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NATURAL KILLER CELLS AND LYMPHOCYTES INCREASE IN WOMEN WITH BREAST CANCER FOLLOWING MASSAGE THERAPY

MARIA HERNANDEZ-REIF
TIFFANY FIELD

Touch Research Institutes
University of Miami School of Medicine
Miami, Florida, USA

GAIL IRONSON

Department of Psychology
University of Miami School of Medicine
Miami, Florida, USA

JULIA BEUTLER

Office of Research
University of Miami School of Medicine
Miami, Florida, USA

YANEXY VERA

Touch Research Institutes
University of Miami School of Medicine
Miami, Florida, USA

JUDITH HURLEY

Sylvester Cancer Center
University of Miami School of Medicine
Miami, Florida, USA

MARY ANN FLETCHER

Department of Medicine EM Papper Laboratory
University of Miami School of Medicine
Miami, Florida, USA

SAUL SCHANBERG
CYNTHIA KUHN

Department of Pharmacology
Duke University Medical School
Durham, North Carolina, USA

MONICA FRASER

Biotone
San Diego, CA, USA

Women diagnosed with breast cancer received massage therapy or practiced progressive muscle relaxation (PMR) for 30-min sessions 3 times a week for 5 weeks or received standard treatment. The massage therapy and relaxation groups reported less depressed mood, anxiety, and pain immediately after their first and last sessions. By the end of the study, however, only the massage therapy group reported being less depressed and less angry and having more vigor. Dopamine levels, Natural Killer cells, and lymphocytes also increased from the first to the last day of the study for the massage therapy group. These findings highlight the benefit of these complementary therapies, most particularly massage therapy, for women with breast cancer.

One in seven women in the United States have a lifetime probability of developing breast cancer (Weir et al., 2003), which ranks as the second leading cause of cancer deaths in women (American Cancer Society, 2004). Women with breast cancer have been reported to have higher cortisol levels (Sephton et al., 2000; Van der Popme et al., 1998) and lower numbers of Natural Killer (NK) cells (Brittenden al., 1996; Luecken & Compas, 2002; Vgenopoulou et al., 2003). Cortisol is noted to destroy NK cells and has been associated

with tumor development (Ben-Eliyahu et al., 1999; Brittenden et al., 1996). Inasmuch as NK cells destroy tumor cells (Brittenden et al., 1996; Locke et al., 1984), interventions that reduce cortisol and increase NK cells would benefit women with breast cancer.

Women with breast cancer have been noted to benefit from relaxation therapy. In one study, those receiving chemotherapy reported being more relaxed and having improved quality of life following relaxation therapy (Walker et al., 1999). In another study, women with breast cancer showed an increase in NK cell activity (Gruber et al., 1993) following relaxation training along with guided imagery and EMG biofeedback. And in a study on women with advanced breast cancer, less pain was reported after participating in a combination of relaxation, visualization, and cognitive training. (Arathuzik, 1994). In these studies, it is difficult to determine which of the multiple techniques led to the positive changes.

Massage therapy has also been noted to increase Natural Killer cells. In a recent pilot study by the present group, women with early stage breast cancer who received massage therapy three times a week for five weeks (versus a standard care control group) reported reduced anxiety, depression and anger, increased urinary dopamine, serotonin and increased NK cells and lymphocytes (Hernandez-Reif et al., 2004). The increased dopamine and serotonin may have contributed to the increased NK cells and lymphocytes.

The present study added subjects to the massage group of the pilot study and compared the massage group to a relaxation therapy group in order to determine whether the positive effects of the pilot study were due to simple relaxation effects or whether massage itself (i.e., the moderate pressure stimulation of the skin) increased Natural Killer cells and lymphocytes. The sessions for the massage and relaxation groups were conducted on the same time-table of three 30-min sessions per week for five weeks. The data for the standard treatment control group were previously reported (Hernandez-Reif et al., 2004) and are presented again in the current article as a no treatment comparison group. A step effect was predicted, with massage therapy resulting in a greater increase in Natural Killer cells than relaxation therapy, which, in turn, was expected to lead to a greater increase than standard treatment alone.

METHOD

Participants

Fifty-eight women (M age = 53 years, SD = 11.6) diagnosed within the past three years with early stage (I–III) breast cancer were recruited. Following a

screening on exclusion and inclusion criteria, the women were assigned to a massage ($n = 22$), relaxation ($n = 20$), or standard treatment control group ($n = 16$). The groups did not differ on type of surgery (67% mastectomy). However, socioeconomic status (SES) and ethnicity differences were observed in the preliminary analyses, so these factors were covaried in the subsequent analyses (see Table 1).

Procedures

Following the university's human subjects approval, participants were recruited by (1) referrals from the attending physicians at the university's oncology clinic and a university cancer center, (2) responses to flyers distributed by a university support group, and (3) referrals or responses to flyers left at the university cancer center. Following informed consent the women were screened for eligibility using a semi-structured interview that included questions on mental and physical health, cancer stage, surgery and treatment, alcohol and illicit drug use, psychiatric problems, the use of beta-blockers or other medications that might affect the immune system, and other chronic medical conditions. Because surgery and radiation therapy have been shown to affect immune measures, participants were not entered into the study until they were at least 3-months postsurgery and/or had completed their last radiation and/or chemotherapy session. Eligible participants were then scheduled for baseline assessments and assigned to a (1) massage therapy, (2) progressive muscle relaxation therapy, or (3) standard treatment control group.

Table 1. Means for background variables (and standard deviations in parentheses) and type of surgery for massage therapy, relaxation and control groups

Variables	Groups			p-values	
	Massage	Relaxation	Control	F	X²
Age	53 (9.5)	54 (14.0)	53 (11.7)	.96	
SES	2.5 (.9)	3.2 (.8)	2.5 (.9)	.04	
Race and ethncity					.01
White (non-Hispanic)	73%	30%	75%		
White (Hispanic)	23%	45%	25%		
Black	4%	25%	0%		
Surgery					.11
Mastectomy	59%	5%	56%		
Lumpectomy	41%	15%	44%		

At the beginning and at the end of the five-week study period, participants provided a urine sample, had their blood drawn, and completed self-report measures. During the 5-week study period, the women assigned to the massage therapy group received three 30-min massages each week, and those assigned to progressive muscle relaxation listened to an audiotape describing the step-by-step relaxation procedure, which they practiced at home on the same schedule as the massage therapy group (30 min sessions 3 times a week for 5 weeks). The first and last day's sessions for the relaxation group were conducted in the authors' institute. The women in the relaxation therapy group were also given written instructions on the relaxation therapy, a calendar log to record the time of their relaxation sessions, and they were contacted on alternate weeks during the 5 weeks to check compliance. The logs were collected at the end of the 5-week period. The standard treatment control group received standard medical care (as did the other groups) and was assessed only at the beginning and end of the 5-week study. At the end of the study, women in the relaxation and control groups were offered complimentary massages.

Therapies

Massage Therapy. Women assigned to the massage therapy group received 30-minute massage sessions (3 massages per week for 5 weeks) conducted by different massage therapists who were trained on a protocol that had been effective in the authors' previous massage therapy study on breast cancer (Hernandez-Reif et al., 2004). The therapists were instructed to refrain from conversing during massage sessions (and to encourage the participants also to refrain from talking), except when asking questions about pressure and tender areas. The participants were accompanied to a small, quiet room and asked to undress (except for undergarments), and then make themselves comfortable in a supine position on a massage table that was draped with two cotton sheets. Soft pillows were used to maximize comfort to the breast area when lying prone.

Using unscented massage oil (Biotone Spa, Replenishing Light Massage Oil, San Diego, CA 92120), and with the participant in a supine position, the therapist massaged the following areas for 15 min: *NECK/FACE*—lengthening the neck (traction), stroking forehead, circular stroking and stretching jaw area; *SHOULDER*—pressing down on the shoulders with the palms of the hands and pressing mid-shoulder trigger points; *ARMS*—slow, progressive compressions from the armpit to the chest; compressions along the arm starting

at the shoulder and compressing 4–6 inches at a time to the wrist and return-
ing to shoulder again; circular movements with the flat of the hand to the
chest from the sternum to the armpit; and, stroking from the sternum to the
armpit and from the wrist to the shoulder; range of motion to each arm;
TORSO—placing one hand on the diaphragm, holding and gently rocking;
LEGS/FEET—holding both legs together at the heels and then pulling them
(traction), as well as pulling the legs together to the right and to the left;
massaging the bottom and top of the feet and squeezing the heel; stroking the
lower leg from the ankle to the knee; stroking and kneading of the anterior
thigh region; stroking from the hip to the foot. Asking the participant to
move into the prone position with a soft pillow under the breast area for
comfort, the therapist continued for 15 min massaging the following areas:
LEGS—flexion and extension of the foot; stroking and kneading the calf
muscles; shaking the leg with the knee flexed; stroking from the heel to up
and over the buttock; round stroking to the buttock area; stroking from the
buttock to the feet. *BACK*—with the hands positioned on either side of the
spine, stretching the back muscles by pressing outward to the sides (10 times)
and stroking from the base of the spine to the shoulders and out over the
arms; squeezing neck and shoulder areas, using the edge of the hand rubbing
alongside the spine from the top to the bottom of the back; squeezing and
stretching the neck muscles; pressing on the hip area; stroking from the shoulders
down the entire back and legs to the feet.

*Progressive Muscle Relaxation (adapted from Bernstein & Borkovec,
1973).* The participants assigned to this group practiced progressive muscle
relaxation for 15 sessions (3 sessions per week for 5 weeks) by following the
instructions on a 30-min audiotape. The tape was made available in English
and Spanish. The relaxation therapy session began by asking the participant
to remove her shoes, and in a supine position on the massage table (or her
bed at home) uncross her legs, loosen any tight clothing, and close her eyes.
While taking a deep breath, the participant was asked to tighten the muscles
of a particular area for 10 s. Then, while letting her breath out, she was asked
to relax the muscles and concentrate on how warm the muscles felt when
they were relaxed. The relaxation started with the feet and progressed to the
calves, thighs, abdomen, hands, arms, back, and face in that order. The in-
structions were repeated twice for each muscle group. The tape ended by
asking the participant to inhale slowly and exhale twice and then to take 5
min to concentrate on how relaxed her entire body felt. The first and last
relaxation sessions were conducted at the authors' institute to collect pre-post

baseline measures, and the women were asked to conduct the in-between sessions at home using the audiotape at the same time of day each time, 3 times a week for 5 weeks.

Standard Treatment Control Group. The participants assigned to this group came in only on the first and last days of the 5-week study to complete assessments, have their blood drawn, and provide a urine sample. At the end of the study period, the control group was offered complementary massages.

Assessments

Self-report Measures. On the first and last days of the 5-week study, the women completed scales that assessed immediate (pre-to-post session) and longer-term (first-to-last day) effects of the intervention on depression, anxiety, anger, vigor, and pain. Longer-term intervention effects were also evaluated by comparing the first and last day's pre-session measures.

Depressed Mood and Symptoms

Depressed mood and symptoms were evaluated using the Profile of Mood States (POMS) depression subscale and the depression subscale of the Symptom Checklist 90 Revised (SCL-90R). The POMS was used to assess the immediate effects of therapy on depressed mood and the SCL-90 R served to assess the longer-term effects on depressive symptoms.

On the *Profile of Mood States (POMS; McNair et al., 1971) depression items (15 items)* the participants rate their present feelings including "sad," "blue," "discouraged," "unhappy," and "helpless" (on a Likert scale ranging from [0] Not at all to [4] Extremely). A lower score indicates less depressed mood. The POMS has adequate concurrent validity and excellent internal consistency ($r = .95$; McNair & Lorr, 1964) and has been shown to measure adequately intervention effectiveness (Pugatch et al., 1969).

The Symptom Checklist 90 Revised (SCL-90R) Depression Subscale (Derogatis, 1983) is comprised of 15 problems causing distress during the past 7 days (including today) on a Likert scale of 0 (Not at all) to 4 (Extremely). Characteristic depression problems include "Feeling lonely," "Worrying too much about things," "Feeling no interest in things," "Feelings of worthlessness." A lower score is optimal. Internal consistency for the depression dimension of the SCL-90 R has been estimated as .90 and test-retest reliability as .82 (Derogatis, 1983).

Anxiety

Anxiety was assessed by having the women complete the State Anxiety Inventory (STAI) before and after their first and last sessions (immediate effects). Longer-term anxiety effects were examined by comparing the pre first day and pre last day measures on the STAI and by the SCL-90R anxiety subscale administered on the first and last days of the intervention.

The *State Anxiety Inventory (STAI; Spielberger et al., 1970)* includes 20 items including "I feel nervous," "I feel anxious," "I am tense," and "I am worried" that are rated on a feeling "right now" scale of 1 (Not at all) to 4 (Very much so). The STAI has adequate concurrent validity (Spielberger et al., 1970) and internal consistency ($r = .83$; Spielberger, 1972).

The *Symptom Checklist 90 Revised (SCL-90R) Depression Subscale (Derogatis, 1983)* includes 8 anxiety problems experienced over the past week such as "nervousness or shakiness inside," "suddenly scared for no reason," "feeling tense or keyed up," and "the feeling that something bad is going to happen" rated on a Likert scale of 0 (Not at all) to 4 (Extremely). The internal consistency for the anxiety dimension of the SCL-90 R is .85 and the test-retest reliability is .80

Anger and Vigor

The women also completed the *anger* and *vigor* POMS subscales pre and post sessions on the first and last day. Characteristic items on these 0 to 4 Likert scales include "angry," "annoyed," "bad-tempered," and "bitter" for the anger scale and "lively," "vigorous," "full of life," and "energetic" for the vigor scale. Adequate concurrent validity and internal consistency have been reported for the POMS subscales (McNair & Lorr, 1964; Pugatch, et al., 1969).

Pain

Pain perception and pain level were assessed on the *Short-form McGill Pain Questionnaire (SF-MPQ; Melzack, 1987)*, consisting of 11 questions on pain perception and 4 questions on pain level on a Likert scale from 0 = none to 3 = severe. This questionnaire has been shown to correlate with longer, standard pain questionnaires (Melzack, 1987). The SF-MPQ was given pre and post the first and last session of the study.

Neuroendocrine, Neurotransmitter and Immune Function Measures. Neuro-

endocrine and neurotransmitter levels were assayed from urine, and immune assays were made from blood samples collected at the beginning and end of the 5-week study. The participants provided fasting blood and urine samples, and to control for diurnal variations, these were collected between 9:00 and 11:00 in the morning on the first and last day of the 5-week study period.

Urine Assays. The urine samples were logged, frozen, and sent to Duke University School of Medicine (Drs. Schanberg and Kuhn) for assaying norepinephrine, epinephrine, dopamine, serotonin, and cortisol after correcting for creatinine levels. Catecholamines, cortisol, and serotonin metabolites (5-HIAA) were assayed by an RIA methodology using a 1251-labeled kit (Diagnostic Products Corp. Los Angeles, CA) following the instructions provided by the supplier. This method has intraassay and interassay coefficients of variation of 4% and 6%, respectively.

Immune Assays. These included NK cell number and NK cell cytotoxicity and were assayed using the whole blood chromium release assay as described by Fletcher et al. (1987). The NK sensitive erythroleukemia K562 cell-line was used as the target cell line. The assays were done in triplicate at four target-to-effector cell ratios with a 4-h incubation.

RESULTS

Data Reduction and Analyses

A multivariate analysis of variance (MANOVA) was conducted on the self-report data, covarying for SES and ethnicity (significant X^2s, see Table 1) and with treatment group (massage, relaxation, control) as the grouping factor. Following a significant MANOVA, $F(24,23) = 2.07$, $p < .05$, change scores (post minus pre scores) were computed to examine shorter-term (within session effects) and longer-term effects (first to last day's session) of the intervention across the treatment groups using ANOVAs and Bonferroni alpha corrected t-tests.

Depressed Mood and Depressive Symptoms

Immediate Effects. An analysis of variance (ANOVA) on the POMS depression first day change score (pre-to-post) revealed a significant group effect, $F(2,57) = 6.08$, $p < .05$. Bonferroni t-tests supported the predicted step effect pattern with the massage group reporting the greatest decrease in depressed mood scores followed by the relaxation group who, in turn, showed

a greater decrease in depressed mood scores than the control group (see Table 2).

Longer-term Effects. A significant group effect was attained for the ANOVA on the SCL-90R depression change score, $F(2,51) = 3.35$, $p < .05$. The Bonferroni *t*-tests revealed that the massage group had a greater change score on depressive symptoms than the control group. The massage versus relaxation group's change score was marginally significant ($p = .06$, one-tailed) (see Table 2).

Anxiety

Immediate Effects. An ANOVA on the STAI revealed a significant group effect on the first day's change scores, $F(2,56) = 8.15$, $p < .001$, and subsequent Bonferroni *t*-tests revealed reduced anxiety scores for the massage and relaxation groups when compared to the control group (see Table 2).

Longer-term Effects. The SCL-90R anxiety subscale change scores did not differ significantly among the three groups.

Table 2. Change score means (and standard deviations in parentheses) for the self-report measures for the massage therapy, relaxation and control groups

Measures	Massage therapy First day/last day	Relaxation First day/last day	Control group First day/last day
Depression			
POMS depression	$-7.2(8.5)_a/-3.0(5.6)_a$	$-4.2(5.2)_b/2.0(9.0)_a$	$-.1(1.9)_c/-.4(4.0)_a$
SCL-90 R depression	$-6.5(10.2)_a$	$-.8(13.8)_a$	$2.5(8.5)_b$
Anxiety			
STAI	$-10.7(10.2)_a/-8.8(7.4)_a$	$-6.6(6.9)_a/-5.1(9.8)_a$	$1.4(9.8)_b/-3.4(6.1)_{ab}$
SCL-90 R anxiety	$-2.2\ (6.2)_a$	$-.9(7.3)_a$	$.2(4.7)_a$
Mood			
Anger	$-7.3(7.9)_a/-2.6(6.3)_b$	$-3.5(4.3)_b/-1.1(4.3)_b$	$1.6(3.2)_b/-.7(2.6)_b$
Vigor	$.2\ (5.5)_a/2.9(4.9)_a$	$.4\ (3.5)_a/-0.1(3.7)_b$	$.9\ (5.2)_a/.8(3.5)_b$
Pain	$-3.8(4.1)_a/-1.0(1.2)_a$	$-2.5(3.3)_{ab}/-1.7\ (2.2)_{ac}$	$-.6(1.4)_b/.6(1.1)_b$

Note. Different letter subscripts denote the Bonferroni *t*-tests for significantly different means at $p < .05$. For example, the First Day POMS depression change score for the control group (–.1) differs from the massage (–7.2) and the relaxation groups' (–4.2) First Day change scores. And, the massage (–7.2) and relaxation (–4.2) groups' change scores also differ from each other and therefore they also have different subscripts.

Anger and Vigor

An ANOVA on the POMS anger change scores revealed a significant group effect for the first day, $F(2,55) = 4.81$, $p < .05$, with the Bonferroni t-tests revealing a greater decrease in anger scores for the massage than for the relaxation or control groups (see Table 2). A group effect was obtained for the vigor scale change scores for the last day of the study, $F(2,56) = 3.25$, $p < .05$. A greater increase in the vigor score was noted for the massage versus the relaxation group and the massage versus the control group (see Table 2).

Pain

ANOVAs revealed a significant main effect of groups on the pain change score for the first, $F(2, 56) = 4.50$, $p < .05$, and for the last day of the study $F(2,51) = 9.28$, $p < .001$. For the first day, pain score reductions were greater for the massage group than the control group, but the massage and relaxation group's change scores did not differ. For the last day, the Bonferroni t-tests revealed greater pain score reductions for the massage versus the control group and for the relaxation versus the control group (see Table 2).

Urine and Plasma Assays

Neuroendocrine and Neurotransmitter Assays. An inspection of the urine data revealed uneven distributions and large variances, so the data were analyzed via nonparametric statistics. Because there was not sufficient power, between group's analyses were not conducted. Instead, Wilcoxon signed rank paired sample tests were conducted for each group separately. These analyses revealed increased dopamine and serotonin (5-HIAA) levels for the massage group from the first to the last day (see Table 3).

Immune Assays. The immune data were also unevenly distributed. Therefore, the data were subjected to nonparametric tests, which revealed a modest and statistically significant increase in NK cells and lymphocytes for the massage group and a significant increase in NK cytotoxicity for the relaxation group (see Table 4).

DISCUSSION

In the current study, women with early stage breast cancer were assigned to a massage therapy, progressive muscle relaxation therapy or a control group,

Table 3. Mean change score/percent increase or decrease for the urinary measures for the massage therapy, relaxation and control groups

Measures	Massage Therapy	Relaxation	Control group
Urinary (ng/mL)			
Cortisol	13/19% ↑	101/79% ↑	6/3% ↓
Norepinephrine	7/10% ↑	−.25/2% ↓	31/74% ↑
Epinephrine	2/39% ↑	.35/31% ↑	1/17% ↑
Dopamine*	123/59% ↑ [1]	13/14% ↑	57/25% ↑
Serotonin (5-HIAA)*	837/36% ↑ [1]	903/23% ↑	61/2% ↑

Note: Change scores are computed by subtracting last day's value from first day's value. A positive change score reflects an increase in the measure from the first to the last day of the study, whereas a negative change score indicates a decrease. *Indicates that a positive change score is optimal. [1] = $p < .05$.

with the treatment groups receiving three 30-min sessions per week for 5 weeks. As compared to the control group, the massage and relaxation groups reported lower levels of depressed mood, anxiety, and pain immediately after their first session. Greater anger score decreases were noted for the massage group on the first day, and greater vigor score increases and pain score decreases were noted for the massage group after the sessions on the last day.

The authors had hypothesized step effects with massage therapy having the greatest benefits for women with breast cancer followed by relaxation therapy, which was expected to benefit the women more than a standard treatment alone. This step effect was noted in the already mentioned immediate

Table 4. Mean change score/percent increase or decrease for the immune measures for the massage therapy, relaxation and control groups

Measures	Massage therapy	Relaxation	Control group
Immune			
NK cell number	28/12% ↑ [1]	22/7% ↑	−18/7% ↓
NK cyctotoxicity	1.4/9% ↑	5/19% ↑ [1]	0/0%
Lymphocytes	3/9% ↑ [1]	.7/2% ↑	0/0%

Note: Change scores are computed by subtracting last day's value from first day's value. A positive change score reflects an increase in the measure from the first to the last day of the study, whereas a negative change score indicates a decrease. For all measures, a positive change score is optimal. [1]Indicates significant differences at $p < .05$ between first and last day's scores within group.

effects measures. The step effect was also evident in the long-term depression and anxiety measures, with massage being associated with longer-term reduction in depression and anxiety scores. Only the massage therapy group showed an increase in dopamine and serotonin from the first to the last day of the study. These findings are consistent with other massage studies reporting increased dopamine for women with anorexia (Hart et al., 2001) and bulimia (Field et al., 1998), and with pregnant women (Field et al., 1999), and increased serotonin (5-HIAA) levels following massage therapy for infants of depressed mothers (Field et al., 1996) and adults with migraine headaches (Hernandez-Reif et al., 1998). The dopamine increase may explain the massage group's enduring improved mood and the report of greater vigor in that dopamine is an activating neurotransmitter, influencing both behavior and movement. Dopamine might also contribute to enhanced immune function (Carr et al., 2003). The increased serotonin (5-HIAA) levels corroborate the improved mood following massage therapy and might also explain the reduced pain perception for this group (Grothe et al., 2004; Iyengar et al., 2002).

The pivotal finding in this study was the increase in NK cells and lymphocytes for the women with breast cancer who received massage therapy. Their clinical condition would be expected to improve inasmuch as NK cells are noted to destroy tumor cells (Brittenden et al., 1996). The positive effects of massage therapy on the immune system have been reported in several studies, including increased NK cell number and NK cell cytotoxicity in men with HIV (Ironson et al., 1996), increased NK cell number, CD4 and CD4/CD8 ratio in adolescents with HIV (Diego et al., 2001), and increased white blood count and neutrophil count in children with leukemia (Field et al., 2001). Taken together, these findings suggest a generalized boost to the immune system from massage therapy across varying age groups (children, adolescents, and adults), gender and conditions (cancer and HIV) and for at least two forms of cancer (leukemia and breast cancer). Relaxation therapy was associated with increased NK cell cytotoxicity, but not with increased NK cell production or increased lymphocytes, suggesting that although relaxation therapy is beneficial, massage therapy may be a more powerful treatment, even though it may not be as cost-effective as relaxation therapy. Stimulation of pressure receptors via massage therapy might be the underlying mechanism for the increased NK cells and lymphocytes. Stimulation of pressure receptors, such as in friction and stroking from massage, may decrease sympathetic and increase parasympathetic activity, leading to enhanced immune function (Diego et al., 2004). The role of relaxation therapy is less clear.

In sum, the findings from this study support the use of massage therapy for reducing depression, anger, anxiety, and pain in women with breast cancer. Moreover, the massage therapy group experienced an increase in dopamine, serotonin, NK cells, and lymphocytes. A future study with a larger sample might examine the relationship among these variables via path analyses. Support was also found for the use of relaxation therapy to reduce depressed mood, anxiety, and pain in women with breast cancer and increase NK cell cytotoxicity. These findings highlight the many benefits of these two complementary therapies, but most especially massage therapy, for women with breast cancer.

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