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

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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 (BREATHE) 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 BREATHE is superior to CAU alone. BREATHE 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 + BREATHE (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 + BREATHE 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 + BREATHE 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 BREATHE reduced distress among BCSs, but this effect was not sustained during follow-up.

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, is characterized by physical, emotional, and social recovery. Women report high unmet care needs 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. Approximately 70% of breast cancer survivors (BCSs) ie, women who have completed primary breast cancer treatment with no evidence of recurrence adjust well during the re-entry phase, but a substantial proportion report high levels of distress.

Better diagnosis and therapy mean that more women survive breast cancer, and self-management strategies and e-health 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, the Internet is promising for providing psycho-oncological interventions. However, there are few randomized controlled trials (RCTs) of Web-based interventions to support re-entry adjustment. To date, most Web-based interventions including

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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...
from interviews). BREATH is a pure self-help program without therapist contact (also known as self-administered therapy⁴¹). 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 (Radboudumc 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.³² 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).³³ 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 (general³⁴,³⁵ and cancer-specific distress,³⁶ fatigue,³⁷ helplessness,³⁸ and fear of cancer recurrence³⁹,⁴⁰) and positive adjustment (self-efficacy,⁴¹ remoralization,⁴² personal control,⁴³ quality of life,⁴⁴ fulfillment,⁴⁵ reevaluation,⁴⁵ new ways of living,⁴⁵ and valuing life⁴⁵). For details of secondary outcomes, see our study protocol²⁸ (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.⁴⁶ 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, Armonk, 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 + BREATH and CAU alone with a medium effect size of 0.50, plus a 25% dropout rate. The level of significance in the sample size calculation was adjusted to \( P \leq .025 \) 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 + BREATH would be superior to CAU alone in decreasing distress and increasing empowerment, 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 + BREATH 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 differences 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 samples was calculated using the pooled standard deviations and unadjusted 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, Schauenburg and Strack calculated 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.

**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 assessments (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 + BREATH and CAU alone were tested using independent samples \( t \) tests.

**RESULTS**

Between August 2010 and March 2012, 170 women were referred and 151 (89%) underwent random assignment (Fig 1). Data collection was finalized in February 2013. One woman was erroneously enrolled (metastatic disease) and excluded after the random assignment, leaving a final ITT sample of 150 BCSs (70 CAU + BREATH, 80 CAU alone). At baseline, the two groups did not differ on demographic characteristics (Table 1) and study outcomes (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. Overall, 124 participants (58 CAU + BREATH; 66 CAU alone) completed 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 + BREATH participants 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 + BREATH led to significant improvements in five of seven negative adjustment variables (general and cancer-specific distress, fatigue, 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 + 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 a clinically significant improvement (\( P = .03 \)). We had hypothesized that more high-distress BCSs would show a clinically significant improvement after CAU + BREATH than after CAU alone, but this was not the case (10 of 21 [48%]; 95% CI, 28.3 to 67.6) vs 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%] vs 2 of 27 [7%], respectively; \( P = .06 \)). Of the low-distress BCSs, more CAU + BREATH participants than CAU-alone participants showed clinical improvement or no change (41 of 49 [84%]; 95% CI, 71.0 to 91.5) vs 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 + BREATH participants showed more clinically significant improvement (29 of 49 [59%] vs 18 of 53 [34%], respectively; \( P = .06 \)) and less deterioration (8 of 49 [16%] vs 18 of 53 [34%], respectively; \( P = .02 \)). The empowerment hypothesis was not tested, because empowerment was not significantly different between CAU + BREATH 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 × 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></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>
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<tr>
<td>Distress (SCL-90†)</td>
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<tr>
<td>T0</td>
<td>135.44 (37.532)</td>
<td>140.33 (41.045)</td>
<td>−4.882 (−17.640 to 7.875)</td>
<td>.451</td>
<td></td>
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<tr>
<td>T1 (unadjusted)</td>
<td>124.90 (26.956)</td>
<td>135.84 (37.975)</td>
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<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>
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<tr>
<td>Empowerment (CEQ†33)</td>
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<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>
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<tr>
<td>T1 (adjusted)</td>
<td>157.946 (1.293)</td>
<td>156.240 (1.206)</td>
<td>1.706 (−1.787 to 5.200)</td>
<td>.336</td>
<td>0.16</td>
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<tr>
<td><strong>Secondary outcomes</strong></td>
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<tr>
<td><strong>Negative adjustment variables</strong></td>
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<tr>
<td>General distress (HADS-total score)†</td>
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<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>
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<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>
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<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>
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<tr>
<td>T1 (adjusted)</td>
<td>3.862 (0.249)</td>
<td>3.858 (0.232)</td>
<td>−0.016 (−0.068 to 0.477)</td>
<td>.566</td>
<td>0.22</td>
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<tr>
<td>General fatigue (CIS)†</td>
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<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>
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<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>
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<tr>
<td>Cancer specific (fear of recurrence [CWS] †39)</td>
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<tr>
<td>T0</td>
<td>14.31 (4.454)</td>
<td>15.36 (4.392)</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>
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<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>
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<tr>
<td>T0</td>
<td>5.11 (1.584)</td>
<td>5.45 (1.630)</td>
<td>−0.336 (−0.084 to 0.856)</td>
<td>.204</td>
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</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>4.90 (1.395)</td>
<td>5.51 (1.567)</td>
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<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>
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<tr>
<td>Cancer specific (helplessness [ICQI]†38)</td>
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<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>
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<tr>
<td>T1 (unadjusted)</td>
<td>9.39 (2.975)</td>
<td>9.45 (3.023)</td>
<td></td>
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<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>
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<tr>
<td>Cancer specific (distress [IES-total score]†38)</td>
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<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>
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</tr>
<tr>
<td>T1 (unadjusted)</td>
<td>11.81 (12.240)</td>
<td>17.35 (14.371)</td>
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<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>
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<tr>
<td><strong>Positive adjustment variables</strong></td>
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<tr>
<td>General (self-efficacy [SES]†41)</td>
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<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 (3.217)</td>
<td>20.23 (2.556)</td>
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<tr>
<td>T1 (adjusted)</td>
<td>21.130 (2.920)</td>
<td>20.133 (2.971)</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>
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<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>
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<tr>
<td>T1 (unadjusted)</td>
<td>3.28 (0.495)</td>
<td>3.08 (0.540)</td>
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<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>
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<tr>
<td>General (personal control [Mastery]†)</td>
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<tr>
<td>T0</td>
<td>23.93 (4.604)</td>
<td>23.64 (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>
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</tr>
<tr>
<td>T1 (adjusted)</td>
<td>24.695 (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>
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<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 + BREATH 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 BREATH and Other Resources
Use of the BREATH 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 (\(r = −0.007; P = .96\)), total duration (\(r = 0.000; P = 1.00\)), or activity (\(r = −1.072; P = .55\)).

At T1, similar proportions of women in CAU + BREATH 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 + BREATH 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).

At the start of the re-entry phase, 4-month access to BREATH 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 + BREATH 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 BREATH on fear of cancer recurrence was sustained during follow-up. Access to BREATH did not influence empowerment or clinical distress improvement in high-distress BCs. Low-distress BCs showed a greater clinical improvement and less deterioration with CAU + BREATH 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 models of survivorship care stress patient empowerment,57,58 ment is a new research area and poses multiple challenges. Although secondary positive adjustment variables. The study of positive adjust-
ment 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 representa-
tive, 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

Results should be considered with caution for several reasons. Consistent with the scarce literature on Web-based interventions for cancer patients,60 BREATH did not have a sustained effect on distress. This may be because access to the Web site was for 4 months only. Although the limited access enabled accurate postin-
tervention assessments, in retrospect it might have been better to allow participants to retain access, especially because information often remains available with other psychoeducational interven-
tions 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.

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because the patients in our sample were expected to improve on distress over the study period.8,9 The multicenter recruitment strategy guaranteed referrals from both secondary and tertiary care centers. The recruitment procedure, which ensured minimal in-
volvement of the research team, and lack of assistance regarding intervention use and adherence support the ecological validity of BREATH. In the absence of RCTs evaluating similar unguided Web-based interventions for BCSs, the effect size of BREATH is consistent with that of two recent meta-analyses of guided face-to-
face (effect size range 0.26 to 0.38)54 and Web-based (effect size range, 0.17 to 0.21)55 interventions for people with cancer54 and chronic somatic conditions.55

The secondary outcomes revealed that CAU + BREATH de-
creased general and cancer-specific distress, fatigue, and fear of cancer recurrence, which may reflect the multicomponent nature of distress in cancer patients.56 The clinical relevance of these outcomes needs to be addressed in future research.

CAU + BREATH did not significantly change empowerment relative to the effect of CAU alone and had inconsistent effects on the secondary positive adjustment variables. The study of positive adjust-
ment is a new research area and poses multiple challenges. Although new models of survivorship care stress patient empowerment,57,58 there is no consensus about the empowerment construct. Conse-
quently, positive adjustment questionnaires, such as the CEQ, are new, but not extensively validated in BCSs and lack information on sensitivity to change. Furthermore, in psycho-oncology, resource-
oriented therapeutic models59 are lacking, and interventions are tradi-
tionally aimed at diminishing deficits instead of enhancing strengths. It is possible that BREATH does not include a sufficient number of empowerment modules (only 4 of the 16 weekly modules targeted empowerment).
functioning during the first year after treatment. As in other studies of patients with breast 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 BCSS in the years 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 BCSSs 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**

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.