Original Article

Headache Outcomes of a Sleep Behavioral Intervention in Breast Cancer Survivors: Secondary Analysis of a Randomized Clinical Trial

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BACKGROUND: Breast cancer survivors often have persisting headache. In a secondary analysis of the Brief Behavioral Therapy for Cancer-Related Insomnia (BBT-CI) clinical trial (ClinicalTrials.gov identifier NCT02165839), the authors examined the effects of BBT-CI on headache outcomes in patients with breast cancer. **METHODS:** Patients with breast cancer who were receiving chemotherapy were randomly assigned to receive either the BBT-CI intervention or the Healthy EAting Education Learning for healthy sleep (HEAL) control intervention, and both were delivered over 6 weeks by trained staff. Headache outcomes and heart rate variability (HRV) were measured at baseline, 6 weeks, 6 months, and 12 months. Mixed-effects models were used to examine longitudinal headache outcomes in the groups according to the intention to treat. Principal component analysis and agglomerative hierarchical clustering were conducted to reduce 16 variables for data-driven phenotyping. **RESULTS:** Patients in the BBT-CI arm (n = 73) exhibited a significant reduction in headache burden over time (P = .02; effect size [Cohen d] = 0.43), whereas the reduction was not significant among those in the HEAL arm (n = 66). The first principal component was positively loaded by headache, sleep, fatigue, and nausea/vomiting and was negatively loaded by cognitive, physical, and emotional functioning. Agglomerative hierarchical clustering revealed 3 natural clusters. Cluster I (n = 58) featured the highest burden of headache, insomnia, and nausea/vomiting; cluster II (n = 50) featured the lowest HRV despite a low burden of headache and insomnia; and cluster III (n = 31) showed an inverse relation between HRV and headache-insomnia, signifying autonomic dysfunction. **CONCLUSIONS:** BBT-CI is efficacious in reducing headache burden in breast cancer survivors. Patient phenotyping demonstrates a headache type featuring sleep disturbance, nausea/vomiting, and low physical functioning—revealing similarities to migraine. ***Cancer* 2021;127:4492-4503**. © *2021 American Cancer Society*.

LAY SUMMARY:

- Breast cancer survivors often have persisting headache symptoms.
- In patients with cancer, treatment of chronic headache disorders using daily medications may be challenging because of drug interactions with chemotherapy and other cancer therapies as well as patients' reluctance to add more drugs to their medicine list.
- Headache and sleep disorders are closely related to each other.
- This study demonstrates that a sleep behavioral therapy reduced headache burden in breast cancer survivors.
- In addition, the majority of headache sufferers had a headache type with similarities to migraine—featuring sleep disturbance, nausea/vomiting, and low physical functioning.

KEYWORDS: behavior therapy, breast neoplasms, clinical trial, headache, sleep initiation and maintenance disorders.

INTRODUCTION

Although cancer survival rates continue to improve, one-half of survivors are afflicted by chronic conditions, including insomnia.[1] Headache and insomnia are common, bidirectional, disabling comorbidities in which 1 is a risk factor for the other.[2,3] Insomnia and headache disorders (eg, migraine) share neuroanatomic networks (eg, brainstem-cortical),[4] neurophysiologic mechanisms (eg, reduced slow-wave sleep),[4,5] neurochemical signaling (eg, aberrant serotonergic, adenosine, and melatonin),[6-11] autonomic dysfunction,[12,13] and allodynia.[14-16] These shared pathways and comorbidities have led researchers to speculate on the presence of a headache-insomnia endophenotype.[4,17,18] Although many cancer survivors complain of headache-related disability, there is a scarcity of headache research in cancer survivors without intracranial tumors. To our knowledge, no study to date has examined the prevalence of new-onset chronic headache or exacerbation of preexisting primary headache disorders (eg, migraine) in cancer survivors.

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The diagnosis of insomnia and headache disorders relies on patient-reported symptoms and headache or sleep diaries.[19,20] The validity of these patient-reported symptoms can be influenced by recall and response biases.[21,22] Actigraphy-based measurements (eg, heart rate variability [HRV] measures)[23-25] complement the data quality of self-reported symptoms.[22] Autonomic dysfunction, depicted by low levels of HRV, is a common accompaniment of headache[23,26] and insomnia.[24]

In patients with cancer, treatment of chronic headache disorders using daily medications may be challenging because of drug-drug interactions with chemotherapy and other cancer therapies as well as patients' reluctance to add more drugs to their regimen. An effective, nonpharmacologic intervention is an unmet medical need. It is useful to explore the efficacy of brief sessions of behavioral therapy that can be administered by clinic staff while patients are receiving chemotherapy. No study to date has focused on headache management in cancer survivors. Does controlling cancer-related insomnia reduce headache burden? Is there heterogeneity in the clinical presentations of headache among cancer survivors? Hence examining the efficacy of behavioral interventions that target cancer-related insomnia may help for headache relief, which, in turn, may reduce insomnia symptoms and improve overall quality of life (QoL). Furthermore, it is important to explore natural subtypes of headache in cancer survivors for improved understanding and development of personalized management therapies.

In this study, we examined the headache-reducing effect of a sleep behavioral intervention developed to manage insomnia in cancer survivors (brief behavioral therapy for cancer-related insomnia [BBT-CI]). Moreover, we explored for patient phenotypes using self-reported outcomes and HRV measures.

MATERIALS AND METHODS

Study Design

The participants were randomized to receive either BBT-CI[24] or Healthy EAting Education Learning for healthy sleep[24] (HEAL) (control intervention) following a Consolidated Standards of Reporting Trials[27] flow diagram. This is a secondary analysis of the study Brief Behavioral Intervention for Insomnia During Chemotherapy trial (ClinicalTrials.gov identifier NCT02165839). We applied definitions of *cancer survivor* used by the American Cancer Society[28] and the National Coalition for Cancer Survivorship.[29] According to the American Cancer Society, a cancer survivor is any person who has been diagnosed with cancer, from the time of diagnosis through the balance of life.[28] Similarly, according to the National Coalition for Cancer Survivorship, a cancer survivor is any person living with, through, and beyond a cancer diagnosis.[29] Both of these definitions are accepted by the National Cancer Institute (NCI) Office of Cancer Survivorship[30] and the NCI Dictionary of Cancer Terms.[31]

Patient Recruitment, Inclusion and Exclusion Criteria, and Randomization

Sites of recruitment were the Stanford Women's Cancer Center and the Stanford Cancer Center Infusion Treatment Area. Inclusion criteria were: 1) female patients with a breast cancer diagnosis (stages I-III), 2) aged ≥21 years, 3) patients who received ≥6 weeks of chemotherapy, 4) patients with scores ≥8 on the Insomnia Severity Index (ISI)[32], and 5) patients able to speak and read English. Exclusion criteria were: 1) the presence of a medical or psychiatric condition and 2) the presence of substance abuse. Eligible participants were randomized to either receive BBT-CI or HEAL. A randomization sequence was programmed in SAS software (SAS Institute Inc) using a random-number generator with an arbitrary seed number. To maintain blinding, we used sealed security envelopes, each with the randomization arm listed on a printed label within the envelope. To maintain randomization order, a sequence number was printed both on the outside of the envelope and on the label inside the envelope. These envelopes were stored in a locked file cabinet in the project coordinator's office. Therefore, only the database manager held the randomization blind until all envelopes were opened. Envelopes were only distributed when study participants were enrolled and arrived for an on-campus baseline appointment. At each baseline appointment, the project staff (intervener) was given the next randomization envelope in sequence, and the envelope was opened in the presence of the study participant, who was immediately informed of their group assignment. The project director was also immediately notified and maintained a spreadsheet of the randomization sequence to be shared with the database manager to review randomization integrity. The rest of the team, including the assessment team, principal investigator, co-principal investigator, and biostatistician, were blinded to the study assignment. Participants were asked to keep their study assignment condition confidential.

Study Intervention and Follow-Up

The study interventions are described elsewhere in detail.[24,33,34] Briefly, BBT-CI consisted of 6 sessions: 2

face-to-face sessions and four 15-minute phone calls, including the following components: 1) chronorehabilitation education and techniques (eg, the connection between sleep, circadian disruption, and cancer), 2) light and stimulus control (increase light exposure during the day, minimize light exposure at night; education about melatonin as a circadian hormone; and associate the bed with sleep and sex only), 3) encouragement of sleep activity and protocol for napping, and 4) sleep compression (go to bed later by 15 minutes if sleep quality is low). The HEAL arm was matched to the BBT-CI arm with regard to time and attention and consisted of 2 face-to-face sessions and 4 phone calls. The content of HEAL was informed by the NCI publication PDQ Nutrition in Cancer Care[35] as well as the books *The Cancer Fighting Kitchen: Nourishing, Big-Flavor Recipes for Cancer Treatment and Recovery*[36] and *Healthy Eating During Chemotherapy*,[37] which have been adapted for the study and include information on symptom management of nausea, constipation, and dehydration and education about nutrition for good sleep.

Baseline and Outcome Measures

All participants completed the European Organization for Research and Treatment of Cancer (EORTC) QoL core questionnaire (EORTC QLQ-C30, version 3.0[38]) as well as the breast cancer supplementary module (QLQ-BR23).[39] The QLQ-C30 is a validated, 30-item questionnaire that contains 9 symptom scales (fatigue, pain, nausea and vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), 5 functioning domains (physical, role, emotional, cognitive, and social functioning), and 1 global health status scale (QoL).[38] The QLQ-BR23 is a validated, 23-item questionnaire specific to breast cancer survivors that incorporates 4 symptom scales (systemic therapy side effects, breast symptoms, arm symptoms, and upset by hair loss) and 4 functional scales (body image, sexual functioning, sexual enjoyment, and future perspective).[39] For this secondary analysis, we selected the following headache-related outcome measures: symptom scales (burden of headache, pain, and nausea and vomiting), functional scales (emotional functioning, cognitive functioning, and physical functioning), and global health status (QoL). Except for physical functioning, all outcome measures were reported for the past week. Scores were rescaled from 0 to 100 according to *The EORTC QLQ-C30 Scoring Manual* recommendations.[40] For headache, pain, and nausea and vomiting, lower scores indicate better outcomes, whereas higher scores indicate poor outcomes. For the functional scales and global health status outcomes, lower scores indicate poor outcomes, whereas higher scores indicate better outcomes. EORTC outcome measures were compared with references extracted from EORTC QLQ-C30 breast cancer population reference values.[38,40] Headache burden was measured using the question, "During the past week, have you had headaches?" The answers were rated from 1 to 3 as follows: 1 (not at all), 2 (a little), 3 (quite a bit), or 4 (very much). History of migraine diagnosis was extracted by chart review from the electronic health records of participating patients. Other self-reported outcomes used for this secondary analysis included the ISI to measure insomnia levels,[32] the Pittsburgh Sleep Quality Index (PSQI) to measure sleep quality,[41] and the Brief Fatigue Inventory (BFI) to assess fatigue.[42,43]

The ISI is a brief, self-administered screening tool that has been validated for the measurement of insomnia severity and consists of a 7-item questionnaire.[32] Respondents rate the severity of each item in the past 2 weeks on a 5-point Likert scale.[32] The ISI questions involve the severity of insomnia symptoms (falling asleep, staying asleep, and waking up too early), the satisfaction rate with sleep patterns, the extent of insomnia interference with daily functioning, the degree to which the patient finds their insomnia noticeable to others in terms of impairment to their QoL, and the level of distress created by the sleep problem.[32] The global ISI score is obtained by adding scores from all 7 items and ranges from 0 to 28, with lower scores considered good outcomes and increasingly higher scores indicating higher insomnia levels. ISI scores are clinically interpreted as follows: scores from 0 to 7 indicate no clinically significant insomnia; from 8 to 14, subthreshold insomnia; from 15 to 21, clinical insomnia (moderate severity); and from 22 to 28, clinical insomnia (severe).[32]

The PSQI is a validated, self-administered questionnaire that evaluates sleep quality in the past 1 month.[41] It takes 5 to 10 minutes to complete and involves 19 items grouped into 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction.[41] The global PSQI score is derived by summing the 7 component scores and ranges from 0 to 21.[41] A global PSQI cutoff score >5 indicates poor sleep quality.[41]

The BFI is a self-administered, rapid-assessment tool that has been validated for evaluating fatigue levels in cancer survivors and interference with daily life functioning in the past 24 hours.[42,43] It takes 5 minutes to complete and contains 9 items measured on an 11-point Likert

scale.[42,43] The global fatigue score is derived by averaging all 9 items and ranges from 0 to 10,[42,43] with increasing scores indicating higher fatigue levels. Suggested BFI cut-off points for fatigue levels are from 1 to 3 (mild), from 4 to 7 (moderate), and from 8 to 10 (severe).[42,43]

HRV was measured using the Firstbeat device, an ambulatory heart rate (HR) monitor that measures 2 time domains (standard deviation of normal-to-normal R-R intervals [SDNN] and root mean square of the successive differences [RMSSD]), 3 frequency domains (high frequency [HF], low frequency [LF], and LF-to-HF ratio [LF/HF] ratio), and HR. The Firstbeat device is a validated tool for HRV detection and has been shown to provide RR intervals that are as accurate as those obtained with an electrocardiogram.[44,45] The cyclic aspects that generate HRV are depicted by SDNN values,[46,47] whereas the vagal tone is reflected by RMSSD[48] and HF[49] values. Unlike the HF value, the RMSSD is not affected by respiratory changes.[50] The LF value represents a mixture of sympathetic and parasympathetic activity,[46,51] whereas the LF/HF ratio is considered to be an indicator of sympathovagal balance.[47] Twenty minutes of HRV data were recorded, which was more than the required 5 minutes to measure SDNN, RMSSD, HF, LF, and the LF/HF ratio.[44,52] HRV outcomes were compared with reference values from breast cancer survivors.[53] All of the above-mentioned outcomes were repeatedly measured at baseline, 6 weeks, 6 months, and 12 months.

Ethical Clearance

All procedures performed involving human participants were in accordance with the ethical standards of our University Office for Human Subject Protection and the Declaration of Helsinki (World Medical Association, 1964) and its later amendments. All participating patients signed a written informed consent form before study participation.

Statistical Analysis

Descriptive statistics were used for baseline self-report outcomes (median and interquartile range [IQR]) and HRV data (mean and standard deviation [SD]). Linear mixed-effects models for repeated measures were used for the intention-to-treat (ITT) comparison between the BBT-CI and HEAL conditions in terms of the change in headache from baseline to the end of study. The fixed-effects model included time and treatment arm as independent variables. For random effects, we allowed for random intercepts and slopes as well as their correlation. Our primary goal was to examine whether there was a significant reduction in headache burden over time in the 2 treatment arms. In addition, we conducted piecewise growth modeling to assess the immediate and long-term effects of treatment by comparing segment 1 (from baseline to end of treatment [EOT] at week 6) to segment 2 (from EOT to 1-year follow-up). Missing data because of patient attrition or dropout were handled assuming a missing at random (MAR)[54] condition on observed information. The Little test[54] was used to estimate whether missing data followed the MAR assumption. Effect sizes were calculated using the Cohen d method.[55] Effect sizes were interpreted as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$) based on Cohen's recommendations.[55]

Principal component analysis (PCA) and agglomerative hierarchical clustering (AHC) were conducted to examine patient phenotypes by reducing 16 variables (age, headache score, pain, nausea and vomiting, emotional functioning, cognitive functioning, physical functioning, global health status, ISI, PSQI, BFI, and HRV outcomes [SDNN, RMSSD, HR, HF, and LF/HF ratio]). Considering the different measurement scales, all data were standardized by subtracting the mean for each observed value and dividing by the standard deviation. For PCA, the Kaiser-Meyer-Olkin[56,57] measure was used to assess sampling adequacy. The Bartlett sphericity test[58] was used to determine the suitability of the data set for PCA and to rule out an identity matrix. A PCA plot of the first 2 PCs was used to examine the variables driving the largest variabilities and to describe the relations among the variable loadings. Furthermore, AHC was used to demonstrate the accuracy of our PCA findings and to identify natural clusters. AHC was performed using the Ward agglomeration method with squared Euclidean distance metric and a dendrogram to observe the clustering process. The significance level was set at $P < .05$. Statistical analyses were conducted using the Statistical Package for Social Sciences (version 27.0; SPSS Inc). MetaboAnalyst version 4.0 (https://www.metaboanalyst.ca) was used for AHC and to create the heatmap.

RESULTS

Baseline Characteristics

In total, 139 patients participated in the study; of these, 73 were randomized to the BBT-CI intervention, and 66 were randomized to the HEAL control intervention. Of those randomized, 65 (89%) and 61 (92%) patients completed the study up to the last time point of 1-year follow-up in the BBT-CI and HEAL arms, respectively (Fig. 1). The patients were middle-aged, with a median age of 52

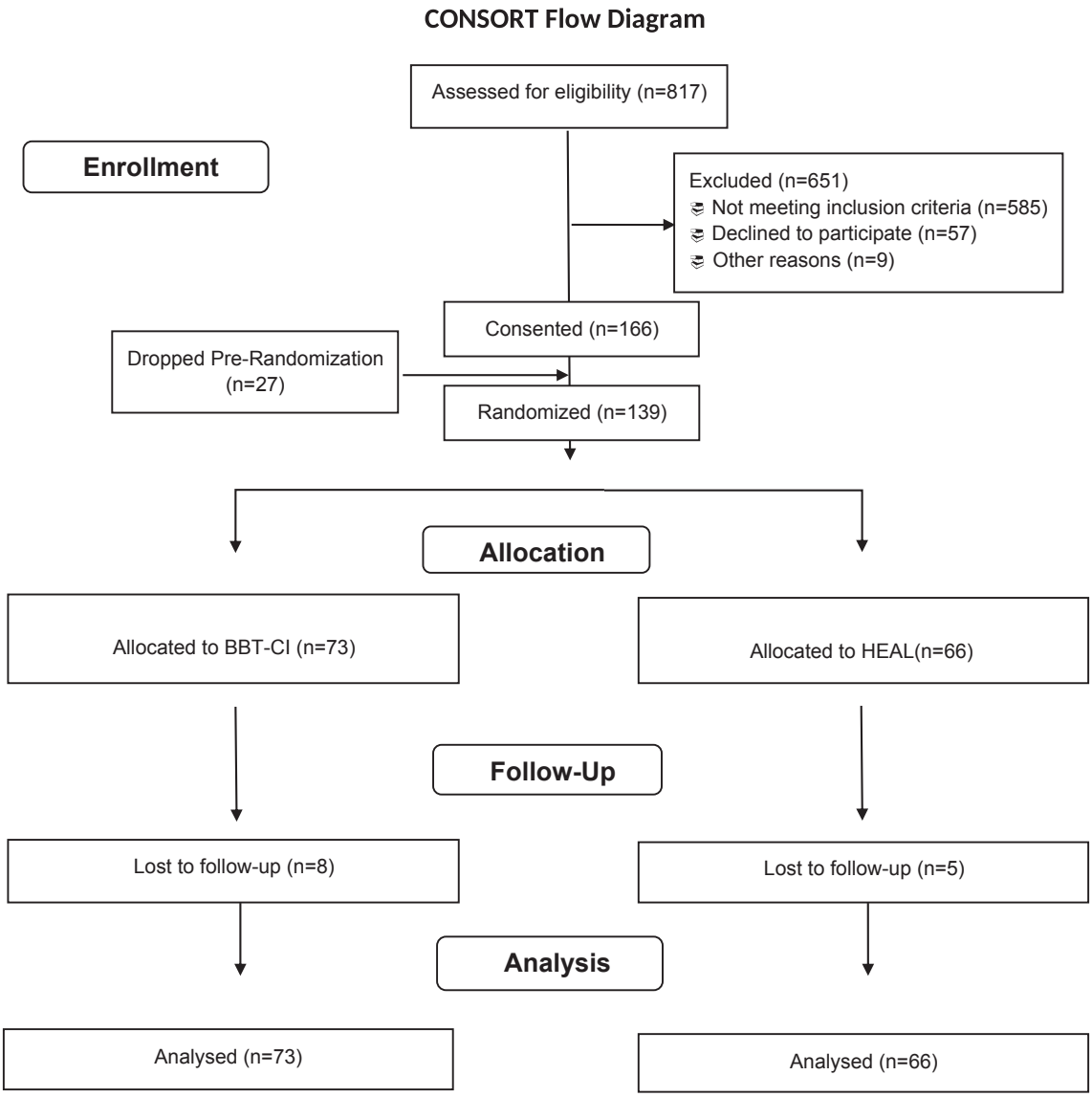

Figure 1. This is a CONSORT (Consolidated Standards of Reporting Trials) flow diagram of the clinical trial. BBT-CI indicates Brief Behavioral Therapy for Cancer-Related Insomnia; HEAL, Healthy EAting Education Learning.

years (IQR, 42-58 years) in the BBT-CI arm and 49 years (IQR, 44-56 years) in the HEAL control arm. The majority of patients had stage II cancer, ie, 51% in the BBT-CI arm and 44% in the HEAL control arm. Both groups exhibited a median headache score of 2 on a scale from 1 to 4. The median scores for body pain, nausea and vomiting, and physical functioning in all participating patients were similar to those in the EORTC breast cancer population reference data.[38,40] Both groups demonstrated lower median levels of global health status, emotional functioning, and cognitive functioning compared with median levels from the EORTC breast cancer population reference data.[38,40] ISI scores indicated clinical levels of insomnia with moderate severity in both groups, ie, ISI scores of 15 (IQR, 12-18) in the BBT-CI arm and 14 (IQR, 11-17) in the HEAL control arm. Both groups featured a median PSQI score of 9, which reflected poor sleep quality, and a median BFI score of 4, which suggested moderate fatigue. HRV measures were suboptimum compared with those from another breast cancer population.[53] There was no statistically significant difference in any baseline characteristic between the randomized groups

(Table 1).[32,38,39,40,41,42,43,53] Of the total 139 participating patients, 12 (9%) had a migraine diagnosis on chart review, of whom 7 were randomized to the BBT-CI arm and 5 were randomized to the HEAL control arm.

Treatment Efficacy Results

In ITT analysis, there was a significant reduction in headache burden over time for patients in the BBT-CI arm ($P = .02$; medium effect size [Cohen d], 0.43), whereas headache reduction in the HEAL arm was not statistically significant. BBT-CI reduced the mean headache burden from 2.04 at baseline to 1.74 at 12 months compared with a reduction from 1.78 to 1.73 for HEAL (Fig. 2, observed values). Although there was no statistically significant difference in the piecewise growth modeling results, the data observably showed that both arms demonstrated an immediate impact at week 6 (EOT). However, the effect of BBT-CI was sustained in the absence of further treatment, whereas headache burden increased in the HEAL arm from EOT to 1-year follow-up. Among the 12 patients who had migraine, the mean headache reduction was not significant in either group, with a reduction from 3.29 at baseline to 2.67 at 1 year in the BBT-CI arm and a reduction from 2.60 at baseline to 2.25 at 1 year in the HEAL control arm. Both groups demonstrated a significant reduction in insomnia, with the ISI score reduced from 15 at baseline to 9 at 1 year in the BBT-CI arm ($P = .006$) versus a reduction from 14 at baseline to 10 at 1 year in the HEAL control arm ($P = .02$). One-year complete data were available for 94% of baseline participants in the HEAL arm and for 82% of baseline participants in the BBT-CI arm. Overall, 12% of patients had missing data. The Little MAR test ascertained the MAR assumption ($P = .10$).

PCA Results

In PCA, the Kaiser-Meyer-Olkin measure (0.60) showed sampling adequacy. The Bartlett sphericity test proved the appropriateness of the data set for PCA ($P < .0001$). The first 2 PCs (PC1 and PC2) explained 40% of the data set's variability at baseline. PC1 explained 21% of the variability positively loaded by headache, insomnia, fatigue, poor sleep, pain, and nausea and vomiting and negatively loaded by cognitive, physical, and emotional functioning and better global health. PC2 explained 18% of the variability positively loaded by RMSSD, HF, and SDNN and negatively loaded by HR, the LF/HF ratio, and age (Fig. 3).

AHC Results

The AHC heatmap revealed 3 major clusters of patients, as indicated by the first branching of the dendrogram

TABLE 1. Baseline Characteristics of Participating Patients[a]

Variable	BBT-CI, n = 73	HEAL, n = 66
Age: Median [IQR], y	52 [42-58]	49 [44-56]
Race: No. (%)		
White	47 (64.4)	40 (60.6)
Black/African American	4 (5.5)	2 (3.0)
Native Hawaiian/Pacific Islander	1 (1.4)	1 (1.5)
Asian/Asian American	15 (20.5)	17 (25.8)
Other	6 (8.2)	6 (9.1)
Stages of cancer at recruitment: No. (%)		
I	20 (27.4)	19 (28.8)
II	37 (50.7)	29 (43.9)
III	16 (21.9)	18 (27.3)
Headache score, 1-4 scale: Median [IQR]	2 [1-3]	2 [1-2]
EORTC scores, 1-100 scale: Median [IQR]		
Pain: Reference, 17 [0-50]	17 [0-50]	17 [0-50]
Nausea and vomiting: Reference, 0 [0-0]	0 [0-17]	0 [0-17]
Mean ± SD: Reference, 7.7 ± 17.3	12 ± 17	13 ± 22
Emotional functioning: Reference, 75 [50-83]	67 [42-75]	71 [58-75]
Cognitive functioning: Reference, 83 [67-100]	67 [50-83]	67 [50-83]
Cognitive functioning: Reference, 87 [67-93]	93 [73-100]	87 [80-100]
Global health status: Reference, 67 [50-83]	58 [42-67]	58 [44-67]
Other scores: Median [IQR]		
ISI, 0-28 scale	15 [12-18]	14 [11-17]
PSQI, 0-21 scale	9 [7-12]	9 [6-12]
BFI, 0-10 scale	4 [2-6]	4 [3-6]
HRV measures: Median [IQR]		
SDNN, msec	23 [17-28]	20 [13-25]
Mean ± SD: Reference, 39 ± 16	23 ± 9	20 ± 8
RMSSD, msec	17 [12-21]	16 [9-19]
Mean ± SD: Reference, 29 ± 24	17 ± 6	15 ± 7
HR, beats per min	82 ± 15	82 ± 12
Mean ± SD: Reference, 79 ± 11		
HF, msec^2	115 [58-173]	95 [32-163]
Mean ± SD; Reference, 136 ± 63	127 ± 89	119 ±114
LF/HF ratio,	3 [2-5]	2 [1-4]
Mean ± SD; Reference, 1.4 ± 0.82	3.6 ± 3.6	3.1 ± 2.5

Abbreviations: BBT-CI, Brief Behavioral Therapy for Cancer-Related Insomnia; BFI, Brief Fatigue Inventory[42,43]; EORTC, European Organization for Research and Treatment of Cancer; HEAL, Healthy EAting Education Learning; HF, high-frequency power; HR, heart rate; HRV, heart rate variability; IQR, interquartile range; ISI, Insomnia Severity Index[32]; LF/HF ratio, low frequency to high frequency ratio; msec, milliseconds; PSQI, Pittsburgh Sleep Quality Index[41]; QLQ, quality-of-life questionnaire; RMSSD, root mean square of the successive differences; SD, standard deviation; SDNN, standard deviation of normal-to-normal R-R intervals.

[a]The EORTC Quality-of-Life Core questionnaire (EORTC QLQ-C30, version 3.0[38]) and the breast cancer supplementary module (QLQ-BR23)[39] were used to measure the burden of headache, pain, nausea and vomiting, emotional function, cognitive function, physical function, global health status. Headache burden was measured using the question, "During the past week, have you had headaches?" (not at all = 1, a little = 2, quite a bit = 3, very much = 4). EORTC outcome measures were compared with references extracted from EORTC QLQ-C30 breast cancer population reference values.[38,40] HRV outcomes were compared with reference values from breast cancer survivors.[53] The global ISI score is interpreted as follows: scores from 0 to 7 = no clinically significant insomnia, scores from 8 to 14 = subthreshold insomnia, scores from 15 to 21 = clinical insomnia (moderate severity), and scores from 22 to 28 = clinical insomnia (severe),[32] A total PSQI cutoff score >5 indicates poor sleep quality.[41] Suggested BFI cutoff points for fatigue level are: from 1 to 3 = mild, from 4 to 7 = moderate, and from 8 to 10 = severe.[42,43] There were no statistically significant group differences in any variables (Mann-Whitney *U* test for inter-median comparisons, Student *t* test for inter-mean comparisons, and χ^2 test for ratios, $P > .05$).

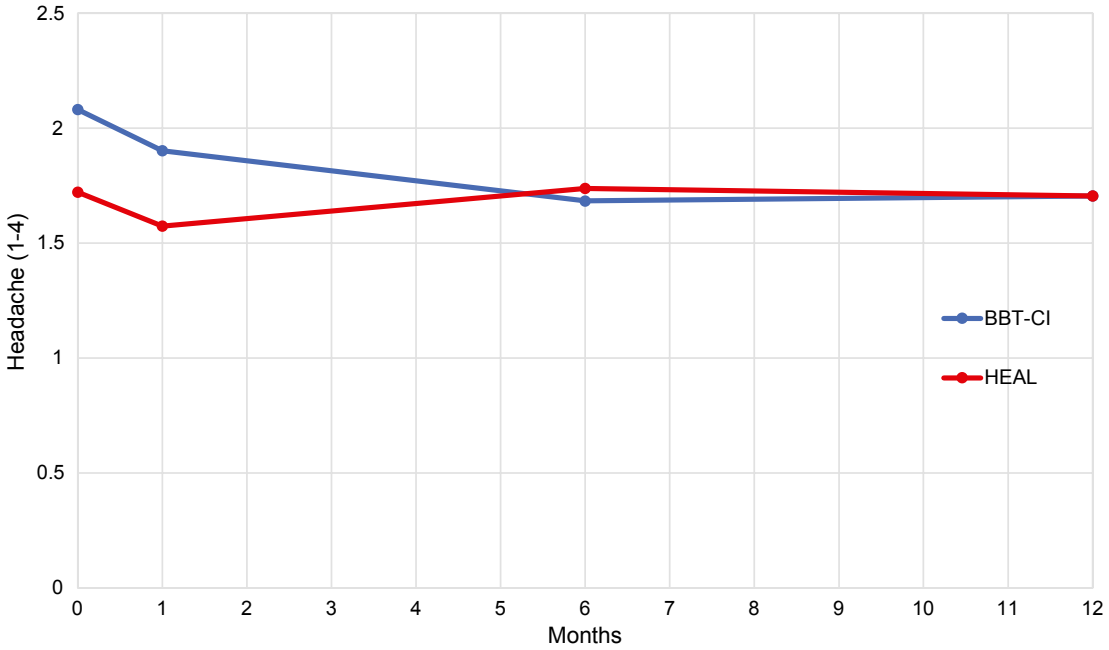

Figure 2. Observed changes in mean headache scores are illustrated as measured at baseline and 1.5 months, 6 months, and 12 months postintervention for the 2 treatment arms: Brief Behavioral Therapy for Cancer-Related Insomnia (BBT-CI) (blue line) and Healthy EAting Education Learning (HEAL) (red line).

above the heatmap in Figure 4.[32,41,42,43] Cluster I (n = 58) (Fig. 4, right in dendrogram) featured the highest levels of headache, insomnia, fatigue, poor sleep, pain, and nausea and vomiting and decreased levels of cognitive, physical, and emotional functioning and global health. Cluster II (n = 50) (Fig. 4, middle in dendrogram) exhibited features contrary to those in cluster I, with decreased levels of headache; comorbidities such as insomnia, fatigue, poor sleep, pain, nausea and vomiting, and HRV; and increased levels of cognitive, physical, and emotional functioning and better global health. Cluster III (n = 31) (Fig. 4, left in dendrogram) showed the highest HRV values as well as increased cognitive, physical, and emotional functioning and better global health while featuring low levels of headache and comorbidities such as insomnia, fatigue, poor sleep, pain, and nausea and vomiting (Fig. 4).

DISCUSSION

This study showed the efficacy of a sleep behavioral intervention to reduce headache burden in breast cancer survivors. Headache burden reduction was accompanied by insomnia improvement. The 1-year follow-up demonstrated the lasting effect of the 6-week BBT-CI intervention. The results provide evidence that a brief behavioral therapy delivered in 2 face-to-face sessions and 4 phone calls (compared with 8-12 cognitive behavioral therapy sessions), administrable by clinic staff (eg, nurses) while patients are receiving chemotherapy, can be used to reduce headache burden. An additional advantage of the BBT-CI is its focus on stimulus control without engaging sleep restriction.[24] In patients with cancer, stimulus control is a more favorable and safer therapy than sleep restriction.[24] The active components of the BBT-CI intervention (ie, stimulus control,[59] physical activity,[60] and circadian entrainment[61,62]) are also known to be important methods in headache management. Hence, BBT-CI can be a potent therapy for headache management in cancer survivors.

Our patient phenotyping analysis demonstrated a headache type featuring sleep disturbance, nausea and vomiting, and intolerance to physical functioning—revealing similarities to migraine.[19] Chemotherapy-associated side effects and migraine share symptoms such as nausea and vomiting[19,63] and photophobia,[19,64] leading us to speculate that there may be common mechanisms. However, it is not clear whether chemotherapy-associated headache attacks can occur long after chemotherapy. Does chemotherapy trigger a migraine or a migraine-like headache? What are the susceptibility patterns, and how can such disabling chronic headache attacks be prevented? On the basis of our findings, we speculate a potential role

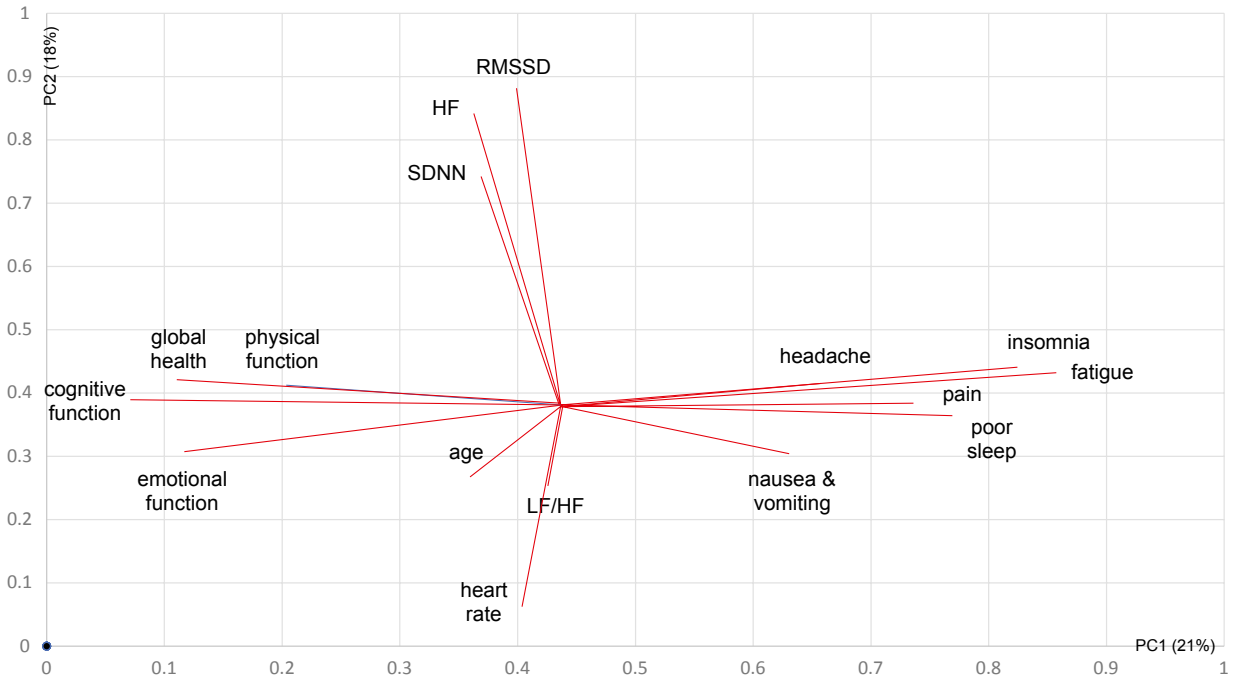

Figure 3. This is a principal component analysis plot. Principal component 1 (PC1) (21% of variability explained) showed a major pattern of variables positively loaded by headache and comorbidities such as insomnia, fatigue, poor sleep, pain, nausea/vomiting and negatively loaded by cognitive, physical, and emotional functioning and better global health. PC2 (18% of variability explained) was positively loaded by the root mean square of the successive differences (RMSSD), high-frequency power (HF), the standard deviation of normal-to-normal R-R intervals (SDNN) and negatively loaded by heart rate (HR), the low frequency (LF)/HF ratio, and age. Measurements were done using the following: insomnia was measured using the Insomnia Severity Index (ISI), poor sleep was measured using the Pittsburgh Sleep Quality Index (PSQI), and fatigue was measured using the Brief Fatigue Inventory (BFI). Headache, physical function, cognitive function, global health status, and emotional function were derived from the European Organization for Research and Treatment of Cancer questionnaire.

for the autonomic nervous system in the pathophysiology of this type of headache attack. The autonomic nervous system can be optimized by regular sleep,[65] regular exercise,[66] regular hydration,[67] and healthy nutrition.[68] Hence, we suggest that maintenance of these regular, healthy behaviors in the prechemotherapy/radiotherapy and postchemotherapy/radiotherapy periods may help prevent the development of chronic headache disorders in cancer survivors.

The study participants were representative of breast cancer survivors with moderate symptom burden and low QoL comparable to the EORTC reference population.[38,40] Most patients (62%) were burdened by headache—9% of whom received migraine diagnosis on chart review. The 1-year prevalence of active headache disorder is 50% in the general population[69] and 10% for those with migraine.[70] Because this study assessed headache burden in the past week, the 1-year headache prevalence is expected to be >62%. These results provoke a line of questions: Do cancer survivors get a new-onset headache de novo, a migraine variant or its exacerbation, or a secondary headache purely from treatment-associated side effects?

We found apparent heterogeneity in terms of patient characteristics at baseline that was evenly distributed between the 2 treatment arms during randomization. Participants' mean HRV measures were lower than those in the reference breast cancer population,[53] indicating autonomic dysregulation. In cluster III, the inverse relation between HRV and headache-insomnia burden, as well as the positive correlation between HRV and QoL measures, is indicative of the involvement of autonomic dysfunction in this subgroup of patients. Cluster II patients featured the lowest HRV measure despite having low burden of headache and insomnia—signifying the presence of another factor suppressing HRV outcomes. HRV measures such as vagal nerve activity (RMSSD, HF) are lower in patients who have primary headache disorders (eg, migraine, tension-type headache) compared with healthy controls.[23,26,71] Our results suggest that HRV may serve as

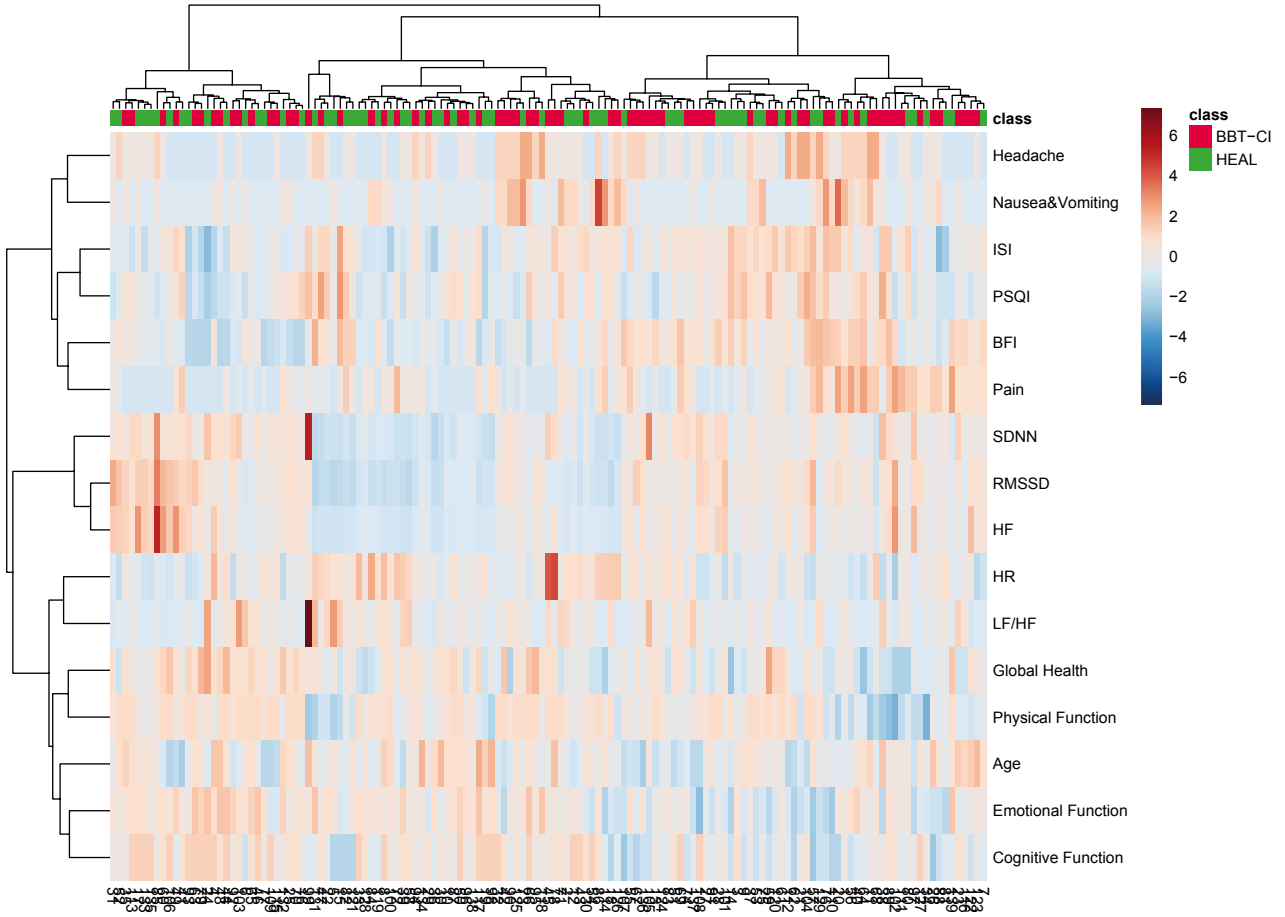

Figure 4. This heatmap illustrates the results from agglomerative hierarchical clustering analysis with dendrogram. Three major natural clusters of patients were identified, as depicted by the first branching of the dendrogram above the heatmap. Cluster I (n = 58 patients; right in dendrogram) demonstrated the highest levels of headache and comorbidities such as insomnia and fatigue. Cluster II (n = 50; middle in dendrogram) featured the lowest heart rate variability (HRV) outcomes (standard deviation of normal-to-normal R-R intervals [SDNN], root mean square of the successive differences [RMSSD], and high-frequency power [HF]). Cluster III (n = 31; left in dendrogram) showed the highest physical, emotional, and cognitive function as well as the highest level of global health status and HRV. There were comparable numbers of patients randomized to Brief Behavioral Therapy for Cancer-Related Insomnia (BBT-CI) (green bars) and Healthy EAting Education Learning (HEAL) (red bars). ISI indicates Insomnia Severity Index[32]; PSQI, Pittsburgh Sleep Quality Index[41]; BFI, Brief Fatigue Inventory[42,43]; HR, heart rate; LF/HF ratio, low frequency to high frequency ratio.

an endogenous biomarker to identify headache-insomnia patients who have autonomic dysregulation. HRV data can be used as an enrichment strategy for the study population in biomarker-driven clinical trials for a precision medicine approach.

The strengths of this randomized clinical trial involve adequate study duration lasting 1 year, the use of multiple self-report outcomes and actigraphy, standardized treatment protocol, ITT analysis, and attention placebo control (HEAL) to match for attention and time in the BBT-CI intervention. Furthermore, data-driven identification of patient phenotypes is consistent with emerging precision medicine. By virtue of using a single behavioral therapy targeting 2 conditions simultaneously (headache and insomnia), this study was innovative.

The limitations of this study are because of the secondary analysis. The study did not include a headache diary to compute monthly headache frequency. Headache classification was missing at baseline. Monthly migraine frequency outcomes provide a better understanding of episodic-to-chronic migraine conversion or chronic-to-episodic migraine remission.[19] The retrospective chart review of ascertaining migraine diagnosis could have underestimated migraine prevalence in our study population. That being said, our study provides initial findings to inform future behavioral clinical trials to manage

headache in cancer survivors. Another limitation is the single-item headache measure, which does not provide as a broad range of construct as multi-item questionnaires. It is not feasible to classify headache subtypes nor to measure internal consistency using single-item, patient-reported outcome measurements. However, single-item measures may be preferable because of their brevity for reducing participant burden and for cost effectiveness. In this study, our concept of interest was straightforward, ie, to show whether a brief behavioral therapy can reduce headache burden. Single-item instruments have been recommended for use by regulatory bodies in measuring conceptual frameworks that are straightforward, eg, pain intensity.[72] Our primary aim was not to delve into outcomes of all headache-related symptoms. The most common symptom of headache disorders is the headache itself, which can be measured by its severity or frequency.[19] For this reason, we believe the single-item question (which indicates the presence and severity of headache) can address our primary aim. In addition, outcomes from the other instruments used in our study are known headache symptoms, eg, insomnia, fatigue, poor sleep, pain, nausea and vomiting, low HRV, and poor QoL, in addition to effects on physical, cognitive, and emotional functioning. The PCA results we observed between headache burden and these multiple outcomes can indirectly indicate the validity of the single-item headache measurement. Prior studies that only used 1 subscale as the main variable have demonstrated that the psychometric properties, eg, validity, reliability, and responsiveness (anchor-based and distribution-based), are similar to those of multi-item scales.[73-77] By providing an indication of the presence as well as the severity of headache burden, results from the single-item headache question will serve us to design multi-item headache assessments in cancer survivors for an in-depth understanding and for capturing the domains of headache phenotypes.

CONCLUSION

Breast cancer survivors often have persistent headache symptoms. In patients with cancer, treatment of chronic headache disorders using daily medications may be challenging because of drug interactions with chemotherapy and other cancer therapies as well as patients' reluctance to add more drugs to their medicine list. Headache and sleep disorders are closely related to each other. In this study, we demonstrated that a sleep behavioral therapy reduced headache burden in breast cancer survivors. In addition, the majority of headache sufferers had a headache type with similarities to migraine—featuring sleep disturbance, nausea/vomiting, and low physical functioning.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Yohannes W. Woldeamanuel: Study design, data analysis, data interpretation, writing–initial draft, writing–critical revision, and final approval. **Douglas W. Blayney:** Data interpretation and final approval. **Booil Jo:** Data interpretation and final approval. **Sophie E. Fisher:** Data extraction, data interpretation, and final approval. **Catherine Benedict:** Data interpretation and final approval. **Ingrid Oakley-Girvan:** Data interpretation and final approval. **Shelli R. Kesler:** Data interpretation and final approval. **Oxana Palesh:** Study design, data interpretation, and final approval.

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