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Symptom response analysis of a randomized controlled trial of reflexology for symptom Management among Women with Advanced Breast Cancer

Alla Sikorskii, PhD[a,b], **Pratim Guha Niyogi, PhD(c)**[b], **David Victorson, PhD**[c], **Deimante Tamkus, MD**[d], **Gwen Wyatt, RN, PhD, FAAN**[e]

[a]Department of Psychiatry, Michigan State University, East Lansing, USA

[b]Department of Statistics and Probability, Michigan State University, East Lansing USA

[c]Feinberg School of Medicine, Northwestern University, Evanston USA

[d]College of Human Medicine, Michigan State University, East Lansing, USA

[e]College of Nursing, Michigan State University, 1355 Bogue Street #C345, East Lansing, MI, U.S.A 48824

Abstract

Purpose—To examine symptom responses resulting from a home-based reflexology intervention delivered by a friend/family caregivers to women with advanced breast cancer undergoing chemotherapy, targeted and/or hormonal therapy.

Methods—Patient-caregiver dyads (N=256) were randomized to 4 weekly reflexology sessions or attention control. Caregivers in the intervention group were trained by a reflexology practitioner in a 30-minute protocol. During the 4 weeks, both groups completed telephone symptom assessments using the M. D. Anderson Symptom Inventory. Those who completed at least one weekly call were included in this secondary analysis (N=209). Each symptom was categorized as mild, moderate, or severe using established interference-based cut-points. Symptom response meant an improvement by at least one category or remaining mild. Symptom responses were treated as multiple events within patients and analyzed using generalized estimating equations technique.

Results—Reflexology was more successful than attention control in producing responses for pain [OR=1.84, 95% CI (1.05, 3.23), p=.03], with no significant differences for other symptoms. In the reflexology group, greater probability of response across all symptoms was associated with

Correspondence: Gwen Wyatt, RN, PhD, FAAN, Michigan State University College of Nursing, 1355 Bogue Street, East Lansing, MI 48824, gwyatt@msu.edu, Phone: 517-884-4630, Fax: 517-353-4587.

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lower number of comorbid condition and lower depressive symptomatology at baseline. Compared to odds of responses on pain (chosen as a referent symptom), greater odds of symptom response were found for disturbed sleep and difficulty remembering with older aged participants.

Conclusions—Home-based caregiver-delivered reflexology was helpful in decreasing patient-reported pain. Age, comorbid conditions and depression are potentially important tailoring factors for future research, and can be used to identify patients who may benefit from reflexology.

Keywords

Symptom management; Breast cancer; Reflexology; Symptom response

Introduction

Approximately 38% of women diagnosed with breast cancer annually have advanced disease [1], and experience the burden of unmanaged symptoms resulting from cancer and its treatment. Symptom burden is the strongest predictor of health-related quality of life (HRQOL) for cancer patients [2–4]. To manage symptoms from cancer and its treatment, more than 80% of women with breast cancer turn to complementary and integrative health (CIH) therapies [5]. Reflexology is a frequently used CIH therapy [5] that applies a firm walking-motion pressure to specific areas on the feet referred to as reflexes. Reflexology is based on the premise that stimulation of the foot reflexes mirrors organs of the body to create systemic balance [6].

The parent study of this secondary analysis tested the benefits of a caregiver-delivered home-based intervention of foot reflexology for improving HRQOL in women treated with chemotherapy, targeted and/or hormonal therapy for advanced breast cancer. For the primary outcome of the parent study, multiple symptoms were combined in an summed index, which demonstrated overall symptom reduction in the reflexology group compared to attention control [7]. Unscheduled health services use was also reduced, and workplace productivity improved by the reflexology intervention [8]. This secondary analysis extends the evidence of the efficacy of reflexology with respect to meaningful improvements in specific symptoms, or symptom responses, in order to inform personalization and tailoring of the intervention to specific symptoms and characteristics of the individual.

Related studies have noted both specific and summed symptom index change. A randomized clinical trial (RCT) of 4 weekly sessions of reflexology delivered by licensed reflexologists to women with advanced breast cancer indicated its efficacy with respect to improvement in physical functioning and reduction in dyspnea during treatment. [9] Numerous symptom management trials have focused on managing a specific symptom [10, 11] or a group of symptoms [12–15] without accounting for associations among multiple symptoms within patient or by simply combining severities of multiple symptoms into one summed score. [16, 17]. In this report, we apply an alternative method, a symptom response analysis, to the data from a recently completed symptom management trial of reflexology in order to illustrate how this analytical approach identifies symptoms for which this intervention is helpful, and characteristics of individuals who will receive the greatest benefit.

In the parent study, patients were asked to rate severity of their symptoms from the M. D. Anderson Symptom Inventory (MDASI) [18] using a 1 to 10 rating scale. For this analysis, those scores were converted to mild, moderate, or severe symptom categories by applying established and validated cut-points [19, 20]. These cut-points are anchored in how much the symptom interferes with enjoyment of life, relations with others general daily activity, and emotions. As severity of a given symptom increases along the 1 to 10 rating scale, interference may not increase linearly, so the cut-points were placed where there was greatest increase in interference as severity increased between successive integers. The cut-points vary for different symptoms, and have been shown to provide consistent differentiation of the levels of interference over time [21]. For example, for pain and fatigue, mild category corresponds to a severity score of 1, moderate corresponds to scores 2-4, and severe corresponds to scores 5-10, because the greatest increases in interference with activities of daily living occurred as severity increased from 1 to 2 and from 4 to 5. For sleep disturbance, the mild category is 1-3, moderate is 4-6, and severe is 7-10 because the greatest increases in interference with sleep occurred as severity increased from 3 to 4 and from 6 to 7. A patient's symptom response was defined as symptom improvement by at least one level (severe → moderate, or moderate → mild) during the 4-week intervention or symptom not rising to a moderate or severe level during the 4 weeks.

Aims

The aims of this study were:

1. To determine the effects of a 4-week, home-based reflexology intervention delivered by a friend/family caregiver compared to attention control on responses for multiple symptoms as determined by weekly symptom assessments, in order to overcome drawbacks of traditional approaches which sum symptom severities into an index or focus on single symptoms.
2. In the reflexology group, to explore which individual, disease, and treatment characteristics were associated with symptom responses.

Methods

Study design

This RCT enrolled 256 patient-caregiver dyads that were randomized to either 4 weeks of reflexology or attention control. During the 4-week intervention, symptoms were assessed in both arms using brief weekly telephone assessments. A total of 209 patients who completed at least one weekly call were included in this secondary analysis.

Participants

Patient inclusion criteria were: 1) age ≥ 21; 2) stage III or IV breast cancer; 3) able to perform basic activities of daily living (ADLs); 4) undergoing chemotherapy, targeted or hormonal therapy at the time of enrollment; 5) able to speak and understand English; 6) having access to a telephone; 7) able to hear normal conversation; and 8) cognitively oriented to time, place, and person (determined via recruiter). Patient exclusion criteria were: 1) diagnosis of major mental illness in the medical record, verified by the recruiter; 2)

residing in a nursing home; 3) bedridden; 4) currently receiving regular reflexology; or 5) diagnoses of symptoms of deep vein thrombosis or painful foot neuropathy.

Friend/family caregiver inclusion criteria were: 1) age ≥18; 2) able and willing to provide at least one 30-minute protocol session per week for 4 consecutive weeks; 3) able to speak and understand English; 4) access to a telephone; 5) able to hear normal conversation; and 6) cognitively oriented to time, place, and person (determined via recruiter). Exclusion criterion was: 1) unwilling to perform a return demonstration of the protocol according to training procedures.

Procedures

Dyads were recruited from nine community-based oncology clinics and two comprehensive cancer centers in the Midwest. Patients identified a friend or family member (caregiver) willing to be instructed in the 30-minute reflexology protocol, and to provide at least one weekly session over four consecutive weeks. Informed consent was obtained from both members of the dyad, patient and caregiver. The investigators' university granted Institutional Review Board (IRB) approval, and subsequently from all recruitment sites. Baseline interviews and weekly symptom assessments were administered by trained data collectors via telephone.

Randomization.—Following the baseline interview, randomization to either caregiver-delivered reflexology or attention control was implemented from the central study office using a minimization procedure. Balancing variables were recruitment location, presence of metastasis, type of treatment (hormonal therapy only versus other combinations of chemotherapy, targeted and hormonal therapies) and the level of fatigue at baseline. For dyads randomized to the reflexology group, caregivers were trained in reflexology by a study reflexologist and asked to provide at least one weekly reflexology session to patients. The number of sessions and patient symptoms were assessed during weekly telephone calls to patients. For dyads randomized to the attention control group, the patients received weekly telephone symptom assessments only. Because of the nature of two randomized conditions, dyads were not blinded to the group assigmnent.

Reflexology Intervention protocol.—The protocol for training of the caregiver in the manualized reflexology protocol by a reflexology practitioner are reported elsewhere [7]. Caregiver training was performed during two home visits by a study reflexologist. The first visit was used to demonstrate the specific study protocol and train the caregiver to perform the stimulation of reflexes, until a return-demonstration on the reflexologist by the caregiver was performed with 90% accuracy. Session one was then performed on the patient by the caregiver, while the reflexologist observed and coached. During the caregiver delivery of session two to the patient, the study reflexologist observed the delivery and offered adjustments in technique as needed. Caregivers were asked to deliver at least one 30-minute reflexology session per week for 4 weeks, with the number of sessions not restricted but tracked. The minimum dose requirement of 4 weekly sessions of reflexology and 30-minute session duration (15 minutes per foot) were tested in previous work with women with advanced breast cancer [9].

Data Collection During Intervention.—Weekly symptom assessment calls were made to all patients during intervention weeks 1-4. While the weekly symptom calls were part of data collection, they also provided a limited amount of social interaction between the patient and the interviewer. This happened equally between the two trial arms and equalized attention that could affect patient symptom reporting. The weekly calls documented the process of change in symptoms and allowed for investigation of symptom specific responses.

Measures

Patient demographic information collected in the baseline interview included age, race, and ethnicity, level of education, employment, income, and relationship to the caregiver. The number of comorbid conditions was assessed using the Bayliss tool that queries 20 conditions [22], omitting the cancer item since all patients had breast cancer. Data on cancer and medical treatments administered during the study were obtained from medical records.

Center for Epidemiologic Studies-Depression CES-D [23] was administered during the baseline interview. Higher scores indicate worse depressive symptoms. The internal consistency reliability in tins study was 0.91.

The M.D. Anderson Symptom Inventory (MDASI) [18] was administered at baseline and weeks 1-4. It evaluates severity of 13 symptoms (i.e., pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering, decreased appetite, drowsiness, dry mouth, sadness, vomiting, numbness/tingling) on a scale from 0=not present to 10=as bad as you can imagine, and the interference of these symptoms with daily life on a scale from 0=does not interfere to 10=completely interferes. Reliability and validity of the instrument are established [18].

Symptom Response.—Interference-based cut-points for mild, moderate or severe symptoms were available for 8 out 13 symptoms included in the MDASI: pain, fatigue, disturbed sleep, shortness of breath, difficulty remembering, decreased appetite, dry mouth, and numbness/tingling. Cut-points were also available for nausea/vomiting; in this sample, 90% of patients' nausea never reached moderate or severe levels. Symptoms of sadness and distress from the MDASI were combined, using the severity rating for the higher of the two, and cut-points for depression were applied. This process resulted in an array of 9 symptoms categorized as mild, moderate, or severe at each time point. For each of these 9 symptoms, symptom onset was defined as the date of the baseline interview or first weekly call when a symptom reached moderate or severe level. An anchor-based definition of symptom response was applied: women who reported moderate or severe levels on a symptom were classified as responders to the intervention if they moved from severe to moderate or to mild/none, or moderate to mild/none between onset time and the last symptom assessment. Patient-symptom cases that remained mild during the 4 weeks were also classified as responses since these symptoms never rose to moderate or severe level. Patient-symptom cases that moved from mild or moderate at onset to moderate or severe at the last weekly call, or were severe at onset and severe at the last weekly call, were classified as non-responders. As a result, a woman could be a responder on some symptoms and a non-responder on others.

Analysis

Baseline characteristics were summarized by study group for outcome values and potential covariates. The unit of analysis was patient-symptom; multiple symptoms were treated as nested within the patient being analyzed, using methodology described by Given et al. [24] and Sikorskii et al. [17] Patient-symptom responses were treated as multiple events, and associations among responses to multiple symptoms within patients was accounted for by specifying the exchangeable correlation structure in the generalized estimating equations (GEE) model. The GEE model was fitted using the GENMOD procedure in SAS 9.4 [25]. A dummy symptom variable with 9 levels was included in the interaction with the trial arm to differentiate potentially different effects of reflexology on different symptoms. Patient-level covariates included age, number of comorbid conditions, type of treatment (chemotherapy or targeted therapy with or without hormonal therapy versus hormonal therapy only), and the CES-D score at baseline. Odds ratios (ORs) and their 95% confidence intervals (CIs) were obtained for the essential parameter of study group for each symptom.

For the second aim, the GEE model was fitted for those in the reflexology group, and interactions of the patient-level covariates (age, comorbidity, type of treatment, and CES-D score at baseline) with the dummy symptom variable were included to determine whether responses to each symptom could be predicted by these patient, disease, and treatment characteristics. For this exploratory analysis, p-value≤.10 was used to indicate potential importance of the interaction term. When p-value for the interaction term was greater than .10, the interaction term was removed from the model, and the main effects were interpreted.

Results

The baseline characteristics of the sample analyzed (N=209) are presented in Table 1. Women were on average 55 years of age, and the majority were married or living with a partner. Approximately 1/3 had recurrent cancer, over 60% had metastatic disease, and 82% were receiving chemotherapy or targeted therapy at intake, with or without hormonal therapy, while 18% were on hormonal therapy only. Fatigue was the most prevalent symptom, and for all but 4 participants fatigue reached moderate or severe level during the study (Table 2). Moderate or severe pain was experienced by 86% of the women. In the intervention group, reflexology was enacted at least once per week by 72% of participants in week 1, 90% in week 2, 87% in week 3, and 82% in week 4. The majority of the participants completed 1 or 2 sessions, with approximately 6% completing 3 or more sessions each week.

In the comparison of trial arms on symptom responses, reflexology was more successful than attention control in producing responses for pain [OR=1.84, 95% CI (1.05, 3.23), p=.03], with no significant differences for other symptoms (Table 3). For fatigue, the point estimate for the OR of 1.76 [95% CI (0.99, 3.12)] favored reflexology, but this effect did not reach statistical significance (p=.06).

In the exploratory analysis of factors associated with responses to reflexology, the p-value for interaction of age with a dummy symptom variable was .06, while the p-values for other

interactions were all greater than . 10, meaning that that responses on different symptoms differed by age but did not differ with respect to the number of comorbid conditions, treatment type, or depressive symptomatology at baseline. The results from the model with age by symptom interaction and other variables as main effect are in Table 4. Probability of response across all symptoms was lower with greater number of comorbid conditions [OR=0.87, 95% CI (0.80, 0.94), p<.01] and higher CES-D at baseline [OR=0.96, 95% CI (0.94, 0.99), p<.01]. In contrast to comorbidity and CES-D score, the effects of age on symptom response were different across symptoms. As age increased, greater odds of symptom response were found for disturbed sleep [OR=1.06, 95% CI (1.01, 1.10), p=.02] and difficulty remembering [OR=1.05, 95% CI (1.00, 1.11), p=.04] as compared to odds of response on pain (chosen as a referent symptom).

Discussion

This secondary analysis implemented an approach to analysis of multiple symptom experience using an anchor-based definition of response for each symptom, and accounting for nesting of multiple symptom responses within patients. Improvements in symptoms from severe to moderate or mild, and from moderate to mild represent meaningful reductions in how much symptoms interfered with daily activities, and in the past were shown to be related to improvements in physical function [19].

Multiple-symptom research, often referred to as poly-symptom research, has advanced the science of supportive care in cancer and other chronic conditions; however the science of design and evaluation of symptom management interventions still often focuses on a single symptom or a composite outcome that reflects a poly-symptom experience in a single summed score. While it is convenient in RCTs to have a single primary outcome measured via such a summed score, this approach to symptom measurement and evaluation of symptom management interventions has multiple drawbacks documented in the literature [16, 17]. One such drawback of summed scores is the lack of ability to discern intervention effects for specific symptoms, representing a barrier to personalized tailoring of symptom management interventions. The symptom response analysis reported in this paper overcomes this drawback.

In contrast to past uses of symptom response analysis, where responses were only defined for symptoms that reached moderate or severe level [17,24], in this analysis we also included symptoms that remained mild. This is because unlike psycho-educational interventions that are directed at specific elevated symptoms, reflexology is a holistic approach to symptom management. In addition, some symptoms remaining mild could be due to the fact that other elevated symptoms were successfully managed. We believe that even for interventions that specifically target individual symptoms, all symptoms need to be included in symptom response analysis. Such inclusion also ensures no missing values in the GEE analysis and minimizes potential biases due to missing values.

The symptom response methodology allowed isolation of disparate intervention effects on different symptoms within a single statistical GEE model. Specifically, reflexology intervention had a significantly greater response rate on pain, but not on other symptoms as

compared to attention control. When analyzed separately using traditional repeated measures methodology for the mean scores, differences between reflexology and attention control were statistically significant for both pain and fatigue [7], with mean group differences of approximately 1 point on the 0-10 scale. The limitation of that analysis of not accounting for the associations among symptoms could be one explanation for the difference in findings on fatigue. The present analysis also reflects the fact that reductions in severity of the same magnitude may have different meaning depending on where on the scale they occur. This is another explanation of why the analysis of mean scores of fatigue favored reflexology [7], while in the symptom response analysis did not significantly favor reflexology over attention control. Mean scores for fatigue in the reflexology arm were between 3 and 4 over time, [7], which is in the moderate fatigue category, with reflexology arm being about 1 point lower. The mean differences between arms on pain were also near 1 point, but in contrast to fatigue, the mean pain severity scores were between 2 and 3, [7] near to the cut-point of 2 separating mild from moderate levels. The transition from moderate to mild pain was noted as symptom response, leading to the same efficacy conclusion from the consideration of mean pain scores in [16] and responses on pain in the present analysis.

In designing a study that targets multiple and difficult to manage symptoms, preliminary work regarding dose, delivery and protocol are essential. In a typical clinical practice of a reflexologist, a session may run as long as a full hour [26]. However, the research literature on cancer patient populations, report sessions ranged from 15-30 minutes [27–31]. Among such oncology studies, various symptoms have been evaluated. One study reported significantly lower anxiety among multiple types of cancer patients [27]; another found lower pain among patients with mixed cancers [28]; a third reported decreased pain among digestive cancer patients [29];a fourth, using a bundled intervention, found reflexology plus self-initiated support promoted relaxation among post-surgical early-stage breast cancer patients [30]; and a fifth study involved a mixed sample of hospitalized cancer patients where partners were taught to conduct one session, resulting in an immediate decrease in pain intensity and anxiety [31]. While these studies support the value of reflexology for symptom management, they often were scant on protocol details such as who provided the sessions. The one oncology study by Stephenson [32] was explicit on the use of 30 minutes total by a certified reflexologist, but this level of reporting is lacking in many publications. Studies that do mention the reflexology providers have used students, partners and caregivers. It is difficult to replicate past studies and advance the science when details such as dose, session delivery and protocol details are omitted in reports of intervention fidelity.

In order to deal with the inconsistent details in the reflexology literature, we considered and established a dose needed for symptom response in oncology work. We found caregivers and cancer patients were able to sustain 30-minute sessions [9, 33], which corresponded with the published research. With the 30-minute time constraint in mind, the oncology reflexology protocol was tailored to nine reflexes selected by our panel of expert reflexologists [33]. In early studies [9, 33], practicing reflexologists demonstrated a significant improvement in the symptom dyspnea, but not pain. Interestingly in the same study, the control group of lay caregiver-delivered reflexology reduced fatigue among cancer patients. Subsequent studies have shown improvement in the summed symptom score on the MADASI, with the strongest results for pain and fatigue. [34, 35] Whether the reflexologist provides direct

delivery of the session or not, it is critical to have their expertise for protocol development and training for the direct care providers. In an area such as reflexology where limited rigorous research has been established, these preliminary steps –dosage, delivery and protocol - are critical considerations.

Factors such as higher comorbidity and depressive symptoms predicted lower response rates across the array of symptoms, while older age was associated with greater response rate on disturbed sleep and difficulty remembering compared to response rate on pain. The findings regarding comorbidity and depressive symptoms agree with those of others [36–38] that indicated the number, severity and persistence of symptoms during chemotherapy for solid tumors can be predicted in part by comorbid conditions and depressive symptoms. All three of these easily identifiable factors (age, depressive symptoms and comorbidity) could be used for therapeutic decision making.

Study limitations include lack of assessment of the caregiver hand strength in terms of the pressure caregivers applied while delivering reflexology. In this study, caregivers received two training sessions from practicing reflexologists, and it is possible that more training could have resulted in more robust caregiver skills in reflexology delivery. The exclusion of women who were not able to perform basic ADLs or bedridden narrowed the population to which the findings are generalizable. Future research is needed to test reflexology for symptom palliation among those with potentially highest symptom burden.

Conclusions

Based on symptom response data from this RCT, home-based caregiver-delivered reflexology is useful for managing pain. Further, comorbid conditions, age, and depressive symptoms at baseline could guide tailoring of interventions and identify patients who may benefit from symptom reduction through reflexology. Symptom response analyses similar to this one can inform tailoring of other supportive care interventions that target multiple cancer- and treatment-related symptoms.

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Table 1.

Demographic and clinical characteristics of the analyzed sample at baseline.

	Reflexology N=102	Attention Control N=107
	N (%)	**N (%)**
Metastatic cancer		
Yes	59 (58)	66 (62)
No	43 (42)	41 (38)
Recurrent cancer		
Yes	31 (30)	30 (28)
No	71 (70)	77 (72)
Treatment type		
Chemotherapy or targeted therapy (with or w/o hormonal)	82 (80)	86 (80)
Hormonal therapy only	20 (20)	21 (20)
Race		
White	87 (85)	94 (88)
Black or African American	8 (8)	7 (7)
Other	6 (6)	5 (4)
Missing	1 (1)	1 (1)
Ethnicity		
Hispanic or Latino	3 (3)	4 (4)
Not Hispanic or Latino	99 (97)	103 (96)
Employment		
Full time	24 (23)	31 (30)
Part time	9 (9)	11 (10)
Other	34 (33)	38 (35)
Retired	35 (34)	27 (25)
Education		
High school graduate (or GED) or some high school	23 (23)	22 (21)
Some college or 2-year degree	25 (25)	33 (31)
4-year college graduate	26 (25)	26 (24)
More than a 4-year college degree	27 (26)	26 (24)
Missing	1 (1)	0 (0)
Marital status		
Never Married	10 (10)	10 (9)
Married or Living with Partner	71 (70)	73 (68)
Divorced/Separated	15 (15)	16 (15)
Widowed	6 (5)	8 (8)

	Reflexology N=102	**Attention Control N=107**
	N (%)	**N (%)**
	Mean (SD)	**Mean (SD)**
Age in years	58.95 (11.32)	55.54 (10.08)
Number of comorbid conditions	4.55 (3.02)	4.48 (3.09)
CESD at baseline	14.39 (10.39)	14.67 (9.81)

Table 2.

Descriptive statistics for symptoms and symptom responses.

Symptom	Group	Onset severity		Response	Non-response
Fatigue	Reflexology (Group1)	Severe	74	42 (56.76%)	32 (43.24%)
		Moderate	25	9 (36%)	16 (64%)
		Mild (always stayed mild)	2	2 (100%)	0 (0%)
	Control (Group 2)	Severe	67	31 (46.27%)	36 (53.73%)
		Moderate	38	9 (23.68%)	29 (76.32%)
		Mild (always stayed mild)	2	2 (100%)	0 (0%)
Pain	Reflexology (Group1)	Severe	44	32 (72.73%)	12 (27.27%)
		Moderate	40	15 (37.5%)	25 (62.5%)
		Mild (always stayed mild)	18	18 (100%)	0 (0%)
	Control (Group 2)	Severe	44	24 (54.55%)	20 (45.45%)
		Moderate	48	14 (29.17%)	34 (70.83%)
		Mild (always stayed mild)	15	15 (100%)	0 (0%)
Disturbed Sleep	Reflexology (Group1)	Severe	44	34 (77.27%)	10 (22.73%)
		Moderate	36	24 (66.67%)	12 (33.33%)
		Mild (always stayed mild)	22	22 (100%)	0 (0%)
	Control (Group 2)	Severe	42	29 (69.05%)	13 (30.95%)
		Moderate	49	32 (65.31%)	17 (34.69%)
		Mild (always stayed mild)	16	16 (100%)	0 (0%)
Shortness of breath	Reflexology (Group1)	Severe	16	12 (75%)	4 (25%)
		Moderate	33	19 (57.58%)	14 (42.42%)
		Mild (always stayed mild)	52	52 (100%)	0 (0%)
	Control (Group 2)	Severe	10	7 (70%)	3 (30%)
		Moderate	38	29 (76.32%)	9 (23.68%)
		Mild (always stayed mild)	59	59 (100%)	0 (0%)
Remembering	Reflexology (Group1)	Severe	35	23 (65.71%)	12 (34.29%)
		Moderate	47	25 (53.19%)	22 (46.81%)
		Mild (always stayed mild)	19	19 (100%)	0 (0%)
	Control (Group 2)	Severe	38	25 (65.79%)	13 (34.21%)
		Moderate	53	31 (58.49%)	22 (41.51%)
		Mild (always stayed mild)	16	16 (100%)	0 (0%)
Lack of Appetite	Reflexology (Group1)	Severe	16	13 (81.25%)	3 (18.75%)
		Moderate	35	26 (74.29%)	9 (25.71%)
		Mild (always stayed mild)	50	50 (100%)	0 (0%)
	Control (Group 2)	Severe	20	17 (85%)	3 (15%)
		Moderate	29	19 (65.52%)	10 (34.48%)
		Mild (always stayed mild)	58	58 (100%)	0 (0%)
Dry Mouth	Reflexology (Group1)	Severe	13	11 (84.62%)	2 (15.38%)

Symptom	Group	Onset severity		Response	Non-response
		Moderate	45	34 (75.56%)	11 (24.44%)
		Mild (always stayed mild)	44	44 (100%)	0 (0%)
	Control (Group 2)	Severe	13	10 (76.92%)	3 (23.08%)
		Moderate	44	25 (56.82%)	19 (43.18%)
		Mild (always stayed mild)	50	50 (100%)	0 (0%)
Vomiting	Reflexology (Group1)	Severe	4	4 (100%)	0 (0%)
		Moderate	5	3 (60%)	2 (40%)
		Mild (always stayed mild)	92	92 (100%)	0 (0%)
	Control (Group 2)	Severe	3	2 (66.67%)	1 (33.33)
		Moderate	1	1 (100%)	0 (0%)
		Mild (always stayed mild)	103	103 (100%)	0 (0%)
Numbness	Reflexology (Group1)	Severe	13	8 (61.54%)	5 (38.46%)
		Moderate	38	18 (47.37%)	20 (52.63%)
		Mild (always stayed mild)	51	51 (100%)	0 (0%)
	Control (Group 2)	Severe	20	10 (50%)	10 (50%)
		Moderate	42	19 (45.24%)	23 (54.76%)
		Mild (always stayed mild)	44	44 (100%)	0 (0%)
Depression	Reflexology (Group1)	Severe	62	39 (62.9%)	23 (37.1%)
		Moderate	27	18 (66.67%)	9 (33.33%)
		Mild (always stayed mild)	13	13 (100%)	0 (0%)
	Control (Group 2)	Severe	58	30 (51.72%)	28 (48.28%)
		Moderate	34	21 (61.76%)	13 (38.24%)
		Mild (always stayed mild)	15	15 (100%)	0 (0%)

Table 3.

Adjusted odds ratios (ORs) of symptom responses for reflexology arm versus control (adjusted for age, number of comorbid conditions, depressive symptoms at baseline, and treatment type: chemotherapy with or without hormonal therapy versus hormonal therapy alone).

Symptom	OR (95% CI)	P-value
Fatigue	1.76 (0.99, 3.12)	0.06
Pain	1.84 (1.05, 3.23)	0.03
Disturbed sleep	1.45 (0.76, 2.77)	0.26
Shortness of breath	0.58 (0.26, 1.30)	0.19
Remembering	0.96 (0.51, 1.78)	0.89
Lack of appetite	1.05 (0.45, 2.49)	0.91
Dry mouth	1.84 (0.86, 3.94)	0.12
Numbness and tingling	1.40 (0.75, 2.64)	0.29
Depression	1.38 (0.78, 2.43)	0.27

Table 4.

Predictors of symptom responses in the reflexology group.

Predictor	OR (95% CI)	P-value
Age	0.99 (0.96, 1.03)	0.70
Comorbidity	0.87 (0.80, 0.94)	< 0.01
CESD at baseline	0.96 (0.94, 0.99)	< 0.01
Treatment type		
Hormonal therapy only	Ref.	-
Chemotherapy or targeted therapy with or without hormonal therapy	0.64 (0.35, 1.15)	0.13
Symptom		
Pain	Ref.	-
Fatigue	0.35 (0.03, 4.35)	0.41
Disturbed sleep	0.10 (0.01, 1.38)	0.08
Shortness of breath	3.36 (0.07, 151.55)	0.53
Remembering	0.05 (0.00, 0.93)	0.04
Lack of appetite	1.90 (0.08, 43.76)	0.69
Dry mouth	17.06 (0.46, 631.44)	0.12
Numbness and tingling	0.76 (0.04, 16.00)	0.86
Depression	0.55 (0.04, 7.87)	0.66
Symptom*age		
Pain*age	Ref.	-
Fatigue*age	1.01 (0.97, 1.05)	0.67
Disturbed sleep*age	1.06 (1.01, 1.10)	0.02
Shortness of breath*age	1.00 (0.94, 1.06)	0.93
Remembering*age	1.05 (1.00, 1.11)	0.04
Lack of appetite*age	1.02 (0.96, 1.07)	0.56
Dry mouth*age	0.98 (0.93, 1.03)	0.42
Numbness and tingling*age	1.01 (0.97, 1.07)	0.56
Depression*age	1.01 (0.97, 1.06)	0.53