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ORIGINAL ARTICLE

Depression, mood, stress, and Th1/Th2 immune balance in primary breast cancer patients undergoing classical massage therapy

Michaela Krohn · Miriam Listing · Gracia Tjahjono · Anett Reisshauer · Eva Peters · Burghard F. Klapp · Martina Rauchfuss

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Abstract
Purpose Cancer patients frequently suffer from psychological comorbidities such as depression and elevated stress. Previous studies could demonstrate that cancer patients benefit from massage therapy on the physical and psychological level. This pilot study investigates the effects of massage on depression, mood, perceived stress, and the Th1/Th2 ratio in breast cancer patients.
Methods Thirty-four breast cancer patients were randomly assigned to a massage group (n=17) and a control group (n=17). Patients of the massage group received two 30-min classical massages per week for 5 weeks. At baseline, at the end of the intervention period, and 6 weeks after the end of intervention, patients of both groups completed the Perceived Stress Questionnaire (PSQ), the Patient Health Questionnaire (PHQ), and the Berlin Mood Questionnaire (BFS) and blood was withdrawn for determining cytokine concentrations and the Th1/Th2 ratio.
Results Twenty-nine patients were included in the statistical analysis. Depression (PHQ) and anxious depression (BSF) were significantly reduced immediately after massage compared to the control group. Stress (PSQ) and elevated mood (BSF) did not show significant alterations after massage therapy. Changes of cytokine concentrations and Th1/Th2 ratio were insignificant as well, although there was a slight shift towards Th1 in the massage group over time.
Conclusions Massage therapy is an efficient treatment for reducing depression in breast cancer patients. Insignificant results concerning immunological parameters, stress, and mood indicate that further research is needed to determine psychological and immunological changes under massage therapy.

Keywords Massage · Breast cancer · Stress · Depression · Cytokines · Th1/Th2 immune balance

M. Krohn · M. Listing · E. Peters · B. F. Klapp · M. Rauchfuss
Department of Psychosomatics and Psychotherapy,
Charité University Medicine Berlin,
Berlin, Germany

M. Listing · G. Tjahjono · A. Reisshauer
Department of Physical therapy and Rehabilitation,
Charité University Medicine Berlin,
Berlin, Germany

M. Krohn (✉)
Institute of Radiology, Charité University Medicine Berlin,
Charitéplatz 1,
10117 Berlin, Germany
e-mail: michaela.krohn@charite.de

Introduction

Cancer patients frequently suffer from psychological comorbidities such as depression and elevated perceived stress [1–3]. The increasing use of complementary and alternative medicine (CAM), especially by cancer patients, indicates that patients have requirements beyond an efficient medical treatment [4–6]. Studies suggest that CAM may have positive psychological and physiological effects, especially in cancer patients. However, results are contradictory and, to some extent, questionable, primarily due to weak study designs. Stress levels among cancer patients are higher than among matched healthy individuals or patients suffering from other diseases [1, 7, 8]. Chronic stress is associated with persistently elevated catecholamine and glucocorticoid levels, which both have a suppressive

effect on cellular immunity [9–11]. The effect of mood and depression on immunity is widely discussed. For example, many studies report a shift towards Th1 immune response in depressed individuals, while stressed individuals present a weaker Th1 immune response [9, 11, 12].

T helper (Th) cells, which play an important role in the activation or suppression of different immune system components, are differentiated according to their cytokine secretion. Th1 cells support immunity against tumors and infections with the help of cytokines such as interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α), and interleukin (IL) 2. Th2 cells mainly produce IL-4, IL-5, IL-6, and IL-10 and predominantly support humoral immune responses. Cytokine-based Th1/Th2 ratios reflect the immune balance and, therefore, represent immunity against tumors and infections [10]. Studies comparing the Th1/Th2 balance of cancer patients and healthy individuals have demonstrated that there is a Th1 deficit in cancer patients, while Th2 cytokine secretion was found to be increased in cancer patients [13]. These findings indicate that the functionality of the immune system, and especially the Th1/Th2 ratio, is highly relevant for cancer patients, although little is known about the involvement of immunological and psychological conditions in tumor development, progression, and metastasis. Changes of the Th1 and Th2 cytokine response under CAM, especially after massage therapy, have not been investigated so far.

Classical massage is one of the oldest and most frequently used complementary therapies, and it has become more and more popular during the past few years. It has proven to be an effective treatment for symptom relief for non-cancer patients [14]. Cancer patients reportedly benefit from massage therapy as well. They experience pain relief and reduction in nausea, fatigue, and other cancer-related symptoms [15]. Studies have shown that there is a measurable stress reduction under massage therapy in cancer patients; however, some studies found no significant massage effect concerning perceived stress [16–21]. Studies which analyzed depression and mood under massage therapy in cancer patients found inconclusive results [18–26]. Furthermore, a few studies indicate that there are measurable immunological changes following massage therapy [23, 26–32].

Altogether, these findings indicate that massage therapy may be beneficial for the cancer patient on the psychological and physiological level and that it is possibly underestimated as a complementary treatment in the context of psychooncological care and rehabilitation. Most of the above-mentioned studies only tested immediate massage therapy effects in patients receiving massage during chemotherapy or radiation therapy or in a palliative setting. Furthermore, there are no data concerning cytokine profiles under massage therapy. Therefore, this pilot study aims to investigate the short-term and long-term effects of classical massage therapy on cytokine responses and Th1/Th2 ratio, but also on depression, mood, and perceived stress in primary breast cancer patients to evaluate the relevance of classical massage therapy in the context of oncological care. However, this present study was conducted to primarily investigate feasibility of the study design and to evaluate measurability of effect sizes, especially concerning cytokine responses and Th1/Th2 immune balance in order to establish a basis for future studies testing massage in a comparable setting.

Methods

Participants

After obtaining the approval of the local ethics committee, 34 breast cancer patients were enrolled in the study. Inclusion criteria were tumor size ≤T2, nodal state ≤N2, and disease onset ≤4 years ago. Surgery, chemotherapy, and/or radiation therapy had to be completed at least 3 months prior to the beginning of the study. Exclusion criteria were distant metastases, lymphedema of arms or breasts, inflamed skin in the area of massage therapy, psychiatric diseases, and treatment with anticoagulants, cytostatics, corticosteroids, antidepressants or opioids. All participants were asked to sign a declaration of consent.

Study design

Thirty-four women were randomized into two groups by simple randomization. The massage group (n=17) received a 30-min classical massage therapy twice per week for 5 weeks. The control group (n=17) received standard medical care only. The study is structured by three analysis time points: before intervention (T1), at the end of the 5-week intervention period (T2), and 6 weeks after the end of intervention (T3) (Fig. 1). At these three time points, all participants completed the Patient Health Questionnaire (PHQ), the Berlin Mood Questionnaire (BSF), and the Perceived Stress Questionnaire (PSQ), and a blood sample was taken. The blood withdrawal took place at the same time of day for each patient at all three analysis time points. All blood withdrawals were conducted between 8 a.m. and 12 p.m.

Intervention

The classical massage therapy began 1 week after T1. During the 5-week intervention period, participants of the massage therapy group received 30-min classical massages twice per week, while the control group received standard medical care. All massages were performed by one licensed

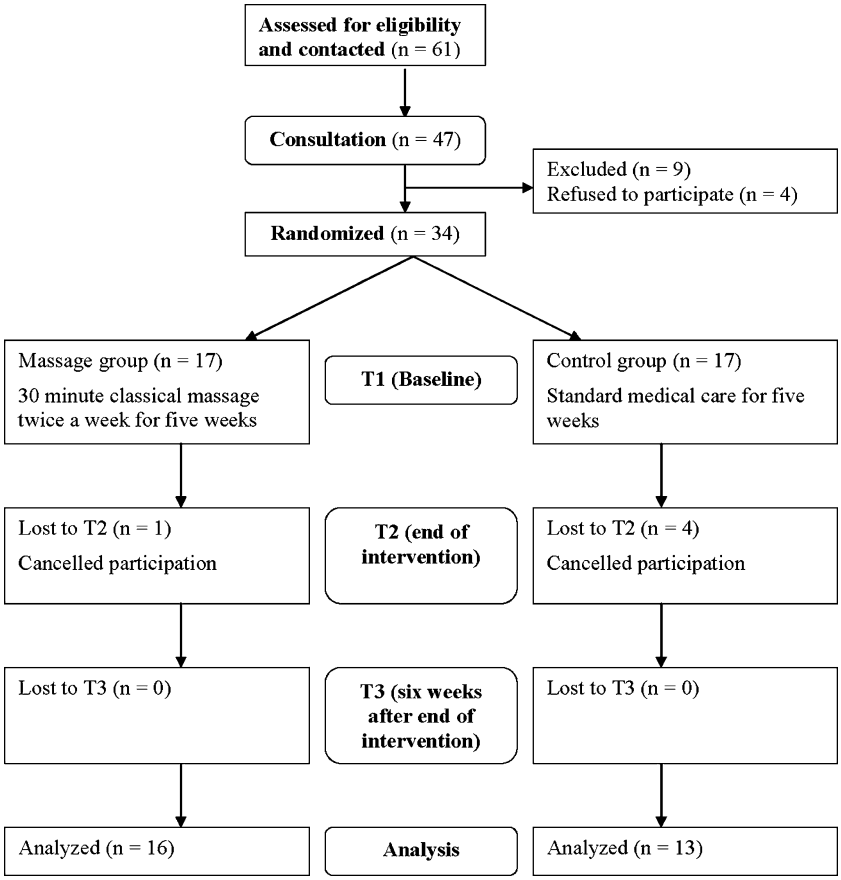

Fig. 1 CONSORT flowchart of participants at each stage of the trial

massage therapist throughout the whole study. Each massage was conducted in a quiet and private room. The patients were treated on a massage table, lying in a prone position. Massage therapy was applied according to a standardized protocol [33]. Stroking, kneading, and frictions were used to massage the following muscles: sternocleidomastoid muscles, trapezius muscles, rhomboid muscles, small neck muscles, supraspinatus muscles, teres major muscles, levator scapulae muscles, autochthonal back muscles, latissimus dorsi muscles, and pectoral muscles.

Questionnaires

The following questionnaires were assessed by self-administration. The patients were given an electronic handheld device by a study nurse, to whom they returned it after finishing the questionnaires.

Perceived Stress Questionnaire (PSQ) The PSQ was developed to assess the subjective experience of stressful situations on the cognitive and emotional level [34]. In this study, the German 20-item version of the PSQ was used [35]. It consists of the four subscales "worries", "tension", "demands", and "joy". For every subscale, five statements have to be rated according to the frequency of occurrence with the help of a four-point Likert scale. The sum scale is calculated from the raw item scores, which are linearly transformed into values between 0 and 100. High scores of the PSQ sum scale correspond to a high level of perceived stress.

Patient Health Questionnaire (PHQ) The PHQ is an instrument for screening, diagnosis and evaluation of disease severity of different psychiatric diseases. The depression score is derived from nine items of the depression module. Each statement has to be rated according to its frequency of occurrence within the last 2 weeks. The depression score is the sum of all nine items varying between 0 and 27. A score between 5 and 10 stands for a mild depressive disorder, a score over 20 represents a severe depressive disorder [36].

Berlin Mood Questionnaire (BSF) The BSF is a self report questionnaire of mood developed on the basis of the Profile of Mood States (POMS) [37]. The 30-item BSF measures six different mood states. Respondents rate on a five-point scale how intense they experience each mood. The scales are calculated from the raw item scores and linearly transformed into values between 0 and 4. For this study, the scales "anxious depression" and "elevated mood" were analyzed.

Immunological measures

For determination of cytokine concentrations, a Cytometric Bead Array (CBA) kit (Becton Dickinson, Franklin Lakes, NJ, USA) was applied. CBA is a method used to simultaneously measure TNF-α, IFN-γ, IL-2, IL-4, IL-5, and IL-10 in one sample with the help of a fluorescence activated cell sorter (FACS) analysis. After blood withdrawal, the heparinized blood samples were stimulated and incubated in a 37°C 5% carbon dioxide incubator for 24 h. After centrifugation, 70 µl of the cell supernatants were pipetted off and frozen in liquid nitrogen at −80°C.

Data analysis

Twenty-nine patients (16 in the massage group, 13 in the control group) were included in the efficacy analysis. One patient had to be excluded from the analysis of immunological data because of highly elevated Th1 cytokine concentrations, so that only 28 patients (15 in the massage group, 13 in the control group) were included into the immunological data analysis. Patients who dropped out were compared to the completers concerning their baseline characteristics. To compare groups at baseline, Pearson's Chi-square test was applied for categorical data, a *t* test for independent variables, and the non-parametric Mann–Whitney test was used for continuous data.

As massage therapy was conducted between T1 and T2, T2 is the most important timepoint in this present study, as it represents the timepoint for immediate massage therapy effects. Between T2 and T3, no massage was conducted, so that effects measured at T3 represent long-term massage effects. To compare the outcome of the questionnaires between the two groups at T2 and T3, an analysis of covariance (ANCOVA) with baseline status (T1) as covariable was applied. Paired *t* tests were applied to analyze changes of the assessment data within the massage group and within the control group over time. Additionally, effect sizes (ES) were calculated for psychometric data.

Because of a skewed non-normal distribution of the lab data, the Mann–Whitney test and the Wilcoxon test were used to compare the immune parameters. The Th1/Th2 ratio was generated by dividing the Th1 by the Th2 sum score. The Th1 sum score is the sum of the three Th1 cytokine concentrations TNF-α, IFN-γ, and IL-2. Accordingly, the sum of the three Th2 cytokines IL-4, IL-5, and IL-10 represents the Th2 sum score.

A p value of <0.05 was considered statistically significant. Statistical analysis was conducted with the help of the software program SPSS 14.0.

Results

Subjects

Thirty-four eligible patients with primary breast cancer were included in the study. The massage group showed no significant differences in sociodemographic and clinical data compared to the control group (Table 1). Twenty-nine patients completed the study. The five dropouts did not differ from the remaining 29 patients in terms of their sociodemographic and clinical data. One further patient had to be excluded from the analysis of immunological data due to highly elevated Th1 cytokines.

Table 1 Sociodemographic and clinical variables at baseline in the massage group ($n=17$) and in the control group ($n=17$); number of patients in each group is presented; percentage of patients in each group shown in brackets

Characteristics		Massage	Control	*p*
Age	Mean (SD)	59.5 (12.1)	59.9 (11.6)	0.92
Marital status	Married	7 (41.2%)	12 (70.6%)	0.37
	Divorced	3 (17.6%)	2 (11.8%)	
	Widowed	5 (29.4%)	2 (11.8%)	
	Single	2 (11.8%)	1 (5.9%)	
Stage	Ductal carcinoma in situ (DCIS)	5 (29.4%)	4 (23.5%)	0.57
	T1(tumor size ≤2 cm)	6 (35.3%)	9 (52.9%)	
	T2 (tumor size 2−5 cm)	6 (35.3%)	4 (23.5%)	
Nodal status	N0 (negative nodal status)	13 (76.5%)	14 (82.4%)	0.89
	N1 (≤3 positive axillary lymph nodes)	3 (17.6%)	2 (11.8%)	
	N2 (≤9 positive axillary lymph nodes)	1 (5.9%)	1 (5.9%)	
Surgery	Lumpectomy	12 (70.6%)	13 (76.5%)	0.70
	Mastectomy	5 (29.4%)	4 (23.5%)	
Treatments	Radiation	11 (64.7%)	12 (70.6%)	0.71
	Chemotherapy	5 (29.4%)	8 (47.1%)	
	Radiation and chemotherapy	4 (23.5%)	6 (35.3%)	

Depression

The group comparison at T2 (immediately after the massage intervention) resulted in a significant difference of PHQ scores between the massage and control groups ($F(1,18)=10.073$; $p=0.005$; ES=1.39). At T3, i.e., 6 weeks after the end of intervention, there was still a significant group difference to be found ($F(1,18)=12.02$; $p=0.003$; ES=1.51). Depression significantly decreased within the massage group during the intervention ($p=0.004$). At T3 (6 weeks after the end of massage therapy), the PHQ score of the massage group slightly increased again, but there was still a significant difference ($p=0.008$) compared to T1 (Fig. 2).

Anxious depression and elevated mood

Anxious depression showed a significant group difference at T2 ($F(1,23)=5.2$; $p=0.03$; ES=0.90). No significant group differences were found for anxious depression at T3 ($F(1,23)=1.89$; $p=0.18$; ES=0.29) and for elevated mood at T2 ($F(1,23)=1.97$; $p=0.17$; ES=0.55) and T3 ($F(1,23)=0.4$; $p=0.53$; ES=0.25). The BSF scale "anxious depression" showed a significant immediate ($p=0.018$) and sustained ($p=0.010$) decrease after massage therapy in the before–after comparison of the massage group. The BSF scale "elevated mood" significantly increased immediately after massage therapy in the before–after comparison of the massage group ($p=0.035$). However, no sustained effect (T3) was detectable for elevated mood (Fig. 3).

Perceived stress

No significant group differences were found concerning perceived stress at T2 ($F(1,25)=0.92$; $p=0.76$; ES=0.37) or T3 ($F(1,25)=0.36$; $p=0.55$; ES=0.23). In the before–after comparison of the massage group, perceived stress showed

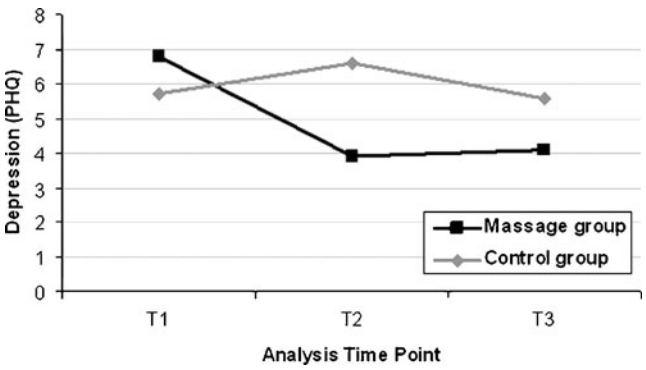

Fig. 2 PHQ score of massage group ($n=16$) and control group ($n=13$); mean scores of the three analysis time points presented. Scores ≤5 represent absence of depression, scores between 6 and 10 represent a mild depressive disorder, and scores ≥10 represent moderate to severe depression [36]

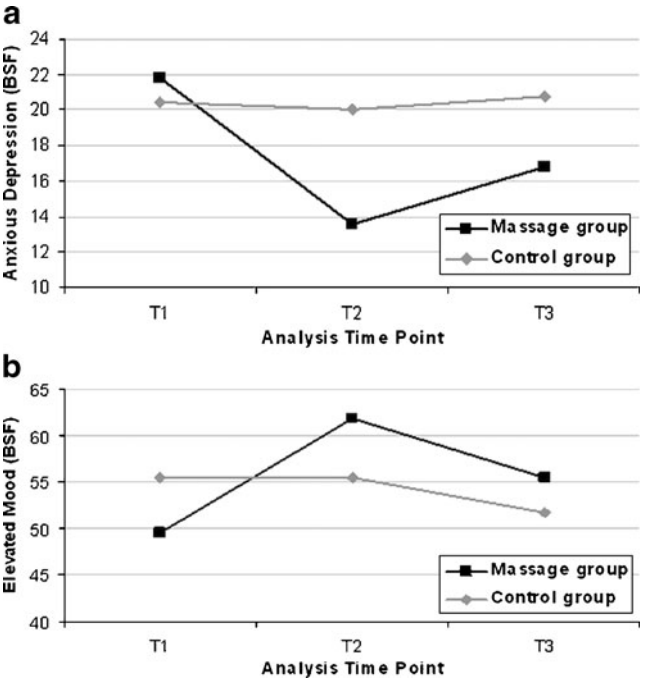

Fig. 3 BSF scales "anxious depression" (**a**) and "elevated mood" (**b**); mean scores of massage group ($n=16$) and control group ($n=13$); high scores of anxious depression represent high level of anxious depression; high scores of elevated mood imply a high level of elevated mood. In healthy subjects, the following scores (means) were reported: anxious depression 20.5; elevated mood 42.3 [44]

a significant decrease directly after massage therapy ($p=0.018$). At T3, the massage group still showed a significant difference compared to T1 ($p=0.024$). However, stress slightly decreased within the control group as well (Fig. 4).

Immunological parameters

The cytokines (TNF-α, IFN-γ, IL-2, IL-4, IL-5, and IL-10), the Th1 and Th2 sum scores, and the Th1/Th2 ratio showed no significant differences between the groups or in the before–after comparison within the massage group (Table 2). Nevertheless, there was a slight increase of the Th1 sum score and of the Th1/Th2 ratio in the massage group. Before–after comparisons of the control group revealed no significant changes of cytokine concentrations or Th1/Th2 ratio.

Discussion

This present study is the first study analyzing short- (T2) and long-term effects (T3) of classical massage on depression, anxious depression, elevated mood, and stress in breast cancer patients. We found a significant group difference concerning depression (PHQ) and anxious depression (BSF) immediately after massage therapy (T2). However, no significant group differences were found for

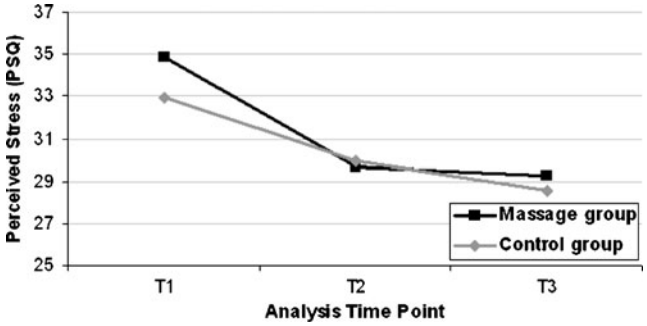

Fig. 4 PSQ sum score of massage group (n=16) and control group (n=13); low PSQ sum scores indicate low perceived stress; mean scores of the three analysis time points presented; in healthy subjects, a PSQ mean sum score of 33 was found [41]; therefore, the scores measured in this study are compatible with the mean PSQ scores of the general adult population

elevated mood. Concerning the PHQ and the BSF scale "anxious depression", we found an immediate (T2) and a long-term (T3) reduction after massage therapy in the before–after comparison, while "elevated mood" showed a short-term increase, which was not sustained over time.

Previous studies found contradictory results concerning reduction of depression and improvement of mood under massage therapy. Hernandez-Reif, Soden, and Cassileth et al. demonstrated that massage can significantly reduce depression, while other studies found no significant effect [18, 21–26]. Post-White, Ahles, and Kutner et al. found an improvement of mood disturbances [18–20]. The inconsistency of existing data may be caused by the choice of measuring instrument. Hernandez-Reif and Post-White et al. used a mood questionnaire (POMS), Cassileth and Wilkie et al. applied a visual analogue scale (VAS), and Kutner et al. used the mood scale of the Memorial Pain Assessment Card (MPAC). Soden, Corner, and Billhult et al. used the Hospital Anxiety and Depression Scale (HADS) and Ahles et al. applied the Beck Depression Inventory (BDI) and the POMS. HADS and BDI, like the PHQ, serve as instruments for detecting depressive symptoms, while the mood questionnaires and visual analogue scales measure present mood and mood disturbances. This present study utilized a screening instrument for depression (PHQ) and a mood questionnaire (BSF), so that the results have to be interpreted differentially. This study could show that massage therapy is able to significantly reduce depressive symptoms and that it has a mood-elevating effect. Soden et al., who applied the HADS, also found a significant reduction of depression in the before–after comparison of the massage group, whereas Ahles, Post-White, and Billhult et al. found no significant changes under massage therapy [18, 19, 22, 24]. However, our outcome validity is limited due to a small study population, although Ahles (n=35), Billhult (n=22), Corner (n=52), and Soden et al. (n=42) tested small study populations as well. The other studies predominantly assessed mood by applying a VAS, the POMS, and the MPAC, but not depressive symptoms. Nevertheless, most of these studies,

Table 2 Immunological parameters (mean, SD) of massage group (n=15) and control group (n=13) in picograms per milliliter; outcome measures are shown at baseline (T1), at the end of intervention (T2), and 6 weeks after end of intervention (T3)

Parameter	Group	Mean (SD)		
		T1	T2	T3
TNF-α	Massage group	3.20 (1.20)	4.86 (6.16)	3.04 (1.41)
	Control group	3.32 (1.22)	2.87 (1.46)	3.37 (1.29)
IFN-γ	Massage group	11.02 (6.71)	12.10 (8.13)	11.09 (10.93)
	Control group	10.53 (5.53)	9.01 (8.17)	12.37 (7.89)
IL-2	Massage group	7.02 (5.01)	8.13 (6.33)	5.44 (5.38)
	Control group	6.42 (3.64)	4.91 (5.10)	6.97 (4.93)
IL-4	Massage group	3.40 (1.67)	3.53 (1.72)	3.08 (1.80)
	Control group	3.23 (1.10)	2.86 (2.17)	3.68 (2.04)
IL-5	Massage group	2.17 (0.92)	2.19 (1.18)	1.98 (0.89)
	Control group	2.29 (0.69)	1.95 (1.09)	2.29 (0.98)
IL-10	Massage group	5.56 (2.10)	6.42 (3.08)	5.23 (1.80)
	Control group	5.57 (1.92)	5.26 (2.89)	6.01 (3.20)
Th1 sum	Massage group	21.24 (12.67)	25.09 (16.70)	19.56 (17.26)
	Control group	20.28 (9.77)	16.78 (14.52)	22.71 (13.72)
Th2 sum	Massage group	11.13 (4.53)	12.14 (5.62)	10.29 (4.25)
	Control group	11.49 (3.14)	10.07 (5.88)	11.97 (5.86)
Th1/Th2	Massage group	1.66 (0.79)	1.93 (0.82)	1.66 (0.79)
	Control group	1.83 (0.52)	1.56 (0.68)	1.98 (0.59)

as did our study, found an elevation of mood and a reduction of mood disturbances under massage therapy in cancer patients.

Unfortunately, no effect sizes were determined in the above-mentioned studies. Moyer et al. calculated effect sizes concerning depression and negative mood for studies which mostly tested massage therapy on other patient groups (non-cancer patients) and healthy persons. The average effect size for depression was 0.62, and the effect size for negative mood was 0.34 [38]. In our study, large effect sizes were achieved for depression (PHQ) immediately (ES=1.39) and 6 weeks after the end of the intervention period. A large effect size was also found for anxious depression (BSF) at T2 (ES=0.90). Weaker effect sizes were found for anxious depression at T3 (ES=0.29) and elevated mood at T2 (ES=0.55) and T3 (ES=0.25).

Concerning perceived stress, no significant group differences could be found at T2 or T3. The PSQ score decreased over time in both the massage group and the control group, but only the massage group showed a significant immediate and sustained reduction of stress. Our findings correspond to results of Ahles et al., who could demonstrate a stress reduction in cancer patients after massage therapy in the before–after comparison [18]. Corner and Wilkie et al. found no significant stress decrease after massage therapy [17, 21]. Ahles and Wilkie et al. applied the VAS for stress assessment, while Corner et al. used the Symptom Distress Scale (SDS) by Holmes and Dickerson. Several studies demonstrated positive massage effects on physiological stress parameters as heart rate, respiratory rate, and blood pressure in cancer patients [16–20, 39]. This stress-reducing effect is also reflected by studies that have measured a reduction of serum or salivary cortisol after massage therapy in cancer patients [40]. However, most studies that tested massage therapy effects in cancer patients found no cortisol decrease after massage therapy, although there are a lot of studies that found a significant decrease of cortisol under massage therapy that did not involve cancer patients [14, 16, 22, 23, 39].

In most of the above-mentioned studies, no effect sizes were determined. In the article of Moyer et al., effect sizes concerning physiological stress parameters under massage therapy in non-cancer patients were analyzed: the average effect size for blood pressure reduction was 0.25, the effect size for heart rate was 0.41 [38]. Kutner et al., who compared massage with healing touch, also analyzed effect sizes concerning physiological stress parameters and found moderate effect sizes of 0.55 concerning respiratory rate and an effect size of 0.60 for heart rate [20]. Studies that analyzed changes of cortisol concentration under massage therapy had a weak average effect size of 0.14 [38]. No effect sizes have been determined for perceived stress. In our study, the effect sizes concerning perceived stress are moderate at T2 (ES=0.37) but weak at follow-up (ES=0.23).

The stress reduction in both groups raises the question why the control group also showed a stress reduction, although no intervention was applied. This may be ascribed to the psychological support in the setting of the study. Furthermore, it should be considered that the mean PSQ scores measured in this study are comparable to PSQ scores of the general adult population, raising the question to what extent a decrease of perceived stress is possible and necessary [41].

Most of the above-mentioned studies included palliative cancer patients or patients undergoing radiation therapy or chemotherapy. Stress and depression scores of such patients, as well as responsiveness to intervention presumably differ from those of this study's participants, who have completed their therapy at least 3 months before, receiving massage therapy in an out-patient setting.

The improvement of psychometric parameters measured in this study may, aside from massage therapy itself, also be influenced by the massage therapist, as all patients were massaged by the same therapist throughout the whole study, which prevented participants from having to adapt to a new person each massage session. This indicates that classical massage also has a certain psychotherapeutic component arising from the therapist's attention [33]. Further investigation will be necessary to identify to what extent the psychological massage effects can be ascribed to the classical massage itself and what part the relationship to the therapist plays [33, 38, 42].

The effects of massage on Th1 and Th2 cytokines and on the Th1/Th2 ratio have never been investigated before. Th1 augmentations under massage therapy seemed to be higher than Th2 increases, which was also reflected by a slightly elevated Th1/Th2 balance after classical massage. However, none of these effects reached significance.

Previous studies found significant changes concerning immune cell counts and immune system activation after massage therapy, which may to some extent correspond to the slight increase of the Th1/Th2 ratio in this study. Most of these studies tested healthy subjects or HIV-positive patients; only Hernandez-Reif et al. included breast cancer patients [23, 26]. An elevated Th1 cytokine secretion is responsible for cellular immune system activation and, therefore, crucial for tumor immunity. For example, natural killer (NK) cell activity and NK cell cytotoxicity have been found to be increased after massage therapy [23, 29, 32]. Elevated NK cell counts, cytotoxic T lymphocyte counts, and overall lymphocyte counts have also been found after massage therapy [23, 26–32]. However, not all studies could demonstrate significant immunological changes under massage therapy [22, 39].

These findings reflect that massage therapy is able to enhance cellular immunity, indicating that it may be beneficial for the cancer patient. In this present study, no

significant effect of massage therapy on cytokine concentrations was found, possibly due to the small number of patients in the present study. On the other hand, there are still no definite data concerning physiological levels of cytokines and their changes under pathological conditions and therapeutic intervention [43]. Furthermore, cytokine levels may physiologically fluctuate or be elevated by coincident immunological processes as infections or chronic diseases, demonstrating that a detailed interrogation and a physical examination at each analysis time point has to take place to clarify the patient's health status at each analysis time point [43].

As mentioned in the "Introduction", this pilot study was conducted to test the feasibility of the study design and to evaluate the measurability of effect sizes, as future massage studies with a comparable setting are planned at the Charité University Hospital. Altogether, the study design is feasible and effect sizes concerning assessment data have been shown to be measurable. However, results concerning cytokines and Th1/Th2 balance indicate that the immunological focus of our planned study should be reconsidered.

Conclusion

In summary, classical massage therapy has been shown to significantly reduce depression in breast cancer patients. Therefore, an integration of classical massage into treatment and aftercare of primary cancer patients, particularly breast cancer patients, appears very recommendable according to the presented results. However, the results of this study are inconclusive concerning perceived stress and elevated mood. The insignificant shift of the Th1/Th2 balance towards a Th1 immune response is, to some extent, comparable to other studies that have found an augmentation of cellular immunity after massage therapy. Further research is needed to evaluate the efficacy of classical massage therapy concerning stress, mood, and immunity and to determine the mechanisms underlying the psychological and immunomodulatory effects of massage and other complementary therapies to evaluate the necessity and relevance of their integration into modern cancer treatment.

Conflict of interest None to declare.

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