BREATH: Web-Based Self-Management for Psychological Adjustment After Primary Breast Cancer—Results of a Multicenter Randomized Controlled Trial

Sanne W. van den Berg, Marieke F.M. Gielissen, José A.E. Custers, Winette T.A. van der Graaf, Petronella B. Ottevanger, and Judith B. Prins

ABSTRACT

Purpose
Early breast cancer survivors (BCSs) report high unmet care needs, and easily accessible care is not routinely available for this growing population. The Breast Cancer E-Health (BREATH) trial is a Web-based self-management intervention to support the psychological adjustment of women after primary treatment, by reducing distress and improving empowerment.

Patients and Methods
This multicenter, randomized, controlled, parallel-group trial evaluated whether care as usual (CAU) plus BREATH is superior to CAU alone. BREATH is delivered in sixteen fully automated weekly modules covering early survivorship issues. Two to 4 months post-treatment, BCSs were randomly assigned to receive CAU + BREATH (n = 70) or CAU alone (n = 80) using a stratified block design (ratio 1:1). Primary outcomes were distress (Symptom Checklist-90) and empowerment (Cancer Empowerment Questionnaire), assessed before random assignment (baseline, T0) and after 4 (T1), 6 (T2), and 10 months (T3) of follow-up. Statistical (analysis of covariance) and clinical effects (reliable change index) were tested in an intention-to-treat analysis (T0 to T1). Follow-up effects (T0 to T3) were assessed in assessment completers.

Results
CAU + BREATH participants reported significantly less distress than CAU-alone participants (−7.79; 95% CI, −14.31 to −1.27; P = .02) with a small-to-medium effect size (d = 0.33), but empowerment was not affected (−1.79; 95% CI, 5.20 to −1.79; P = .34). More CAU + BREATH participants (39 of 70 [56%]; 95% CI, 44.1 to 66.8) than CAU-alone participants (32 of 80 [40%]; 95% CI, 30.0 to 51.0) showed clinically significant improvement (P = .03). This clinical effect was most prominent in low-distress BCSs. Secondary outcomes confirmed primary outcomes. There were no between-group differences in primary outcomes during follow-up.

Conclusion
Access to BREATH reduced distress among BCSs, but this effect was not sustained during follow-up.

J Clin Oncol 33:2763-2771. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Women diagnosed with breast cancer face challenges that do not end with treatment completion. The first year after primary treatment, the so-called re-entry phase,1 is characterized by physical, emotional, and social recovery.2 Women report high unmet care needs3 and have to cope with lingering physical and emotional symptoms of treatment, fear of recurrence, decreasing social support, losing the safety net of care providers, and resuming professional and recreational activities.4-6 Approximately 70% of breast cancer survivors (BCSs) ie, women who have completed primary breast cancer treatment with no evidence of recurrence7) adjust well during the re-entry phase, but a substantial proportion report high levels of distress.8,9

Better diagnosis and therapy mean that more women survive breast cancer, and self-management strategies10 and e-health11 have been proposed as ways to support this growing population. Because approximately half of all BCSs already search the Internet for breast cancer–specific information,12-15 the Internet is promising for providing psycho-oncological interventions.16 However, there are few randomized controlled trials (RCTs) of Web-based interventions to support re-entry adjustment. To date, most Web-based interventions including
women with breast cancer have not been either re-entry specific\textsuperscript{17-20} or breast cancer specific,\textsuperscript{21,22} or have predominantly focused on peer support groups\textsuperscript{23-26} or informational support.\textsuperscript{27} In a recent overview advocating re-entry specific care, Stanton\textsuperscript{2} reported promising but inconclusive evidence from seven RCTs that psychoeducational interventions can be effective in BCSs.

We developed the Breast Cancer E-Health (BREATH) trial,\textsuperscript{28} a Web-based self-management intervention on the basis of cognitive behavioral therapy that provides early BCSs with self-management skills to enable them to take control of, and adjust to, post-treatment survivorship. The intervention was developed using the transactional model of stress\textsuperscript{29} and the model of psychological well-being in cancer survivors,\textsuperscript{30} both of which describe negative and positive outcomes in adapting to a stressor. Thus, the primary aim of this RCT was to study whether care as usual (CAU) plus BREATH (CAU + BREATH) can effectively target negative and positive adjustment. We hypothesized that CAU + BREATH is superior to CAU alone in reducing distress and improving empowerment. Because BCSs exhibit different levels of distress during the re-entry phase, subhypotheses were that CAU + BREATH would reduce distress in high-distress BCSs, keep levels of distress low in low-distress BCSs, and improve empowerment in both distress groups.

PATIENTS AND METHODS

Study Design and Participants

The BREATH study protocol has been published elsewhere.\textsuperscript{28} We conducted a multicenter, randomized, controlled, parallel-group trial to evaluate the efficacy of a Web-based self-management intervention in facilitating psychological adjustment among BCSs. One university hospital and five regional hospitals in the Netherlands participated (Fig 1). Female BSCs were eligible if they had a histologically proven malignancy of the breast and had completed curative-intent primary treatment (defined as surgery plus adjuvant chemotherapy and/or radiotherapy) 2 to 4 months before the baseline assessment. Participant characteristics are listed in Table 1.

The local treatment team monitored patient recruitment and eligibility and obtained informed consent. A researcher (S.v.d.B.) contacted participants to check additional eligibility criteria: understanding the Dutch language, access to the Internet, and having an e-mail address.

Study assessments covered the first year after breast cancer, with baseline at 2 to 4 months after completion of primary treatment (T0), and follow-up assessments at 4 (T1), 6 (T2), and 10 (T3) months after...
Table 1. Baseline Characteristics of Study Participants (N = 150)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CAU + BREATH (n = 70)</th>
<th>CAU alone (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>51.44</td>
<td>50.18</td>
</tr>
<tr>
<td>SD</td>
<td>8.30</td>
<td>9.15</td>
</tr>
<tr>
<td>Educational level*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (ISCED 0-1-2)</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Medium (ISCED 3-4-5)</td>
<td>32</td>
<td>46</td>
</tr>
<tr>
<td>High (ISCED 6-7-8)</td>
<td>24</td>
<td>34</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td>58</td>
<td>83</td>
</tr>
<tr>
<td>Unmarried</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Divorced</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Widowed</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Children (yes)</td>
<td>61</td>
<td>87</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paid work outside home</td>
<td>30</td>
<td>43</td>
</tr>
<tr>
<td>Home management</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>Unemployed</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Sick leave</td>
<td>30</td>
<td>43</td>
</tr>
<tr>
<td>Disability insurance act</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Voluntary work</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Student</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retired</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Treatment type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery + chemotherapy + radiotherapy</td>
<td>48</td>
<td>69</td>
</tr>
<tr>
<td>Surgery + chemotherapy</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td>Surgery + radiotherapy</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>46</td>
<td>66</td>
</tr>
<tr>
<td>Low distress (GSI ≤ 0.57)</td>
<td>51</td>
<td>73</td>
</tr>
<tr>
<td>Frequency of Internet use†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>24</td>
<td>59</td>
</tr>
<tr>
<td>2 to 4 times a week</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>Weekly or less</td>
<td>5</td>
<td>12</td>
</tr>
</tbody>
</table>

NOTE: No significant differences were found between the two conditions (P > .05). Values were calculated using χ² tests for categorical variables and a two-tailed Student’s t test (independent sample) for continuous variables. Abbreviations: BREATH, Breast Cancer E-Health intervention; CAU, care as usual; GSI, General Severity Index; ISCED, International Standard Classification of Education; SD, standard deviation.

*ISCED 2011.
†Percentages do not add up to 100% because more options are possible.
‡CAU + BREATH (n = 41), CAU alone (n = 52).

Baseline. The Radboud University Medical Center Medical Review Ethics Committee (file No. 2009/144) and the ethics boards of local participating centers approved the study (Netherlands Trial Register NTR2935).

Intervention

BREATH (Appendix Fig A1, online only) targets re-entry issues relevant to BCSs during a fixed 16-week modular program for four phases of adjustment to breast cancer (looking back, emotional processing, strengthening, and looking ahead). Intervention components (104 total) are based on cognitive behavioral therapy and include information (26 scripts), assignment (48 tasks, or homework), assessment (10 self-tests followed by automated feedback), and video (20 topics illustrated with clips extracted from interviews). BREATH is a pure self-help program without therapist contact (also known as self-administered therapy). Each week, new materials are released, accompanied by standard e-mail reminders, in an attempt to maintain or improve adherence. Access to BREATH was withdrawn after 16 weeks.

BCSs receiving CAU alone did not have access to BREATH. For both conditions, CAU consisted of visits to an oncologist three times per month and psychosocial care on demand or referral. No restrictions were made regarding use of Internet or psychological or other self-help interventions.

Outcomes

Study assessments and random assignment were conducted online using RadQuest software (Radboudum Medical Psychology, Nijmegen, the Netherlands). Baseline characteristics were obtained with a medical checklist derived from the patient chart.

General psychological distress was assessed with the Symptom Checklist-90 (SCL-90; range, 90-450), which has good psychometric properties in healthy and patient populations. The SCL-90 total score showed good internal consistency at baseline (Cronbach’s α = .97). For the General Severity Index (GSI), which represents the mean score of all responses, transformed item scores (0-4) were used. General psychological empowerment was assessed with the Cancer Empowerment Questionnaire (CEQ). The CEQ presumes that patients can derive strength from themselves (intrapersonal) and from their social surroundings (interpersonal). Baseline internal consistency was good (Cronbach’s α = .92).

Secondary outcomes reflected negative adjustment (general and cancer-specific distress, fatigue, helplessness, and fear of cancer recurrence and positive adjustment (self-efficacy, remoralization, personal control, quality of life, fulfillment, re-evaluation, new ways of living, and valuing life). For details of secondary outcomes, see our study protocol (or the legend of Table 2 with treatment effects).

Information about self-reported use of Internet and other resources (individual support, peer support, rehabilitation support groups) was collected at T1. General Internet use was assessed with the question “Have you consulted the Internet for information on (learning to live with) breast cancer in the past 4 months?” Four-month usage data of CAU + BREATH participants were evaluated. For the current report, correlations were calculated between the mean difference (T0 to T1) in distress and the continuous usage variables of frequency of log-ins, total duration (in minutes), and activity (number of intervention components opened).

Random Assignment and Masking

BCSs were randomly assigned (allocation ratio 1:1) to receive CAU + BREATH or CAU alone. For each center, a randomized block design with stratification by hormone therapy was generated. After baseline assessment, a random number generator with variable block sizes of 4, 6, and 8 automatically ensured blinded allocation until intervention assignment. One researcher (S.v.d.B.) informed participants about treatment assignment by e-mail and was therefore not blinded. In one case, a participant was told an incorrect treatment assignment (CAU instead of CAU + BREATH); this participant received CAU alone and her data were analyzed accordingly.
Statistical Methods
All statistical analyses were performed with SPSS 20 (IBM, Ar- 
monk, NY). The sample size calculation for the primary outcomes at 
T1 was 170: 128 BCSs (64 in each group) at 80% power for differences 
between CAU + BREATHT CAU alone with a medium effect size 
of 0.50, plus a 25% dropout rate.38 The level of significance in the 
sample size calculation was adjusted to \( P \leq 0.025 \) to keep the overall 
chance of type I error at 5%. Inclusion was prematurely stopped at 151 
participants, with approval of the ethics committee, because only 5% 
(7 of 151) of the participants dropped out at T1.

Statistical Effect
The primary hypothesis was that CAU + BREATHT would be 
superior to CAU alone in decreasing distress and increasing empow-
erment, and it was tested in an intention-to-treat (ITT) analysis of data 
for T0 and T1. Missing data at T1 were imputed using last observation 
carried forward. The significance of intervention effects on primary 
and secondary outcomes was tested using one-way between-groups 
analyses of covariance with group (CAU + BREATHT or CAU alone) 
as a fixed factor. Because participants were not preselected before 
inclusion, the analysis of covariance model corrected for baseline 
differences. For primary outcome analyses, baseline distress (SCL-90 
and empowerment (CEQ) were used as covariates. For secondary 
outcome analyses, baseline scores of corresponding questionnaires 
were used as covariates. Interaction effects of mean adjusted differ-
ences between T0 and T1 by group are reported in Table 2, with SEs, 
significance level, and 95% CI. Effect size Cohen’s \( d \) for independent 
groups was calculated using the pooled standard deviations and un-
adjusted means on T1.

Clinically Significant Change
Clinically significant change, assessed with the reliable change 
index (RCI) of the GSI, was tested in ITT analysis (T0 to T1). 
Following Jacobson and Truax,47 Schauenburg and Strack,48 calcu-
lated the GSI cutoff 0.567 to discriminate between low and high 
distress on the basis of normative and psychotherapy samples. The 
magnitude of improvement (defined as RCI \( \leq -0.16 \) for low-
distress participants and RCI \( \leq -0.43 \) for high-distress participants) 
or deterioration (RCI \( \geq 0.16 \) for low-distress participants and 
RCI \( \geq 0.43 \) for high-distress participants) was assessed using 
one-sided \( \chi^2 \) tests.33

Follow-Up Effect
Follow-up effects for primary and secondary outcomes were 
evaluated with mixed within-between repeated-measures analysis of 
variance, including data for participants who completed all four as-
sessments (T0 to T3). Because participants were randomly assigned at 
each center, center was not included as a random effect. Baseline 
variables were taken into account as within factors in the model. 
Differences between CAU + BREATHT and CAU alone were tested 
using independent samples \( t \) tests.

RESULTS
Between August 2010 and March 2012, 170 women were referred 
and 151 (89%) out of these were enrolled (metastatic disease) and excluded after the random assignment,39 leaving a final ITT sample of 150 BCSs (70 CAU + 
BREATHT, 80 CAU alone). At baseline, the two groups did not differ on demographic characteristics (Table 1) and study out-
comes (Table 2). Participants with missing data at T1 (n = 17) had 
higher levels of baseline distress than participants with complete 
data at T1 (mean difference, 23.57; 95% CI, 3.82 to 43.31; \( P \) = .02). 
Levels of baseline empowerment were similar (\( P = .79 \)). Missing 
data at T1 were equally distributed between the two groups. Over-
all, 124 participants (58 CAU + BREATHT; 66 CAU alone) com-
pleted all four assessments, and their data were included in 
follow-up analyses. No metastases or severe illnesses were reported 
during the study. One woman was admitted to a psychiatric clinic;
this was reported as a serious adverse event.

Statistical Effect
The decrease in distress at T1 was significantly greater in 
CAU + BREATHT than in CAU-alone participants, with a 
small-to-medium effect size (\( d = 0.33 \); Table 2). Baseline distress 
explained 53% of the variance in distress at T1 (\( P < .005 \)). No such 
difference in empowerment was found.

Secondary outcome analyses (Table 2) revealed that CAU + 
BREATHT led to significant improvements in five of seven negative 
adjustment variables (general and cancer-specific distress, fatigue, and 
and two fear of cancer recurrence outcomes) with small-to-
medium effect sizes (\( d = 0.37 \) to 0.55), and in 3 of 10 positive adjustment variables 
(self-efficacy, remoralization, new ways of living) with small-to-
medium effect sizes (\( d = 0.26 \) to 0.39).

Clinically Significant Change
More CAU + BREATHT participants (39 of 70 [56%]; 95% CI, 
44.1 to 66.8) than CAU-alone participants (32 of 80 [40%]; 95% CI, 
30.0 to 51.0) showed a clinically significant improvement (\( P = .03 \)). 
We had hypothesized that more high-distress BCSs would show a 
clinically significant improvement after CAU + BREATHT than after CAU alone, but this was not the case (10 of 21 [48%]; 95% CI, 28.3 to 
67.6 \( \nu \) 14 of 27 [52%]; 95% CI, 34.0 to 69.3, respectively; \( P = .39 \)). Post 
hoc analysis revealed that there was no difference in the proportion of 
high-distress BCSs showing clinical deterioration (5 of 21 [24%] \( \nu \) 2 of 
27 [7%], respectively; \( P = .06 \)). Of the low-distress BCSs, more 
CAU + BREATHT participants than CAU-alone participants showed 
clinical improvement or no change (41 of 49 [84%]; 95% CI, 71.0 to 
91.5 \( \nu \) 35 of 53 [66%]; 95% CI, 52.6 to 77.3 respectively; \( P = .02 \)). 
Moreover, explorative post hoc analyses of low-distress BCSs revealed 
that, compared with CAU-alone participants, CAU + BREATHT 
participants showed considerably lower clinical improvement (29 of 49 
[59%] \( \nu \) 18 of 53 [34%], respectively; \( P = .006 \)) and less deterioration 
(8 of 49 [16%] \( \nu \) 18 of 53 [34%], respectively; \( P = .02 \)). The empow-
erment hypothesis was not tested, because empowerment was not 
significantly different between CAU + BREATHT and CAU alone.

Follow-Up Effect
At T2 and T3, distress was significantly reduced regardless of 
group assignment (\( F[3, 120] = 5.88; P = .001; \) Fig 2). This was also 
true for the secondary negative adjustment outcomes of fear of cancer 
recurrence (Cancer Worry Scale; \( F[3, 120] = 5.954; P = .001 \)), fatigue 
(\( F[3, 120] = 4.40; P = .006 \)), and helplessness (\( F[3, 120] = 11.964; 
\( P = .000 \)). A significant time \times group interaction effect was found for
### Table 2. Effect of Treatment (intention-to-treat analysis) on Primary and Secondary Outcomes After 4 Months (N = 150)

<table>
<thead>
<tr>
<th>Treatment Effect</th>
<th>CAU + BREATH (n = 70)</th>
<th>CAU Alone (n = 80)</th>
<th>Mean Difference (95% CI)</th>
<th>P</th>
<th>Effect Size (Cohen’s d)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distress (SCL-90* [32])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>135.44 (37.532)</td>
<td>140.33 (41.045)</td>
<td>−4.882 (−17.640 to 7.785)</td>
<td>.451</td>
<td></td>
</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>124.90 (26.963)</td>
<td>135.84 (37.975)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (adjusted)</td>
<td>126.676 (2.412)</td>
<td>134.463 (2.250)</td>
<td>−7.888 (−14.308 to −1.267)</td>
<td>&lt; .05</td>
<td>0.33</td>
</tr>
<tr>
<td>Empowerment (CEQ†33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>156.90 (13.222)</td>
<td>154.06 (15.133)</td>
<td>2.838 (−1.779 to 7.454)</td>
<td>.226</td>
<td></td>
</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>159.13 (15.116)</td>
<td>155.45 (13.639)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (adjusted)</td>
<td>157.946 (1.299)</td>
<td>156.240 (1.206)</td>
<td>1.706 (−1.787 to 5.200)</td>
<td>.336</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative adjustment variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General distress (HADS-total score)* [35]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>9.07 (6.710)</td>
<td>10.01 (7.259)</td>
<td>−0.941 (−3.208 to 1.326)</td>
<td>.413</td>
<td></td>
</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>7.67 (6.033)</td>
<td>9.89 (6.129)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (adjusted)</td>
<td>8.052 (0.461)</td>
<td>9.621 (0.431)</td>
<td>−1.569 (−2.815 to −0.322)</td>
<td>&lt; .05</td>
<td>0.37</td>
</tr>
<tr>
<td>General (Distress Thermometer*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>3.89 (2.505)</td>
<td>4.53 (2.516)</td>
<td>−0.639 (−1.451 to 0.173)</td>
<td>.122</td>
<td></td>
</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>3.46 (2.506)</td>
<td>4.00 (2.408)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (adjusted)</td>
<td>3.682 (0.249)</td>
<td>3.858 (0.232)</td>
<td>−0.196 (−0.868 to 0.477)</td>
<td>.566</td>
<td>0.22</td>
</tr>
<tr>
<td>General fatigue (CIS)* [37]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>33.29 (12.530)</td>
<td>33.38 (12.627)</td>
<td>0.089 (−4.159 to 3.980)</td>
<td>.965</td>
<td></td>
</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>28.57 (12.913)</td>
<td>32.77 (13.309)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (adjusted)</td>
<td>28.602 (1.205)</td>
<td>32.746 (1.127)</td>
<td>−4.144 (−7.404 to −0.884)</td>
<td>&lt; .05</td>
<td>0.32</td>
</tr>
<tr>
<td>Cancer specific (fear of recurrence (CWS)* [39])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>14.31 (4.454)</td>
<td>15.36 (3.892)</td>
<td>−1.048 (−2.395 to 0.298)</td>
<td>.126</td>
<td></td>
</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>13.13 (3.310)</td>
<td>15.19 (4.119)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (adjusted)</td>
<td>13.452 (0.296)</td>
<td>14.799 (0.277)</td>
<td>−1.347 (−2.149 to −0.545)</td>
<td>&lt; .001</td>
<td>0.55</td>
</tr>
<tr>
<td>Cancer specific (fear of recurrence (CAS)* [40])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>5.11 (1.584)</td>
<td>5.45 (1.630)</td>
<td>−0.336 (−0.814 to 0.856)</td>
<td>.204</td>
<td></td>
</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>4.90 (1.395)</td>
<td>5.51 (1.567)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (adjusted)</td>
<td>5.015 (0.120)</td>
<td>5.398 (0.112)</td>
<td>−0.383 (−0.707 to −0.059)</td>
<td>&lt; .05</td>
<td>0.41</td>
</tr>
<tr>
<td>Cancer specific (helplessness (ICQ†)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>10.36 (3.301)</td>
<td>10.21 (3.133)</td>
<td>0.145 (−0.894 to 1.184)</td>
<td>.784</td>
<td></td>
</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>9.39 (2.975)</td>
<td>9.45 (3.023)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (adjusted)</td>
<td>9.335 (0.274)</td>
<td>9.488 (0.256)</td>
<td>−0.153 (−0.894 to 0.589)</td>
<td>.685</td>
<td>0.02</td>
</tr>
<tr>
<td>Cancer specific (distress (IES-total score)* [38])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>18.11 (15.098)</td>
<td>18.88 (15.730)</td>
<td>−0.761 (−5.754 to 4.232)</td>
<td>.764</td>
<td></td>
</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>11.81 (12.240)</td>
<td>17.35 (14.371)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (adjusted)</td>
<td>12.024 (1.244)</td>
<td>17.143 (1.164)</td>
<td>−5.119 (−8.486 to −1.752)</td>
<td>&lt; .01</td>
<td>0.42</td>
</tr>
<tr>
<td>Positive adjustment variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General (self-efficacy (SES)* [41])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>19.97 (2.756)</td>
<td>20.30 (2.655)</td>
<td>−0.329 (−1.203 to 0.545)</td>
<td>.459</td>
<td></td>
</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>21.03 (2.127)</td>
<td>20.23 (2.556)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (adjusted)</td>
<td>21.130 (0.290)</td>
<td>20.133 (0.271)</td>
<td>0.997 (0.213 to 1.781)</td>
<td>&lt; .05</td>
<td>0.28</td>
</tr>
<tr>
<td>General (remoralization (RS12)* [43])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>3.09 (0.512)</td>
<td>3.06 (0.569)</td>
<td>0.022 (−0.153 to 0.198)</td>
<td>.802</td>
<td></td>
</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>3.28 (0.495)</td>
<td>3.08 (0.540)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (adjusted)</td>
<td>3.275 (0.051)</td>
<td>3.081 (0.047)</td>
<td>0.195 (0.058 to 0.332)</td>
<td>&lt; .01</td>
<td>0.39</td>
</tr>
<tr>
<td>General (personal control (Mastery†)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>23.93 (4.604)</td>
<td>23.84 (4.653)</td>
<td>0.291 (−1.206 to 1.789)</td>
<td>.701</td>
<td></td>
</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>24.74 (4.548)</td>
<td>23.58 (4.957)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (adjusted)</td>
<td>24.655 (0.435)</td>
<td>23.677 (0.407)</td>
<td>0.977 (−0.199 to 2.154)</td>
<td>.103</td>
<td>0.24</td>
</tr>
<tr>
<td>General (acceptance (ICQ)†)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>16.17 (3.996)</td>
<td>16.14 (3.525)</td>
<td>0.034 (−1.180 to 1.247)</td>
<td>.956</td>
<td></td>
</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>17.60 (4.109)</td>
<td>16.94 (3.509)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (adjusted)</td>
<td>17.586 (0.313)</td>
<td>16.948 (0.293)</td>
<td>0.637 (−0.209 to 1.1484)</td>
<td>.139</td>
<td>0.17</td>
</tr>
</tbody>
</table>

(continued on following page)
fear of cancer recurrence (Cancer Worry Scale; F[3, 120] = 4.563; P = .005), with CAU + BREATHT participants reporting less fear than CAU-alone participants at T2 (−1.459; 95% CI, −2.743 to −0.175). Of the positive adjustment outcomes, acceptance significantly improved in both groups (ICQ; F[3, 120] = 8.531; P = .000). Time effects and time × group interactions were not significant for all remaining outcomes, including empowerment (Fig 3).

**Use of BREATHT and Other Resources**

Use of the BREATHT intervention varied considerably. Frequency of logins ranged from 0 to 45, total duration ranged from 0 to 2,324 minutes, and activity ranged from 0 to 104 intervention components opened. The mean difference in distress (SCL-90, T0 to T1) was not correlated with frequency (r = −.007; P = .96), total duration (r = 0.000; P = 1.00), or activity (r = −1.072; P = .55).

At T1, similar proportions of women in CAU + BREATHT and CAU alone had consulted the Internet in the previous 4 months on a monthly (24% v 34%), weekly (13% v 8%), or daily (0% v 2%) basis, or not at all (61% v 58%). There were also no significant differences (n = 126; P = .27) between CAU + BREATHT and CAU-alone participants in the use of individual support (eg, psychologist; 12% v 25%, respectively), peer and rehabilitation support groups (14% v 12%, respectively), or combined individual and group support (21% v 13%, respectively). Half of the participants in both groups did not make use of other support (53% v 50%, respectively).

**DISCUSSION**

At the start of the re-entry phase, 4-month access to BREATHT in addition to CAU resulted in a statistically and clinically significant distress reduction compared with CAU alone. However, this small-to-medium effect was not sustained, and levels of distress were similar at 6 and 10 months. CAU + BREATHT participants also showed a greater decrease than CAU-alone participants in fear of cancer recurrence, fatigue, and general and cancer-related distress. The effect of BREATHT on fear of cancer recurrence was sustained during follow-up. Access to BREATHT did not influence empowerment or clinical distress improvement in high-distress BCSs. Low-distress BCSs showed a greater clinical improvement and less deterioration with CAU + BREATHT than with CAU alone.

The RCT was designed according to quality standards (CONSORT for parallel group,50 nonpharmacologic treatment,51 and eHealth trials).52,53 Statistically and clinically significant changes were evaluated in ITT analyses, with missing data imputed using a conservative method (last observation carried forward)
new, but not extensively validated in BCSs and lack information on targeted empowerment.3,9,62,63 The study sample also proved representative with regard to psychological determinants of intervention use and to study a possible dose-moderation analyses, or usage pattern are needed to gain insight into intervention assessments, in retrospect it might have been better to allow participants to retain access, especially because information often remains available with other psychoeducational interventions or self-help books. Another explanation for lack of a sustained effect may be the small-to-medium effect size, which might not have been enough to compensate for the natural course of emotional recovery. The missing-at-random assumption for imputation was violated. BCSs with missing data for the 4-month assessment had significantly higher levels of distress at baseline. Although not significant, more high-distress BCSs in the CAU + BREATH group showed a clinical deterioration. This leads to a cautious interpretation of the results regarding high-distress BCSs, and suggests that these women may need a more intensive intervention than BREATH.

The limited data on BREATH use means it is not possible to draw firm conclusions about how often the intervention should be used to have an effect. Further investigations with larger samples, mediation analyses, or usage pattern are needed to gain insight into determinants of intervention use and to study a possible dose-response relationship.61 Data for BCSs who declined to participate were not recorded. Although it was not feasible to recruit patients consecutively, our sample seemed homogeneous and representative, because the mean age, treatment type, education, and work situation of participants were comparable to those of other studies evaluating the Dutch breast cancer population.3,9,62,63 The study sample also proved representative with regard to psychological...
functioning during the first year after treatment. As in other studies of patients with breast or other cancer, most patients experienced low levels of distress (n = 102 [68%]).

To the best of our knowledge, this is the first RCT to demonstrate an additional effect of a self-management intervention specifically designed to support BCs in the year after treatment completion. Although small, the primary effect on distress was statistically robust and clinically relevant. Moreover, the intervention does not necessarily require a lot of user commitment. Future research should focus on replicating the current findings, using more valid questionnaires for the positive adjustment variables, and evaluating the follow-up effect beyond 4 months of access. The magnitude of the effect in BCs with low and high distress should be investigated further. BREATH demonstrated its potential as a feasible first step in a matched supportive care model providing evidence-based and easily accessible re-entry care.

REFERENCES


AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Sanne W. van den Berg, Petronella B. Ottevanger, Judith B. Prins
Administrative support: Sanne W. van den Berg
 Provision of study materials or data: Petronella B. Ottevanger
Collection and assembly of data: Sanne W. van den Berg
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

© 2017 by American Society of Clinical Oncology
Acknowledgment

We thank all patients who gave their time to participate and the oncologists, radiotherapists, and research nurses of the participating hospitals: Radboud university medical center, Nijmegen; Rijnstate, Arnhem and Zevenaar; Slingeland, Doetinchem; Hospital Gelderse Vallei, Ede; Canisius-Wilhelmina Hospital, Nijmegen; and Jeroen Bosch, Den Bosch.

Appendix

Fig A1. Screenshot of the BREATH (Breast Cancer E-Health intervention) Web site (in Dutch) with four-phase structure.