among female BRCA1/2 mutation carriers.

Methods

Identification and recruitment of participants

Cancer-free women who were genotyped at the Oncogenetics Unit at Sheba Medical Center between January 1, 2000 and December 31, 2010 were eligible for recruitment if they harbored any pathogenic mutation in either the BRCA1 or the BRCA2 genes. Exclusion criteria were pregnancy, prophylactic mastectomy and severe mental illness. Women who agreed to participate were randomly divided into either the intervention or the control group.

Data collection

Participants were asked to complete the following psychological assessment questionnaires: perceived social support-family scale (PSS-FA), Pittsburgh sleep quality inventory questionnaire (PSQI), cancer-related worry questionnaire (CRW) and brief symptom inventory (BSI). The questionnaires were completed by the women in both groups at the beginning of the study and 12 weeks after the study initiation (end of intervention period). Demographic data was collected from all the participants at the beginning of the study.

Intervention method

The first part of the IBSR technique is to identify the stressful thoughts in a systematic and comprehensive way and to write the thoughts about various situations perceived by the person as stressful by using ‘Judge-your-neighbor’ worksheet (Appendix A) [6]. In the second part, the participants themselves or with the help of a ‘facilitator’ (a person trained in IBSR technique) choose the main thoughts they wrote and investigate them by using four questions and ‘turnarounds’. The guidance is to be in a state of witnessing awareness in which a person observes the thoughts that come into mind without trying to control or direct them. The next stage is the turnarounds, in which
the participants experience a different interpretation of reality as they perceive it.

The IBSR intervention included weekly group meetings (3.5 h/meeting) and weekly individual sessions with a facilitator (1 h/session) for 12 weeks. All the sessions were standardized according to a training manual and were assessed after each session for maintaining consistency in the program. Participants were considered active if they were present in at least 75% of the group meetings and completed 75% of the home practice.

Statistical analysis
Based on the ‘sleep quality’ variable as an anchor with an expected difference of 2 units, we calculated that a sample size of 60 participants is sufficient for 5% alpha and a power of 80%. Pearson correlation coefficients were used to address the correlation between the dependent variables, and a two-way analysis of variance (ANOVA) with a repeated measures factor (time of assessment) to examine the difference between the groups.

Results
One hundred and eighty seven Israeli women, carriers of a pathogenic BRCA1/2 mutation who were followed-up at Sheba Medical Center, were found eligible to participate in the study. Sixty-seven agreed to participate in the study (41 were BRCA1 and 26 were BRCA2 mutation carriers), as presented in Appendix B. Other relevant characteristics of the intervention group (n = 33) and the control group (n = 34) are presented in Table 1. Fifty-six women (83.6%) completed the study. At baseline, there were no significant differences in demographic characteristics and

### Table 1. Demographic and other relevant characteristics of the study participants

<table>
<thead>
<tr>
<th></th>
<th>Intervention group N = 22</th>
<th>Control group N = 34</th>
<th>Difference between groups</th>
<th>Test statistic</th>
<th>df</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>49.63 ± 9.04</td>
<td>46.64 ± 7.89</td>
<td>t test for independent samples t = -1.44</td>
<td></td>
<td>65</td>
<td>.15</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>27 (81.8%)</td>
<td>28 (82.3%)</td>
<td>X² = 0.003</td>
<td>1</td>
<td></td>
<td>.95</td>
</tr>
<tr>
<td>Single</td>
<td>(3%)</td>
<td>2 (5.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>5 (15.2%)</td>
<td>2 (5.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>–</td>
<td>2 (5.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (90.9%)</td>
<td>31 (91.2%)</td>
<td>X² = 1.20</td>
<td>1</td>
<td></td>
<td>.54</td>
</tr>
<tr>
<td>No</td>
<td>3 (9.1%)</td>
<td>3 (8.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>8 (24.2%)</td>
<td>4 (11.8%)</td>
<td>X² = 2.79</td>
<td>2</td>
<td></td>
<td>.24</td>
</tr>
<tr>
<td>Post high-school</td>
<td>7 (21.2%)</td>
<td>5 (14.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic degree</td>
<td>18 (54.6%)</td>
<td>25 (73.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Religiousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secular</td>
<td>26 (78.7%)</td>
<td>24 (70.6%)</td>
<td>X² = 0.95</td>
<td>2</td>
<td></td>
<td>.95</td>
</tr>
<tr>
<td>Traditional</td>
<td>4 (12.2%)</td>
<td>5 (14.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Religious</td>
<td>3 (9.1%)</td>
<td>3 (8.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0%)</td>
<td>2 (5.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country of origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td>27 (81.8%)</td>
<td>28 (82.4%)</td>
<td>X² = 0.003</td>
<td>1</td>
<td></td>
<td>.95</td>
</tr>
<tr>
<td>Others</td>
<td>6 (18.2%)</td>
<td>6 (17.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aCalculated according to the presence or absence of a spouse.
Abbreviations: SD, standard deviation; df, degrees of freedom.

### Table 2. Effect of IBSR technique of Byron Katie within and between the study groups

<table>
<thead>
<tr>
<th></th>
<th>Intervention group N = 22</th>
<th>Control group N = 34</th>
<th>Two-way mixed ANOVA time factor</th>
<th>Two-way mixed ANOVA interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep quality (PSQI)</strong></td>
<td>Before 7.48 (3.83)</td>
<td>7.36 (3.87)</td>
<td>p = 0.002</td>
<td>p = 0.183</td>
</tr>
<tr>
<td></td>
<td>After 5.42 (3.64)</td>
<td>6.36 (2.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Perceived family support (PSS-FA)</strong></td>
<td>Before 14.72 (4.16)</td>
<td>15.35 (4.27)</td>
<td>p = 0.002</td>
<td>p = 0.029*</td>
</tr>
<tr>
<td></td>
<td>After 17.27 (2.97)</td>
<td>15.85 (4.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cancer-related worries (CRW)</strong></td>
<td>Before 2.08 (0.62)</td>
<td>2.38 (0.76)</td>
<td>p = 0.003</td>
<td>p = 0.295</td>
</tr>
<tr>
<td></td>
<td>After 1.96 (0.81)</td>
<td>2.07 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General distress (BSI)</strong></td>
<td>Before 49.37 (7.56)</td>
<td>50.85 (11.48)</td>
<td>p = 0.760</td>
<td>p = 0.253</td>
</tr>
<tr>
<td></td>
<td>After 48.08 (8.01)</td>
<td>51.59 (11.21)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p-value of <0.05 indicating statistical significance.
Abbreviations: ANOVA, analysis of variance; SD, standard deviation.
the measured outcomes between the women who completed the program and those who did not (Appendix C). Table 2 summarizes the results of the four psychological parameters in the intervention and the control groups at study entry and termination. Perceived family support score was significantly improved after the intervention in the intervention group \((p = .009)\), while no difference was observed in the control group \((p = .282)\) (interaction between group and time). The effect size of difference between groups was 2.045 CI 95\% (0.220–3.870), \((p = .029)\). In the intervention group, there was an improvement in sleep quality (average 7.48±3.98 to 5.42±3.64) and cancer-related worries (average 2.08±0.62 to 1.96±0.81); however, these differences were not statistically significant. Clinical distress levels were similar for all the participants, regardless of the intervention.

Discussion

The results of the current study suggest that the practice of IBSR has a significant effect on perceived family support among female high-risk BRCA1/2 mutation carriers. Studies reported that perceived family support was associated with enhanced mental and physical health as it may act as a buffer against the negative implications of stressful situations and encourage health-related behaviors [9]. Given this empirical evidence, it is plausible that women in the intervention group, who practiced IBSR meditation and significantly changed their perception of their family support, will cope better with stressful events or emotional distress related to them being BRCA1/2 mutations carriers.

There were improvements in two additional measured parameters (sleep quality scale and cancer-related worries) among women who completed the intervention, but there was no significant difference between them and the controls. In addition, the intervention had no discernible effect on general distress. These results could be attributed to the short duration of the intervention (12 weeks), or the selection of measures in relation to what might have actually changed more significantly. Alternatively, a study that evaluated the effects of a supportive-expressive therapy among BRCA1/2 carriers showed that anxiety was relieved in women who were at the highest anxiety levels at baseline-60 or more on the BSI scale, which is considered clinical distress [10]. In the current study, women’s mean level of distress was less than 50 on the BSI scale. Thus, the effect of IBSR intervention may be limited only to women with the highest levels of anxiety, not seen in the current study.

We are aware of several limitations in this study. It encompassed Israeli female mutation carriers all from a single medical center in Israel. The number of women under the age of 40 years was small \((n=11)\), and only the short-term effects of a specific mind-body technique were measured on selected psychosocial parameters.

Conclusions

The findings of this first-ever randomized clinical trial of the implementation of IBSR intervention in a population of high risk BRCA1/2 mutation carriers reveal that it has a positive effect on perceived family support. If the data is validated in a large-scale and longer study, it will provide an additional tool to be added and recommended as an adjunct to traditional genetic counseling.

Acknowledgements

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Ethics approval

Sheba Medical Center IRB, Israel (# 8400-10-SMC)

Conflict of interest

The authors declare that they have no conflict of interest.

Key points

- BRCA1/2 mutation carriers have a substantially increased risk for developing breast and ovarian cancer. Such risks may have profound implications on carriers’ psychological well-being and family dynamics.
- Several interventions were carried out for BRCA1/2 mutation carriers, mostly involving a counseling program with an informative or supportive focus. The purpose of the current study was to evaluate the effectiveness of Inquiry-Based Stress Reduction (IBSR), a meditation-based intervention, on quality of life and psychological parameters among BRCA1/2 mutation carriers.
- Sixty-seven women carriers of one of the predominant mutations in BRCA1/2 were randomly assigned to intervention or control groups. A significant improvement in perceived family support was demonstrated in the intervention group compared with the controls.
- This finding has emotional and health implications, as studies demonstrated that perceived family support acts as a buffer against the negative implications of stressful situations and encourage health-related behaviors. Further studies are warranted to devise the means for clinical implementation of IBSR as an adjunct to traditional genetic counseling.
Appendix A. ‘Judge-Your-Neighbor’ worksheet

Judge-your-neighbor • Write it down • Ask four questions • Turn it around

Think of a recurring stressful situation, a situation that is reliably stressful even though it may have happened only once and recurs only in your mind. Before answering each of the questions below, allow yourself to mentally revisit the time and place of the stressful occurrence.

1. In this situation, time, and location, who angers, confuses, or disappoints you, and why?
   I am _________ with _________ because _________
   
   Example: I am angry with Paul because he doesn’t listen to me about his health.

2. In this situation, how do you want them to change? What do you want them to do?
   I want _________ to _________

   Example: I want Paul to see that he is wrong. I want him to stop smoking. I want him to stop lying about what he is doing to his health. I want him to see that he is killing himself.

3. In this situation, what advice would you offer to them?
   _________ should/shouldn’t _________

   Example: Paul should take a deep breath. He should calm down. He should see that his actions scare me and the children. He should know that being right is not worth another heart attack.

4. In order for you to be happy in this situation, what do you need them to think, say, feel, or do?
   I need _________ to _________

   Example: I need Paul to hear me. I need him to take responsibility for his health. I need him to respect my opinions.

5. What do you think of them in this situation? Make a list.
   _________ is _________

   Example: Paul is unfair, arrogant, loud, dishonest, way out of line, and unconscious.

6. What is it in or about this situation that you don’t ever want to experience again?
   I don’t ever want _________

   Example: I don’t ever want Paul to lie to me again. I don’t ever want to see him smoking and ruining his health again.

The four questions
1. Is it true? (Yes or no. If no, move to 3.)
2. Can you absolutely know that it’s true? (Yes or no.)
3. How do you react, what happens, when you believe that thought?
4. Who would you be without the thought?

Turn the thought around
a) to the self, (I don’t listen to myself about my health.)
b) to the other, (I don’t listen to Paul about his health.)
c) to the opposite, (Paul does listen to me about his health.)

Then find at least three specific, genuine examples of how each turnaround is true for you in this situation.

The turnaround for statement 6:
I am willing to _________ (Example: I am willing to have Paul lie to me again.)
I look forward to _________ (Example: I look forward to having Paul lie to me again.)

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Appendix B. Consort diagram of the research design

Initial contact by phone or letter (n=187)

Did no reply (n=29)

Replied (n=158)

Interested and did not meet criteria (n=8)
  - Pregnant (n=3)
  - Diagnosed with cancer (n=5)
Interested and met criteria (n=82)
  - Participated in the program presentation (n=68)
  - Did not participate (n=14)
Refused to participate (n=68)
  - On holiday (n=5)
  - Very busy (n=15)
  - Living too far (n=1)
  - Not interested (n=28)
  - Have not decided (n=19)

Signed up and were randomly assigned (n=67)

Intervention group (n=33)
  - Completed the study (n=22)
  - Did not complete the study (n=11)
    - Did not complete intervention's requirements (n=5)
    - Dropped out during the meetings (n=8)
      - Difficulty arriving before the Sabbath (n=5)
      - Religious reasons (n=1)
      - Reluctant to deal with sad issues (n=1)
      - Difficulty with group format (n=1)

Control group (n=34)
  - Completed the study (n=34)

Results analysis (N=22)

Results analysis (N=34)
Appendix C. Women who completed the IBSR program compared to those who dropped out

<table>
<thead>
<tr>
<th>Completed (N = 59)</th>
<th>Dropped out (N = 8)</th>
<th>Test statistic</th>
<th>p</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep quality (PSQI)</td>
<td>6.93 (3.63)</td>
<td>9.71 (4.64)</td>
<td>t = -1.86</td>
<td>0.07</td>
</tr>
<tr>
<td>Perceived family support (PSS-FA)</td>
<td>15.50 (4.15)</td>
<td>14.62 (6.88)</td>
<td>t = 0.51</td>
<td>0.6</td>
</tr>
<tr>
<td>Cancer-related worries (CRW)</td>
<td>2.31 (0.81)</td>
<td>2.37 (1.19)</td>
<td>t = -1.80</td>
<td>0.8</td>
</tr>
<tr>
<td>General distress (BSI)</td>
<td>49.0 (10.16)</td>
<td>50.8 (9.27)</td>
<td>t = -2.40</td>
<td>0.8</td>
</tr>
<tr>
<td>Age</td>
<td>48.3 (8.3)</td>
<td>46.75 (10.68)</td>
<td>t = 0.48</td>
<td>0.6</td>
</tr>
<tr>
<td>Marital status With spouse</td>
<td>83.5%</td>
<td>75%</td>
<td>( \chi^2 = .31 )</td>
<td>0.65</td>
</tr>
<tr>
<td>Without spouse</td>
<td>16.5%</td>
<td>25%</td>
<td>( \chi^2 = .31 )</td>
<td>0.65</td>
</tr>
<tr>
<td>Children Yes</td>
<td>93.22%</td>
<td>87.5%</td>
<td>( \chi^2 = .45 )</td>
<td>0.79</td>
</tr>
<tr>
<td>No</td>
<td>6.7%</td>
<td>12.5%</td>
<td>( \chi^2 = .45 )</td>
<td>0.79</td>
</tr>
<tr>
<td>Origin Israel</td>
<td>83.5%</td>
<td>75%</td>
<td>( \chi^2 = .31 )</td>
<td>0.65</td>
</tr>
<tr>
<td>Other</td>
<td>16.5%</td>
<td>25%</td>
<td>( \chi^2 = .31 )</td>
<td>0.65</td>
</tr>
<tr>
<td>Education Academic degree</td>
<td>67%</td>
<td>37%</td>
<td>( \chi^2 = 2.81 )</td>
<td>0.094</td>
</tr>
<tr>
<td>Other</td>
<td>32%</td>
<td>62.5%</td>
<td>( \chi^2 = 2.81 )</td>
<td>0.094</td>
</tr>
<tr>
<td>Religiousness Secular</td>
<td>69.5%</td>
<td>100%</td>
<td>( \chi^2 = 2.46 )</td>
<td>0.292</td>
</tr>
<tr>
<td>Traditional</td>
<td>15%</td>
<td>-</td>
<td>( \chi^2 = 2.46 )</td>
<td>0.292</td>
</tr>
<tr>
<td>Religious</td>
<td>6.6%</td>
<td>-</td>
<td>( \chi^2 = 2.46 )</td>
<td>0.292</td>
</tr>
</tbody>
</table>

^*Data were missing for one participant.
Abbreviation: SD, standard deviation.

References