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## Healthcare Service Utilization and Work-related Productivity in Reflexology Intervention for Advanced Breast Cancer Women

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## Abstract

**Purpose:** This project's purpose was to determine the effects of a home-based reflexology intervention on symptom-related use of health services and work-related productivity during the 11-week study.

**Methods:** A total of 256 patients were randomized to four weekly reflexology sessions (each lasting 30 minutes, delivered by lay caregivers who received two training sessions by a professional reflexologist) or attention control. The Conventional Health Service and Productivity Costs Form was used to collect information on health service utilization and out of pocket expenditure of symptom management. The Health and Work Performance Questionnaire was used to measure workplace performance for patients during the study period. We used weighted and unweighted logistic and linear regression analyses.

**Results:** Patients in the reflexology group were less likely to have hospital visits compared to the control group in the weighted unadjusted (odds ratio [OR] = 0.49; 95% confidence interval [CI] = [0.25, 0.97]), unweighted adjusted (OR = 0.35; 95% CI = [0.16, 0.75]), and weighted adjusted (OR= 0.30, 95% CI = [0.13, 0.66]) logistic regressions. Compared to attention control, patients in the reflexology group had lower relative absenteeism in the unweighted adjusted (-0.32; 95% CI = [-0.60, -0.03]) linear regressions and less absolute presenteeism (15.42, 95% CI = [0.87, 29.98]) in the weighted unadjusted analysis.

**Conclusion:** The reflexology intervention delivered by lay caregivers reduced hospital visits and increased workplace productivity in a short-term period, which has potential for cost saving for health care systems and employers.

The authors have declared that there is no conflict of interest.

Clinical Trials Registration: NCT01582971

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#### Keywords

breast cancer; reflexology; health service utilization; health service expenditure

## Introduction

Recent estimates projected that cancer care in the United States (U.S.) would cost \$157 billion annually by 2020, with a 27% increase in medical costs, of which prostate and breast cancer will have the greatest increase during the continuing phases of care [1]. Cancer care costs typically are highest in the first 12 months following diagnosis [2]. Breast cancer is the most common cancer diagnosed among women. According to American Cancer Society, 255,180 persons in the U.S. were diagnosed with breast cancer and 41,070 died in 2017 [3].

Breast cancer patients with surgical treatment experience different levels of pain [4], and chemotherapy treatment gives rise to multiple additional symptoms [5]. Hospitalizations contribute to the increase in medical costs during breast cancer treatment. There is evidence to suggest that reductions in symptoms may be associated with a lower use of unscheduled health services [6, 7]. The purpose of this report was to evaluate the effects of a symptom management intervention on health services utilization, health care expenditures, and productivity using data from a recently completed randomized controlled trial of reflexology for managing symptoms among women with advanced breast cancer undergoing chemotherapy, targeted and/or hormonal therapy [8].

Over 80% of women with breast cancer chose complementary and integrative health (CIH) therapies for at least a component of their symptom management after surgical intervention [9]. Reflexology was reported to be one of the commonly used CIH therapies for symptom management [10]. It involves applying a walking thumb pressure to particular points on the feet that are referred to as reflexes. Reflexology can be considered a supportive treatment used in combination with standard medical care. It is carried out by trained providers to help cancer patients receiving active therapy manage their symptoms and maintain their quality of life [11]. Currently, there is no established mechanism of action for how reflexology works to reduce symptoms. One physiologic theory is that reflexology activates receptors to release oxytocin for its positive effects on well-being [12]. A second theory is that applying pressure improves circulation, which in turn eliminates toxins and supports immune, nervous, and glandular systems [13]. A third theory is that the benefits are derived through activation of the relaxation response [14, 15]. A final theory proposes that reflexology reduces symptoms through the complex inputs and processing in the neuromatrix of the central nervous system [16, 17].

While an agreed upon mechanism of action is yet to be determined, the efficacy of reflexology in mitigating symptoms has been established [18–22]. Our previous studies showed both safety and efficacy of reflexology on improvements in physical function, dyspnea, and fatigue [23]. Our work also established that reflexology could be delivered successfully to patients by friends or family caregiver in the home, who were trained by a certified reflexologist [24], and caregiver-delivered reflexology was efficacious in reducing cancer symptom severity [8].

To date, few studies have examined the effect of reflexology on patient health care service utilization and employment productivity [25]. The aim of this paper was to determine the difference in symptom-related use of health services and employment productivity at study week-11 between women in treatment for advanced breast cancer in a randomized controlled trial who received either: 1) four weekly sessions of home-based reflexology delivered by a trained friend or family lay caregiver; or 2) attention control. We hypothesized that women receiving reflexology compared to women in attention control would use fewer health service for symptom management and maintain higher employment productivity over the 11-week study.

## Design

The study used a randomized clinical trial design [8]. Data were collected by telephone at baseline and week 11.

#### Participants

Women who had advanced breast cancer and were receiving chemotherapy, hormonal and/or targeted therapy were recruited from seven community-based medical oncology clinics and two comprehensive cancer centers in the Midwest. For the intervention arm, one of the patient's friend or family member (caregiver) who was willing to provide the 30 minutes protocol for four consecutive weeks also consented and enrolled. Patient inclusion criteria were: age 21 or older, diagnosed with stage III or IV breast cancer, could perform basic activities of daily living, undergoing chemotherapy, targeted therapy, and/or hormonal therapy for breast cancer at enrollment, able to speak and understand English, able to hear normal conversation over the phone, and cognitively oriented to time, place, and person (determined by recruiters). Patient exclusion criteria were: diagnosis of a major mental illness on the medical record and verified by the recruiter, residing in a nursing home, bedridden, currently receiving regular reflexology or having symptoms of deep vein thrombosis or painful foot neuropathy.

Caregiver inclusion criteria were: age 18 or older, able, and willing to provide at least one 30 minutes protocol session per week for 4 consecutive weeks, could speak and understand English, had access to a telephone, able to hear normal conversations, and cognitively oriented to time, place, and person. Exclusion criterion was unwillingness to perform a return demonstration of the protocol according to training procedures. All the caregivers had two training sessions with a study reflexologist; however, the reflexologist did not work directly with study participants, but only with the caregiver.

## Methods

## **Enrollment and randomization**

Participants were enrolled in dyads (patient-caregiver) by trained recruiter, who were employed by the clinics and did not provide care to patients. Their study training included a script, didactic information, role-playing, problem cases, and return-demonstration. Once consent was received at the clinic and the baseline interview was completed via telephone

from the study office, the dyads were randomized into the reflexology group or the attention control group (weekly symptom calls only). A computerized minimization technique [26] was programmed by the team statistician to balance the groups on stage of breast cancer (III or IV), medical treatment (chemotherapy with or without hormonal therapy versus hormonal therapy alone), the recruitment location (oncology clinic) to control for any minor variations in care between sites, and the severity of the most prevalent baseline symptom of fatigue. The project manager in the study office implemented the randomization to ensure location concealment.

#### Protocol

Women in the intervention group received four consecutive weekly reflexology sessions, each lasting 30 minutes, delivered by a friend or family caregiver and completed weekly telephone symptom assessments by staff in the study office. A study reflexologist trained the friend/family caregiver during two home visits in week 1 and 2. Our previously validated cancer specific protocol included nine locations on the foot referred to as reflexes [23]. This protocol consists of a thumb-walking pressure over each of the nine reflexes for 15 minutes per foot, totaling a 30-minutes session. On the first visit, the study reflexologist demonstrated the specific study protocol and trained the caregiver in stimulation of the nine reflexes, until 90% accuracy was achieved using a standard evaluation via a return demonstration on the reflexologist by the caregiver. The caregiver then performed Session 1 on the patient while the reflexologist observed and coached. During Session 2, the reflexologist observed and offered adjustments in techniques as the caregiver conducted the session on the patient. In the following two weeks caregiver-patient sessions were conducted without the reflexologist present. Laminated instructions and the reflexologist's phone number were left with the dyad as a resource for weeks 3 and 4 of independent delivery of reflexology. Previous work established the minimum dose of reflexology was 4 weekly sessions [27].

Women in the attention control group only received the four weekly telephone symptom assessments. While the weekly symptom calls were part of data collection, they also provided a limited amount of attention and social interaction between the patient and the interviewer because the interview included inquiry about how the patient was doing. Weekly calls were conducted according to a standard script and lasted approximately 10–15 minutes each week for both groups. After the study, patients in the attention control group received a reflexology session or protocol training for a friend or family caregiver.

For a complete description of the trial, see [8]. The study was approved by the Michigan State University Institutional Review Board (IRB) and IRBs of the participating sites. All data were stored in a secure SQL server with firewalls.

## **Outcome Measures**

To measure the number of health services used and the amount of health service expenditure during the study period (11 weeks), the Conventional Health Service and Productivity Costs Form (CHSPCF) was adapted [6]. It captures the number of times the patient visited an oncologist, emergency room, hospital, laboratory, and other providers (including primary

care provider, social worker, psychologist, support group and nurse) for symptom management. It also contains the total co-payment, deductibles, and out-of-pocket expenditure for each service type, in addition to medication, special supplies, and miscellaneous items. Because the utilization and expenditure data were highly skewed and many patients reported zero visits in some categories, data were dichotomized to capture use or no use of oncology, emergency care, hospital and other services.

Among the patients who were working, the World Health Organization Health and Work Performance Questionnaire (HPQ) (7-Day clinical trial version) was used to assess the effect of the intervention on the workplace performance for patients at baseline and at week 11 [28, 29]. Four main absenteeism and presenteeism outcomes were calculated based on the HPQ instruments. The absolute absenteeism was measured by the difference between the expected and actual hours worked in past 7 days, with a negative lower bound if a woman worked more than expected and a positive upper bound equal to the expected hours worked. The relative absenteeism is the ratio between absolute absenteeism and the expected hours worked. It ranges between a negative number and one. Higher absenteeism scores indicated more absenteeism and more loss in productivity. The absolute presenteeism was based on self-rated performance in the past 7 days on a scale from 0 to 100, with a higher score indicating a lower amount of lost performance. The relative presenteeism was the ratio of her own performance and the usual performance of most workers in a job similar to hers. Following the instructions of the instrument's authors, the relative presenteeism was restricted between 0.25 to 2, where the highest performance is 200% of other works' performance [28, 29].

## **Baseline Covariates**

The number of comorbid conditions was assessed using the Bayliss tool that queries 20 conditions [30]. Data on cancer stage, recurrence, metastasis, and medical treatments were obtained from the medical records.

The M.D. Anderson Symptom Inventory (MDASI) [31] evaluates severity of 13 symptoms experienced by cancer patients (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 [28]. Summed symptom severity and interference scores were derived from this instrument.

Physical functioning was measured using Patient Reported Outcomes Measurement Information System (PROMIS) 4-item short from, which has good evidence of reliability and validity [32, 33]. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation 10 for the general population.

Quality of Life Index (QLI) reflects both satisfaction and importance regarding various aspects of life, using 30 items for each [34]. Importance ratings are used to weight

satisfaction responses, so that scores reflect satisfaction with the aspects of life that are valued by the individual. The total QLI score summarizes four domains: health and functioning, psychological/spiritual domain, social and economic.

## Statistical Analysis

This secondary analysis used all available data from week 11. The baseline characteristics between patients lost to follow-up and remaining patients were compared using chi-square or t-tests. Baseline characteristics of patients in the reflexology versus control group among those who remained by week 11 were similarly tested.

When the patients who remained in the study at week 11 had systematically different characteristics from those who were lost to follow-up or when the patients in the two treatment arms had differential loss to follow-up, analyses using only retained patients may suffer from selection bias. Therefore, the inverse probability weighting (IPW) was used to correct potential bias [35]. The weight was the inverse of the probability of remaining in the study by week 11, predicted by baseline characteristics. Unweighted and IPW-weighted logistic regressions were used to explore the effect of reflexology intervention on having specific health service utilization, controlling for baseline covariates. For HPQ analysis, weighted and unweighted linear regression models were used, also controlling for baseline covariates. The trial was powered to detect an adjusted effect size of 0.4 with power 0.80 in two tailed tests at 0.05 significance level for the primary endpoint of symptom severity. This secondary data analysis used all available data by week 11. Data analysis was carried out using Stata (version 15; StataCorp LP, College Station, TX, USA).

## Results

Out of the total 256 patients, 180 (70%) remained in the study at 11 weeks. There were some systematic differences in baseline characteristics between patients who were lost to followup and those who remained in the study. Patients who were lost were more likely to receive chemotherapy (p = 0.006), unmarried (p = 0.024), had fewer comorbid conditions (p=0.014), higher MDASI symptom severity score (p = 0.009), higher MDASI symptom interference score (p = 0.001), lower PROMIS physical function score (p = 0.003), and lower quality of life measure (p = 0.029) (For more details see Appendix Table A). Thus, these variables were used for estimating the weights in the IPW estimation.

Among patients retained at week 11, 89 out of 128 reflexology patients (70%) and 91 out of 128 control patients (71%) remained in the study. During the eleven weeks study period, 3 patients died (2 in reflexology group), 38 patients could not be reached (18 in reflexology group), and 35 patients dropped out due to other reasons (18 in reflexology group). For details about other reasons for attrition, see [8]. There was little systematic difference in baseline variables between the reflexology and control patients who remained in the study (Table 1). Between these two groups, only age had a significant difference at 5% level (p=0.042).

Table 2 shows the proportions of patients who used each category of health services, the median and interquartile range (IQR) for the number of visits and out-of-pocket expenditure

for each category of services, and the productivity measures at week 11 by treatment groups. The numbers of employed women were 28 and 30 in the reflexology and control groups at week 11, respectively. These differed only slightly from the numbers of employed women at baseline (29 and 32, respectively). A lower proportion of reflexology patients had hospital visits (26% versus 40%, p = 0.050). No other service utilization, expenditure or productivity measures differed between the two groups. While not statistically significant, the control group patients had higher absenteeism (less productive) and lower absolute presenteeism (less productive).

Table 3 presents the odds ratios (ORs) for the effect of reflexology on using each type of health care services using unweighted/weighted unadjusted/adjusted logistic regressions. Patients who received the reflexology intervention were less likely to have hospitalizations comparing to the control group during the study period in the weighted/unadjusted analysis (OR=0.49; 95% CI [0.25, 0.97]), the unweighted/adjusted analysis (OR=0.35; 95% CI [0.16, 0.75]), and the weighted/adjusted analysis (OR=0.30; 95% CI [0.13, 0.66]). There were no other significant differences in utilization between the two groups.

Table 4 shows the unweighted/weighted unadjusted/adjusted absenteeism and presenteeism least squares regression results. In weighted/unadjusted models, the reflexology group had higher absolute presenteeism, i.e., better productivity, compared to controls ( $\beta = 15.42$ ; 95% CI [0.87, 29.98]). In unweighted/adjusted models, the reflexology had lower relative absenteeism scores, i.e., less productivity loss, than control group ( $\beta = -0.32$ ; 95% CI [-0.60, -0.03]).

## Discussion

It is important for breast cancer survivors (defined as individuals from the time of diagnosis to end of life [34]) to enjoy all facets of life including accomplishing their social roles at their workplace and in society [1]. Results of this study point to reflexology delivered by friend or family caregivers as an intervention that can reduce hospitalizations and increase workplace productivity (lower absenteeism and higher presenteeism) in a short-term period. These findings complement earlier results on the efficacy of reflexology on patient quality of life and symptom management [8, 23], and are consistent with reports that reductions in symptoms are associated with lower unscheduled health services use [6, 37] and less productivity loss [38]. Studies using cross-sectional survey data for the comparison of healthcare utilization and productivity cost may suffer from confounding bias. Our study is the first that we know of to examine the effect of reflexology on healthcare utilization and productivity loss in a randomized controlled trial for advanced breast cancer patients. This study is also the only one that used the Health and Work Performance Questionnaire (HPQ) to measure productivity for advanced breast cancer patients. The HPQ is the only validated questionnaire to measure all three types of workplace consequences of illness: sickness absence, presenteeism and critical incidents [28, 29]. Productivity loss was reduced for both absenteeism and presenteeism in our study.

We did not conduct a full cost-effectiveness analysis because the intervention was delivered by friend or family caregivers, the time frame was short, and the direct healthcare costs

across settings (e.g., academic versus non-academic) were difficult to ascertain from a societal perspective [39]. However, the findings have implication for economic evaluations of CIH in three ways. First, hospitalization is the largest driving force for escalating healthcare costs. Since reflexology can be taught to friend or family caregivers who can deliver it in the patient's home setting, it represents a promising avenue for curbing the increased medical costs.

Second, the burden of cancer includes not only medical costs but also loss in productivity [38]. Being able to participate fully in the social life is an important part of the survivorship [40], particularly for younger breast cancer survivors [41]. No U.S. studies were found that examined the impact of a specific complementary therapy on cancer survivor's workplace productivity. The present finding supports the potential efficacy of reflexology on reducing societal cancer costs in lost productivity.

Finally, coping with the diagnosis and treatment of breast cancer is stressful and complicated by fear, anxiety and other emotional issues [1]. Having support of family and friends is a critical and most beneficial ingredient to coping [40]. It is possible that reflexology delivered by friend/family caregivers had the added benefit of improving the women's mental health and keeping their mind off their illness. Such benefits cannot be monetized in economic evaluations of any intervention. In our study, both the intervention and control groups received minimal social interaction with the interviewer each week on the phone, thus the effect of reflexology was not due to Hawthorne effect [42].

## Limitation

To reduce interview burden, this study only assessed the health service utilization and expenditure at the end of the study and the study period was short (11 weeks). This timeframe is not long enough to fully evaluate the economic impact of the intervention. However, one difficulty in advanced cancer patient research is that attrition can potentially introduce bias in estimation of the intervention effects. To account for the 30% attrition rate in this study, inverse probability weighting was used to mitigate the potential selection bias, and the fact that the weighted and unweighted estimates lead to the same conclusion is reassuring in terms of robustness of findings. The 7-day clinical trial version of the HPQ was the only measure used to estimate the loss in productivity, due to the relatively short study period. However, the 7-day version of the instrument has been advocated and evaluated by the instrument developers [29]. In a longer-term study, say one year, we can use the 28-day version of the questionnaire to evaluate how productivity changes over time.

## Conclusion

The reflexology intervention delivered by friend or family caregivers can reduce some health service utilization and increase workplace productivity in a short-term period. The technique can be learned by friend and family caregivers, which has potential for reflexology to be an accessible means for cost savings to the health care system and employers. Longer-term evaluations would enhance the real-world applicability of the intervention on reducing costs and burden of cancer.

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## APPENDIX

#### Table A.

Demographic characteristics for patients retained versus lost by reflexologyand control group.

	Follow-up Status (N=256)		56)	R	eflexology (N=1	28)		Control (N=128	)
	Retained N=180 n (%)	Lost N=76 n (%)	p value	Retained N=89 n (%)	Lost N=39 n (%)	p value <sup>a</sup>	Retained N=91 n (%)	Lost N=37 n (%)	p value <sup>a</sup>
Metastatic cancer									
Yes	108 (60)	53 (70)	0.141	52 (58)	28 (28)	0.150	56 (62)	25 (68)	0.521
No	72 (40)	23 (30)		37 (42)	11 (72)		35 (38)	12 (32)	
Recurrent cancer									
Yes	53 (29)	23 (30)	0.896	29 (33)	12(31)	0.839	24 (26)	11 (30)	0.699
No	127 (71)	53 (70)	0.896	60 (67)	27(69)		67 (74)	26 (70)	
Therapy treatment									
Chemotherapy w/ or w/o hormonal therapy			0.006			<sub>0.210</sub> b			<sub>0.021</sub> b
Hormonal therapy	140 (78)	70 (92)		70 (79)	35 (90)		70 (77)	35 (95)	
only	40 (22)	6 (8)		19 (21)	4 (10)		21 (23)	2 (5)	
Race									
White	153 (86)	59 (78)	<sub>0.153</sub> b,c	74 (84)	31 (79)	<sub>0.748</sub> b,c	79 (88)	28 (76)	0.109 b, c
Black or African		12 (16)		8 (9)	5 (13)		6 (7)	7 (19)	
American	14 (8)	5 (7)		6 (7)	3 (8)		5 (6)	2 (5)	
Other	11 (6)								
Marital status									
Never married	13 (7)	14 (18)	0.024	6 (7)	8 (21)	0.071	7 (8)	6 (16)	0.275
Married	130 (72)	46 (61)		65 (73)	24 (62)		65 (71)	22 (59)	
Divorced/separated/wi dowed	37 (21)	16 (21)		18 (20)	7 (18)		19 (21)	9 (24)	
Relationship to caregiver									
Spouse or partner Child	105 (58)	36 (47)	0.312	53 (60)	17 (44)	0.122 b	52 (57)	19 (51)	0.723 b
Child or stepchild	29 (16)	13 (17)		16 (18)	5 (13)		13 (14)	8 (22)	
Friend	19 (11)	9 (12)		6 (7)	5 (13)		13 (14)	4 (11)	
Other	27 (15)	18 (24)		14 (16)	12 (31)		13 (14)	6 (16)	
Employment									
Employed (full- or part-time)	61 (34)	27 (36)	$_{0.098} d$	29 (33)	9 (23)	0.171	32 (36)	18 (49)	0.089 b,C
Retired	55 (31)	14 (18)		30 (34)	10 (26)		25 (28)	4 (11)	
Other	63 (35)	35 (46)		30 (34)	20 (51)		33 (37)	15 (41)	
Education									
High school graduate or some HS			$_{0.289} d$			0.812 C			0.073 <sup>C</sup>
Some college or 2-year degree									
4-year college	35 (20)	23 (30)		20 (23)	9 (23)		15 (16)	14 (38)	
graduate	52 (29)	21 (28)		23 (26)	12 (31)		29 (32)	9 (24)	
More than a 4-year	46 (26)	17 (22)		20 (23)	10 (26)		26 (29)	7 (19)	

	Follow-up Status (N=256)		Re	flexology (N=12	28)	Control (N=128)			
	Retained N=180 n (%)	Lost N=76 n (%)	p value	Retained N=89 n (%)	Lost N=39 n (%)	p value <sup>a</sup>	Retained N=91 n (%)	Lost N=37 n (%)	p value <sup>a</sup>
college degree	46 (26)	15 (20)		25 (28)	8 (21)		21 (23)	7 (19)	
	Mean (SD)	Mean (SD)	p value	Mean (SD)	Mean (SD)	p value d	Mean (SD)	Mean (SD)	p value <sup>d</sup>
Age, years	57.3 (10.9)	54.4 (11.4)	0.057	59.0 (11.0)	56.1 (12.8)	0.219	55.7 (10.5)	52.6 (9.5)	0.109
Number of comorbid conditions	4.7 (3.1)	3.7 (2.6)	0.014	4.6 (3.0)	3.9 (2.5)	0.209	4.7 (3.1)	3.5 (2.6)	0.028
MDASI symptom severity	41.0 (23.3)	49.4 (23.1)	0.009	41.4 (24.8)	51.6 (22.0)	0.022	40.7 (21.8)	47.0 (24.2)	0.173
MDASI symptom interference	20.2 (15.4)	27.7 (15.8)	0.001	20.1 (16.1)	27.3 (14.8)	0.017	20.3 (14.6)	28.1 (16.9)	0.016
PROMIS physical function	42.1 (7.6)	38.9 (8.0)	$_{0.003} d$	42.3 (7.0)	38.6 (8.3)	0.021 C	42.0 (8.1)	39.2 (7.8)	0.070
Quality of life index	21.8 (4.5)	20.5 (4.4)	<sub>0.029</sub> d	22.3 (4.3)	20.4 (4.2)	<sub>0.022</sub> e	21.4 (4.7)	20.6 (4.7)	0.391
Health Productivity Questionnaire	Media n (IQR)	Media n (IQR)		Mean (SD)	Mean (SD)	P-value f	Mean (SD)	Mean (SD)	P-value f
Absolute absenteeism in past 7 days	0 (15.0)	7.5 (26.5)	0.068	5.9 (17.5)	15.1 (14.0)	0.061	10.2 (18.5)	11.3 (26.1)	0.453
Relative absenteeism in past 7 days	0 (0.4)	0.4 (0.9)	0.031	0.1 (0.4)	0.5 (0.4)	0.017	0.3 (0.4)	-0.6 (3.5)	0.569
Absolute presenteeism in past 7 days	80.0 (30.0) <sup>g</sup>	80.0 (10.0) <sup>h</sup>	0.835	73.2 (23.7)	71.1 (17.6)	0.49 4	75.2 (20.3)	80.0 (15.8)	0.687
Relative presenteeism in past 7 days	1.0(0.3) k	1.0 (0.1) <sup>h</sup>	0.579	1.0 (0.4)	1.0 (0.2)	0.83 3	1.3 (1.7)	1.0 (0.1)	0.567

<sup>a</sup>Based on Chi-squared test.

<sup>b</sup>Base on Fisher exact test.

 $^{c}$ Data missing for one patients.

<sup>d</sup>Based on t-test with unequal variance.

<sup>e</sup>Data missing for two patients.

Based on Wilcoxon rank-sum test.

<sup>g</sup>Data missing for seven patients

h. Data missing for six patients

J. Data missing for four patients

*k*. Data missing for eight patients

#### **References:**

- 1. Di Lascio S, Pagani O (2017) Is it time to address survivorship in advanced breast cancer? A review article. The Breast 31:167–172. 10.1016/j.breast.2016.10.022 [PubMed: 27871024]
- Luo Z, Bradley CJ, Dahman BA, Gardiner JC (2010) Colon cancer treatment costs for Medicare and dually eligible beneficiaries. Health Care Financ Rev 31:35–50 [PubMed: 20191756]
- Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. CA: A Cancer Journal for Clinicians 67:7–30. 10.3322/caac.21387 [PubMed: 28055103]
- Ucuzal M, Kanan N (2014) Foot massage: effectiveness on postoperative pain in breast surgery patients. Pain Manag Nurs 15:458–465. 10.1016/j.pmn.2012.03.001 [PubMed: 24882025]
- Cleeland CS, Zhao F, Chang VT, et al. (2013) The symptom burden of cancer: Evidence for a core set of cancer-related and treatment-related symptoms from the Eastern Cooperative Oncology Group Symptom Outcomes and Practice Patterns study. Cancer 119:4333–4340. 10.1002/cncr. 28376 [PubMed: 24114037]
- Given CW, Bradley C, You M, et al. (2010) Costs of novel symptom management interventions and their impact on hospitalizations. J Pain Symptom Manage 39:663–672. 10.1016/j.jpainsymman. 2009.07.014 [PubMed: 20413054]
- Nipp RD, El-Jawahri A, Moran SM, et al. (2017) The relationship between physical and psychological symptoms and health care utilization in hospitalized patients with advanced cancer. Cancer 123:4720–4727. 10.1002/cncr.30912 [PubMed: 29057450]

- Wyatt G, Sikorskii A, Tesnjak I, et al. (2017) A Randomized Clinical Trial of Caregiver-Delivered Reflexology for Symptom Management During Breast Cancer Treatment. J Pain Symptom Manage 54:670–679. 10.1016/j.jpainsymman.2017.07.037 [PubMed: 28743659]
- Boon HS, Olatunde F, Zick SM (2007) Trends in complementary/alternative medicine use by breast cancer survivors: comparing survey data from 1998 and 2005. BMC Womens Health 7:4 10.1186/1472-6874-7-4 [PubMed: 17397542]
- Lengacher CA, Bennett MP, Kip KE, et al. (2006) Relief of symptoms, side effects, and psychological distress through use of complementary and alternative medicine in women with breast cancer. Oncol Nurs Forum 33:97–104. 10.1188/06.ONF.97-104 [PubMed: 16470237]
- Quattrin R, Zanini A, Buchini S, et al. (2006) Use of reflexology foot massage to reduce anxiety in hospitalized cancer patients in chemotherapy treatment: methodology and outcomes. J Nurs Manag 14:96–105. 10.1111/j.1365-2934.2006.00557.x [PubMed: 16487421]
- Cronfalk BS, Strang P, Ternestedt B-M (2009) Inner power, physical strength and existential wellbeing in daily life: relatives' experiences of receiving soft tissue massage in palliative home care. J Clin Nurs 18:2225–2233. 10.1111/j.1365-2702.2008.02517.x [PubMed: 19583654]
- Wilkinson S, Lockhart K, Gambles M, Storey L (2008) Reflexology for symptom relief in patients with cancer. Cancer Nurs 31:354–360; quiz 361–362. 10.1097/01.NCC.0000305756.58615.81 [PubMed: 18772659]
- Sharp DM, Walker MB, Chaturvedi A, et al. (2010) A randomised, controlled trial of the psychological effects of reflexology in early breast cancer. Eur J Cancer 46:312–322. 10.1016/ j.ejca.2009.10.006 [PubMed: 19906525]
- McVicar AJ, Greenwood CR, Fewell F, et al. (2007) Evaluation of anxiety, salivary cortisol and melatonin secretion following reflexology treatment: a pilot study in healthy individuals. Complement Ther Clin Pract 13:137–145. 10.1016/j.ctcp.2006.11.001 [PubMed: 17631256]
- Stephenson NLN, Dalton JA (2003) Using reflexology for pain management. A review. J Holist Nurs 21:179–191. 10.1177/0898010103021002007 [PubMed: 12794960]
- Stephenson NLN, Swanson M, Dalton J, et al. (2007) Partner-Delivered Reflexology: Effects on Cancer Pain and Anxiety. Oncology Nursing Forum 34:127–132. 10.1188/07.ONF.127-132 [PubMed: 17562639]
- Grealish L, Lomasney A, Whiteman B (2000) Foot massage. A nursing intervention to modify the distressing symptoms of pain and nausea in patients hospitalized with cancer. Cancer Nurs 23:237–243 [PubMed: 10851775]
- Stephenson NL, Weinrich SP, Tavakoli AS (2000) The effects of foot reflexology on anxiety and pain in patients with breast and lung cancer. Oncol Nurs Forum 27:67–72 [PubMed: 10660924]
- Magill L, Berenson S (2008) The conjoint use of music therapy and reflexology with hospitalized advanced stage cancer patients and their families. Palliat Support Care 6:289–296. 10.1017/ S1478951508000436 [PubMed: 18662423]
- 21. Ernst E (2009) Is reflexology an effective intervention? A systematic review of randomised controlled trials. Medical Journal of Australia 191:263–266 [PubMed: 19740047]
- 22. Ernst E, Posadzki P, Lee MS (2011) Reflexology: An update of a systematic review of randomised clinical trials. Maturitas 68:116–120. 10.1016/j.maturitas.2010.10.011 [PubMed: 21111551]
- Wyatt G, Sikorskii A, Rahbar MH, et al. (2012) Health-related quality-of-life outcomes: a reflexology trial with patients with advanced-stage breast cancer. Oncol Nurs Forum 39:568–577. 10.1188/12.ONF.568-577 [PubMed: 23107851]
- Wyatt G, Sikorskii A, Siddiqi A, Given CW (2007) Feasibility of a reflexology and guided imagery intervention during chemotherapy: results of a quasi-experimental study. Oncol Nurs Forum 34:635–642. 10.1188/07.ONF.635-642 [PubMed: 17573322]
- Maramaldi P, Dungan S, Poorvu NL (2008) Chapter 3; Cancer Treatments. Journal of Gerontological Social Work 50:45–77. 10.1080/01634370802137793 [PubMed: 18924387]
- Scott NW, McPherson GC, Ramsay CR, Campbell MK (2002) The method of minimization for allocation to clinical trials. a review. Control Clin Trials 23:662–674 [PubMed: 12505244]
- Wyatt G, Sikorskii A, Rahbar MH, et al. (2010) Intervention fidelity: aspects of complementary and alternative medicine research. Cancer Nurs 33:331–342. 10.1097/NCC.0b013e3181d0b4b7 [PubMed: 20467309]

- Kessler RC, Ames M, Hymel PA, et al. (2004) Using the World Health Organization Health and Work Performance Questionnaire (HPQ) to Evaluate the Indirect Workplace Costs of Illness. Journal of Occupational and Environmental Medicine 46:S23 10.1097/01.jom. 0000126683.75201.c5 [PubMed: 15194893]
- 29. Kessler RC, Barber C, Beck A, et al. (2003) The World Health Organization Health and Work Performance Questionnaire (HPQ). J Occup Environ Med 45:156–174 [PubMed: 12625231]
- Bayliss EA, Ellis JL, Steiner JF (2009) Seniors' self-reported multimorbidity captured biopsychosocial factors not incorporated into two other data-based morbidity measures. Journal of Clinical Epidemiology 62:550–557.e1. 10.1016/j.jclinepi.2008.05.002 [PubMed: 18757178]
- Cleeland CS, Mendoza TR, Wang XS, et al. (2000) Assessing symptom distress in cancer patients. Cancer 89:1634–1646. 10.1002/1097-0142(20001001)89:7<1634::AID-CNCR29&gt;3.0.CO;2-V [PubMed: 11013380]
- Cella D, Riley W, Stone A, et al. (2010) The patient-reported outcomes measurement information system (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. Journal of Clinical Epidemiology 63:1179–1194. 10.1016/j.jclinepi. 2010.04.011 [PubMed: 20685078]
- 33. Driban JB, Morgan N, Price LL, et al. (2015) Patient-Reported Outcomes Measurement Information System (PROMIS) instruments among individuals with symptomatic knee osteoarthritis: a cross-sectional study of floor/ceiling effects and construct validity. BMC Musculoskeletal Disorders 16:253 10.1186/s12891-015-0715-y [PubMed: 26369412]
- Ferrans CE (1990) Development of a quality of life index for patients with cancer. Oncology nursing forum 17:15–19; discussion 20 [PubMed: 2342979]
- Robins JM, Finkelstein DM (2000) Correcting for Noncompliance and Dependent Censoring in an AIDS Clinical Trial with Inverse Probability of Censoring Weighted (IPCW) Log-Rank Tests. Biometrics 56:779–788 [PubMed: 10985216]
- 36. American Cancer Society (2016) Cancer Facts & Figures 2016 | American Cancer Society https:// www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-factsfigures-2016.html. Accessed 16 Aug 2018
- Wong A, Azhar A, Cerana MA, et al. (2016) Characteristics of patients with unscheduled versus scheduled visits to outpatient supportive care center (SCC) at a comprehensive cancer center. JCO 34:144–144. 10.1200/jco.2016.34.26\_suppl.144
- Herman PM, Poindexter BL, Witt CM, Eisenberg DM (2012) Are complementary therapies and integrative care cost-effective? A systematic review of economic evaluations. BMJ Open 2:. 10.1136/bmjopen-2012-001046
- 39. Drummond MF, Sculpher MJ, Torrance GW, et al. (2005) Methods for the Economic Evaluation of Health Care Programmes, 3 edition. Oxford University Press, Oxford
- Williams F, Jeanetta SC (2016) Lived experiences of breast cancer survivors after diagnosis, treatment and beyond: qualitative study. Health Expect 19:631–642. 10.1111/hex.12372 [PubMed: 25953316]
- Ekwueme DU, Trogdon JG, Khavjou OA, Guy GP (2016) Productivity Costs Associated With Breast Cancer Among Survivors Aged 18–44 Years. Am J Prev Med 50:286–294. 10.1016/ j.amepre.2015.10.006 [PubMed: 26775908]
- McCarney R, Warner J, Iliffe S, et al. (2007) The Hawthorne Effect: a randomised, controlled trial. BMC Med Res Methodol 7:30 10.1186/1471-2288-7-30 [PubMed: 17608932]

#### Table 1.

## Baseline characteristics for patients

	All Patients (N=256)		Patients Remained	at Week 11 (N=180)	
	Reflexology N=128 n (%)	Control N=128 n (%)	Reflexology N=89 n (%)	Control N=91 n (%)	p value <sup>a</sup>
Metastatic cancer					
No	48 (37.5)	47 (36.7)	37 (41.6)	35 (38.5)	0.670
Yes	80 (62.5)	81 (63.3)	52 (58.4)	56 (61.5)	
Recurrent cancer					
No	87 (68.0)	93 (72.7)	60 (67.4)	67 (73.6)	0.361
Yes	41 (32.0)	35 (27.3)	29 (32.6)	24 (26.4)	
Therapy treatment					
Chemo/hormonal therapy	105 (82.0)	105 (82.0)	70 (78.7)	70 (76.9)	0.780
Hormonal therapy only	23 (18.0)	23 (18.0)	19 (21.3)	21 (23.1)	
Race					
White	105 (82.7)	107 (84.3)	74 (84.1)	79 (87.8)	0.772 <sup>b,c</sup>
Black or African American	13 (10.2)	13 (10.2)	8 (9.1)	6 (6.7)	
Other	9 (7.1)	7 (5.5)	6 (6.8)	5 (5.6)	
Marital status					
Never married	14 (10.9)	13 (10.2)	6 (6.7)	7 (7.7)	0.960
Married	89 (69.5)	87 (68.0)	65 (73.0)	65 (71.4)	
Divorced/separated/widowed	25 (19.5)	28 (21.9)	18 (20.2)	19 (20.9)	
Relationship to caregiver					
Spouse or partner	70 (54.7)	71 (55.5)	53 (59.6)	52 (57.1)	0.405
Child or stepchild	21 (16.4)	21 (16.4)	16 (18.0)	13 (14.3)	
Friend	11 (8.6)	17 (13.3)	6 (6.7)	13 (14.3)	
Other	26 (20.3)	19 (14.8)	14 (15.7)	13 (14.3)	
Employment					
Employed (full/part-time)	38 (29.7)	50 (39.4)	29 (32.6)	32 (35.6)	0.691 d
Retired	40 (31.2)	29 (22.8)	30 (33.7)	25 (27.8)	
Other	50 (39.1)	48 (37.8)	30 (33.7)	33 (36.7)	
Education					
High school degree/some HS	29 (22.8)	29 (22.7)	20 (22.7)	15 (16.5)	0.478 <sup>d</sup>
Some college/2-year degree	35 (27.6)	38 (29.7)	23 (26.1)	29 (31.9)	
4-year college graduate	30 (23.6)	33 (25.8)	20 (22.7)	26 (28.6)	
More than 4-year degree	33 (26.0)	28 (21.9)	25 (28.4)	21 (23.1)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p value <sup>e</sup>
Age, years	58.1 (11.6)	54.8 (10.3)	59.0 (11.0)	55.7 (10.5)	0.042
Number of comorbid conditions	4.4 (2.9)	4.4 (3.0)	4.6 (3.0)	4.7 (3.1)	0.814
MDASI symptom severity	44.5 (24.4)	42.5 (22.6)	41.4 (24.8)	40.7 (21.8)	0.846

	All Patients (N=256)		Patients Remained	Patients Remained at Week 11 (N=180)		
	Reflexology N=128 n (%)	Control N=128 n (%)	Reflexology N=89 n (%)	Control N=91 n (%)	p value <sup>a</sup>	
MDASI symptom interference	22.3 (16.0)	22.5 (15.7)	20.1 (16.1)	20.3 (14.6)	0.955	
PROMIS physical function	41.2 (7.6)	41.2 (8.1)	42.3 (7.0)	42.0 (8.1)	0.805	
Quality of life index	21.7 (4.3)	21.1 (4.7)	22.3 (4.3)	21.4 (4.7)	0.169	
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	p value <sup>f</sup>	
Absolute absenteeism in past 7 days	0 (0, 20)	5 (0, 20)	0 (4, 10)	4 (0, 20)	0.270	
Relative absenteeism in past 7 days	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.141	
Absolute presenteeism in past 7 days	80 (70, 90)	80 (70, 90)	80 (65, 90)	80 (60, 90)	0.833	
Relative presenteeism in past 7 days	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)	0.347	

MDASI = M.D. Anderson Symptom Inventory; PROMIS = Patient Reported Outcomes Measurement Information System; MSPSS = Multidimensional Scale of Perceived Social Support; SD = standard deviation; IQR = interquartile range (25<sup>th</sup>, 75<sup>th</sup> quantile).

<sup>a</sup>.Based on Chi-squared test

b. Data missing for two patients

<sup>c.</sup>Based on Fisher exact test

*d*. Data missing for one patient

e. Based on t-test with unequal variance

f. Based on Wilcoxon rank-sum test

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#### Table 2.

Health services utilization and expenditure at week 11 (N=180).

	Reflexology N=89 n (%)	Control N=91 n (%)	p value <sup>a</sup>
Had oncology visits	76 (85.4)	81 (89.0)	0.467
Had emergent care visits	15 (16.9)	20 (22.0)	0.385
Had hospital visits	23 (25.8)	36 (39.6)	0.050
Had other service visits <sup>C</sup>	64 (71.9)	73 (80.2)	0.191
	Median (IQR)	Median (IQR)	p value <sup>b</sup>
Number of oncology visits	4 (2, 6)	4 (2, 8)	0.605
Number of emergent care visits	0 (0, 0)	0 (0, 0)	0.314
Number of hospital visits	0 (0, 1)	0 (0, 2)	0.060
Number of other service visits <sup>C</sup>	2 (0, 7)	3 (1, 11)	0.054
Oncology expenditure	0 (0, 80)	0 (0, 100)	0.653
Emergency care expenditure	0 (0, 0)	0 (0, 0)	0.692
Hospital expenditure	0 (0, 0)	0 (0, 0)	0.323
Other service expenditure $^{\mathcal{C}}$	210 (7, 720)	279 (60, 829)	0.114
	Reflexology N=28	Control N=30	p value <sup>b</sup>
Absolute absenteeism in past 7 days	0 (0, 6)	2 (0, 10)	0.582
Relative absenteeism in past 7 days	0 (0, 0)	0 (0, 0)	0.365
Absolute presenteeism in past 7 days	90 (75, 95)	80 (60, 90) <sup>d</sup>	0.087
Relative presenteeism in past 7 days	1 (1, 1)	$1(1,1)^{e}$	0.161

IQR = interquartile range  $(25^{\text{th}}, 75^{\text{th}} \text{ quantile})$ 

<sup>a.</sup>Based on Chi-squared test

b. Based on Wilcoxon rank-sum test

<sup>C</sup>. Other service visits include laboratory visits, primary care provider visits, social worker visits, psychology visits, support group visits, nurse visits. Other expenditure in addition includes out of pocket expense for medication, personal care, special supplies and miscellaneous expense related to cancer care.

*d*. Data missing for three patients

e. Data missing for four patients

#### Table 3.

Effect of reflexology on having specific health services at week 11 (N=180)<sup>a</sup>

	Unweighte	ed, Unadjusted	Weighted, Unadjusted <sup>b</sup> Reflexology vs. Control(ref) <sup>c</sup>		
	Reflexology	vs. Control(ref)			
	OR 95% CI		OR	95% CI	
Oncology visits	0.72 [0.30,1.74]		0.96	[0.35,2.61]	
Emergent care visits	0.72	[0.30,1.51]	0.68	[0.30,1.52]	
Hospital visits	0.53	[0.28,1.00]	0.49*	[0.25,0.97]	
Other service visits $d$	0.63 [0.32,1.26]		0.80	[0.37,1.70]	
	Unweighted, Adjusted <sup>e</sup>		Weighted, Adjusted <sup>b,e</sup>		
	Unweight	ed, Adjusted <sup>e</sup>	Weighted	, Adjusted <sup>b,e</sup>	
	Unweight Reflexology	ed, Adjusted <sup><i>e</i></sup> vs. Control(ref) <sup><i>c</i></sup>	Weighted Reflexology	, Adjusted <sup><i>b,e</i></sup> vs. Control(ref) <sup><i>c</i></sup>	
	Unweight Reflexology OR	ed, Adjusted <sup>e</sup> vs. Control(ref) <sup>C</sup> 95% CI	Weighted Reflexology OR	, Adjusted <sup>b,e</sup> vs. Control(ref) <sup>C</sup> 95% CI	
Oncology visits	Unweight Reflexology OR 0.74	ed, Adjusted <sup>e</sup> vs. Control(ref) <sup>c</sup> 95% CI [0.27,2.06]	Weighted Reflexology OR 0.75	, Adjusted <sup>b,e</sup> vs. Control(ref) <sup>C</sup> 95% CI [0.24,2.34]	
Oncology visits Emergent care visits	Unweight Reflexology OR 0.74 0.71	ed, Adjusted <sup>e</sup> vs. Control(ref) <sup>c</sup> 95% CI [0.27,2.06] [0.30,1.68]	Weighted Reflexology OR 0.75 0.67	, Adjusted <sup>b,e</sup> vs. Control(ref) <sup>c</sup> 95% CI [0.24,2.34] [0.27,1.69]	
Oncology visits Emergent care visits Hospital visits	Unweight Reflexology OR 0.74 0.71 0.35**	ed, Adjusted <sup>e</sup> vs. Control(ref) <sup>c</sup> 95% CI [0.27,2.06] [0.30,1.68] [0.16,0.75]	Weighted Reflexology OR 0.75 0.67 0.30**	, Adjusted <sup>b,e</sup> vs. Control(ref) <sup>C</sup> 95% CI [0.24,2.34] [0.27,1.69] [0.13,0.66]	

OR = odds ratio; CI = confidence interval; ref = reference.

\* p<0.05

p < 0.01

\*\*\* p<0.001

a. Outcomes were dichotomized as zero versus one or more visit

*b*. Inverse probability weighting with the probability for remaining in the study by week 11 estimated by logistic regression using baseline covariates in Table 1

<sup>C.</sup>Baseline data missing for four patients

d. Other service visits include laboratory visits, primary care provider visits, social worker visits, psychology visits, support group visits, nurse visits

e. Adjusted by baseline covariates in Table 1.

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#### Table 4.

Effect of reflexology on absenteeism and presenteeism at week 11 (N=58)<sup>a</sup>

	Unweighte	d, Unadjusted	Weighted, Unadjusted <sup>b</sup> Reflexology vs. Control		
	Reflexolog	y vs. Control			
	Coefficient	95% CI	Coefficient	95% CI	
Absolute absenteeism in past 7 days	-2.23	[-9.41, 4.95]	-4.72	[-13.4, 3.94]	
Relative absenteeism in past 7 days	-0.13	[-0.35, 0.08]	-0.19	[-0.42, 0.04]	
Absolute presenteeism in past 7 days <sup>C</sup>	10.62	[-0.53, 21.78]	15.42*	[0.87, 29.98]	
Relative presenteeism in past 7 days $d$	0.11	[-0.06, 0.28]	0.16	[-0.04, 0.36]	

	Unweighte	ed, Adjusted <sup>e</sup>	Weighted, Adjusted <sup>b,e</sup> Reflexology vs. vs. Control (ref)		
	Reflexology	vs. Control (ref)			
	Coefficient	95% CI	Coefficient	95% CI	
Absolute absenteeism in past 7 days	-8.63	[-18.7,1.42]	-9.19	[-22.3,3.91]	
Relative absenteeism in past 7 days	-0.32*	[-0.60,-0.03]	-0.31	[-0.66,0.05]	
Absolute presenteeism in past 7 days <sup>C</sup>	10.82	[-1.75,23.4]	13.93	[-0.90,28.77]	
Relative presenteeism in past 7 days $d$	0.16	[-0.07,0.38]	0.19	[-0.01,0.40]	

CI = confidence interval; ref = reference.

p < 0.05

\*\*\*\* p < 0.001

<sup>a.</sup>Ordinary least squares estimation of linear regression. N=58 for those employed at week 11.

*b*. Inverse probability weighting with the probability for remaining in the study by week 11 estimated by logistic regression using baseline covariates in Table 1.

<sup>C.</sup>Data missing for three patients

*d*. Data missing for four patients

*e.* Adjusted by baseline covariates in Table 1