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13. ABSTRACT *(Maximum 200 Words)*
The objectives and specific aims of the ongoing study are to evaluate massage and relaxation therapies for an ethnically diverse group of women with early stages of breast cancer (Stages 1 and 2) for 1) decreasing anxiety, stress and stress hormones, 2) decreasing depressed mood and increasing serotonin (a biochemical that diminishes with depression) and 3) increasing Natural Killer cell number and cytotoxicity (immune measures that fight tumors and viruses). During the course of the three-year study, 60 women diagnosed with Stage 1 and 2 breast cancer will be recruited and assigned to a massage therapy (n=20), a relaxation therapy (n=20) or a control group (n=20). Women in the massage and relaxation therapies will receive 3 sessions a week for 5 weeks. On the first and last day of a 5 week period, self-report measures will be collected on anxiety and depression and women will submit a urine sample and have their blood drawn to assay treatment effects on stress hormones and immune measures. Findings thus far on a subsample of 46 women reveal for the massage therapy group 1) reduced anxiety, 2) improved mood, 3) increased serotonin and dopamine levels and 4) increased Natural Killer cell numbers and lymphocytes; for the relaxation group, findings include reduced anxiety and improved mood and increased lymphocyte percent. These preliminary findings are encouraging and provide support for the hypotheses that massage and relaxation therapies enhance mood and immune function for women with breast cancer.

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Table of Contents

Introduction

Breast cancer strikes approximately one in nine women in the United States (National Cancer Institute, 1999). A diagnosis of breast cancer is itself a stressor (Antoni, et al., 2001; Glanz & Lerman, 1992) as are concerns about personal, physical and psychological losses, such as the loss of intimacy and body image issues (Carver et al., 1998; Spiegel, 1996). Research reveals that cancer patients have elevated cortisol stress hormone levels (Van der Pompe, Antoni & Heijnen, 1996), reduced Natural Killer (NK) cell number (Brittenden, Heys, Ross & Eremin, 1996) and impaired NK cell cytotoxicity after surgery (Van der Pompe, Antoni & Heijnen, 1998). Although it is unclear if the cancer patient's elevated cortisol level lowers her NK cell number or vice-versa, that the cancer patient has higher cortisol stress hormone levels and an impaired immune function are of concern and suggest the need for intervention. The objectives and specific aims of the ongoing study are to evaluate massage and relaxation therapy effects for an ethnically diverse group of women with early stages of breast cancer (Stages 1 and 2) for 1) decreasing anxiety, stress and stress hormones, 2) decreasing depressed mood and increasing serotonin (a biochemical that diminishes with depression) and 3) boosting immune function (i.e., increasing NK cell number, NK cytotoxicity and lymphocytes). During the course of the three-year study, 60 women diagnosed with Stage 1 and 2 breast cancer will be recruited and assigned to a massage therapy (n=20), a relaxation therapy (n=20) or a control group (n=20). On the first and last day of a 5 week period, self-report measures will be collected on anxiety and depression and women will submit a urine sample and have their blood drawn to assay treatment effects on stress hormones and immune measures.

Body

Task 1

To date we have been successful in screening and training 8 female massage therapists. We have also been successful in developing relations at the breast health center on our medical campus where we have been recruiting participants for the study.

Task 2

To date we have been successful in screening and recruiting 54 women with Stage 1 or 2 breast cancer who met our inclusion/exclusion criteria.

Task 3

To date we have completed testing for 46 of the 54 women we recruited (n=5 dropped, 1 ongoing and 2 have been screened and are scheduled to start after they complete their radiation therapy).

Task 4

We have completed the construction of our data entry spreadsheet, entered data and conducted data analyses for the self-report measures for the 46 women who have completed the first and last day's measures of the 5-week study. We have also entered and analyzed the biochemical assays (urine) for the massage and control group and the immune measure assays (blood) for all three groups. We still have a batch of urine samples in the freezer that need to be assayed for the relaxation group. The results of the data analyses completed thus far are summarized below and presented in Table 1.

Participants

Forty-six women (M age = 53, sd = 11.2) diagnosed with Stage I or II breast cancer recruited from a university cancer center have completed the protocol. The ethnic distribution was 65% Caucasian, 31% Hispanic and 4% Black. The women were middle to lower middle socioeconomic status (M = 3.6 on the Hollingshead two-factor index). Participants were matched on support group and age and then assigned to a massage therapy group (N=18), relaxation group (N=12) or standard treatment control group (N=16). The massage is 30-minutes long, three times a week for 5-weeks. The relaxation therapy sessions are also 30-minutes long and 3 times a week and consist of progressive muscle relaxation (PMR).

Results

On the first and last day of the study, the women completed two self-report questionnaires to measure their anxiety levels (STAI) and mood (POMS). In addition, they provided urine samples, to assay for cortisol stress hormone and mood (serotonin -5HIAA and dopamine) levels and their blood was drawn to assay NK cell number, NK cytotoxicity and lymphocytes.

Data Analyses

A Multivariate Analysis of Variance (MANOVA) test yielded a significant group effect, F (32,52) = 1.71, p=.042 for the self-report measures. Because the lab is still working on assaying the urine samples and we did not have enough power, the biochemical data were not subjected to a MANOVA. The MANOVA on the immune measures yielded a marginal significant effect of group, F (16, 54) = 2.20, p = .06. Means and standard deviations are presented in Table 1 along with the alpha levels for data assayed or analyzed thus far. A summary of the results is presented in the next paragraph.

Immediately following the first session, a reduction in anxiety (STAI) and depressed mood (POMS) was reported by the massage therapy, STAI: t (17) = 5.47, p < .001; POMS: t (17) = 4.02, p = .001 and relaxation group therapy group, STAI: t (10) = 2.47, p = .03; POMS: t (10) = 2.62, p = .03, respectively. However, only the massage therapy group continued to report decreased anxiety and improved mood for the last day of the study,STAI: t (17) = 5.64, p < .001; POMS: t(17) = 2.33, p = .03. For the biochemical measures, the massage therapy group is revealing increased serotonin (5-HIAA), Z=1.64, p = .05 and dopamine levels, Z=1.49, p=.06, which correspond with the improved mood (Non parametric Wilcoxon Signed Ranks tests were conducted for the biochemical data because the data violated the assumption of normal distribution). The control group failed to show changes in self-reports or biochemistry levels (all ps > .05). A positive correlation was found between urine cortisol and anxiety (STAI) scores, r = .64, p < .001, n=26 suggesting that the higher stress hormone values were associated with higher anxiety scores. The immune measures analyses with the additional subjects reveal for 1) the massage therapy group a significant increase in NK cell numbers, t (15) = 2.01, p = .03, and lymphocytes, t (15) = 2.11, p = .025 2) the relaxation group an increase in

lymphocytes, t (9) = 2.49, p = .038 and 3) the control group no change in immune response, although there is a marginal trend toward a decline in NK cell number (p= .06) (see Table 1).

Discussion

The immediate psychological effects of massage therapy for women with breast cancer were decreases in anxiety and depressed mood on both the first and last days of the study. Similar massage therapy effects have been reported for other chronic illnesses including HIV (Diego, et al., 2001; Ironson, et al., 1996), multiple sclerosis (Hernandez-Reif, Field, Field & Theakston, 1998), fibromylagia (Sunshine, Field, et al., 1996) and chronic fatigue syndrome (Field, Sunshine, Hernandez-Reif, et al., 1997). The women in the massage therapy group also reveal increased serotonin and dopamine levels, which corroborate with their self-reports of improved mood. A reduction in serotonergic and dopaminergic activity has been implicated in depression (Weiss, Demetrikopoulos, West & Bonsall, 2000). The relaxation group is also showing decreases in anxiety and depressed mood but these are only revealed on the first day of the study. The effect of the relaxation therapy on the biochemical measures is unknown at this time but given the self-report measures, we predict that there may be no change from the first to the last day of the study. The treatment effects on immune measures revealed an increase in NK cell number and lymphocytes for the massage therapy group and only an increase in lymphocytes for the relaxation group. The increase in NK cell number supports an earlier HIV men's massage therapy finding (Ironson, Field, et al., 1996) and a recent HIV adolescent girls massage therapy study (Diego, et al., 2001). The increase in lymphocytes for the massage therapy group has not been previously reported and is important in that lymphocytes are precursor cells of immunological function as well as regulators and effectors of immunity. The increase in lymphocytes for the relaxation group, together with the reduction in anxiety and improved mood for the first day suggests that this intervention may also be effective for attenuating psychological and immunological symptoms associated with breast cancer. However, in that NK cell numbers were not affected by relaxation therapy and reduced anxiety was only observed on the first

day of the study suggests that relaxation therapy alone three times a week for 5 weeks may not be sufficient.

Recommended Changes

While it was our intention to conduct the 6-month follow-up assessments, we learned that some of the women continued receiving massages on their own after the 5-week intervention while others did not. In addition, those who continued receiving massages after the intervention ended were doing so at different rates. Thus, the follow-up data are uninterpretable and the sample size is too small to make sense of the effects of massage 6-months later. In place of the 6-month follow-up assessment we are suggesting to run a pilot group of women who would receive a sham massage (or light massage therapy) protocol to test the hypothesis that the increase in NK cell number we observed in the intervention was the result of applying pressure on the skin. We have designed and pilot tested a sham/light pressure massage therapy protocol. Once approval is given, we will revise the USARMY IRB protocol and submit for approval. The sham/light pressure massage (sham massage) will be conducted on the same time schedule as the massage therapy group. The sham massage group would be evaluated on the first and last day of the 5-week study using the same measures we are using for the other three approved groups. This sham massage group would allow us to compare light versus moderate pressure massage effects on the biochemistry and immune response of women with Stage 1 or 2 breast cancer . If the sham massage group does not show changes in the measures, then this would suggest that 1) the massage effects are not a placebo effect, and 2) massage may be stimulating deep tissue receptor cells, which underlie the cascade of events that lead to the positive changes in the biochemical and immune measures we are observing.

Key Research Accomplishments

- Screened 54 women with breast cancer.
- Completed treatment protocol for 46 of the 54 women (in addition we have one ongoing and two who are scheduled to start after completion of radiation therapy).
- Comparison of 1st versus last day's measures for women in the massage therapy group support our hypothesis including:
    - **a)** decreased anxiety and depression (or improved mood)
    - **b)** increased urinary serotonin and dopamine levels
    - **c)** increased Natural Killer cell numbers and lymphocytes
- Comparison of pre versus post 1st day's measures for women in the relaxation therapy group show
    - **a)** decreased anxiety and depression
- Comparison of 1st versus last day's measure for the relaxation group revealed
    - **a)** increased lymphocytes.

Reportable Outcomes

Manuscripts:

Hernandez-Reif, M., Ironson, G., Field, T., Katz, G., Weiss, S., Fletcher, M., Schanberg, S., & Kuhn, C. (2001). Breast Cancer patients have improved immune functions following massage therapy. (submitted manuscript).

Hernandez-Reif, M., Field, T., Beutler, J., Ironson, G., Hurley, J., Fletcher, M., Schanberg, S., & Kuhn, C. (2001). Breast Cancer patients show improved mood and increased lymphocytes following progressive muscle relaxation (manuscript in preparation).

Funding applied for based on work supported by this award:

1. Ovarian Cancer, Massage Therapy and Group Therapy, IDEA Award, DOD.
2. Prostate Cancer, Massage Therapy and Group Therapy, IDEA Award, DOD.

Conclusions

The findings thus far include for the massage therapy group: 1) reduced anxiety and depressed mood, 2) increased urinary serotonin and dopamine values for women in the massage therapy group and 3) increased lymphocytes and NK cell numbers. These findings support the hypothesis that massage therapy effectively attenuates multiple symptoms associated with breast cancer. Findings for the relaxation therapy group thus far include 1) reduced anxiety and depressed mood on the first session and 2) increased lymphocytes after three 30-min relaxation therapies a week for 5 weeks. The relaxation group's results suggest that this cost-effective intervention may also attenuate psychological and immunological symptoms associated with breast cancer. However, because relaxation did not increase NK cell numbers, which would be important for destroying virus-infected cells and tumor cells, this suggests that relaxation therapy alone may not be sufficient. Future studies might examine the effects of daily or longer progressive muscle relaxation therapy for enhancing these

immune functions. We are also hoping to conduct a pilot study that would examine potential underlying mechanisms for massage therapy effects, including the hypothesis that pressure might be critical for obtaining the positive findings we are reporting.

"So What"

If the findings are substantiated over the 3-year study, then this would suggest that massage therapy is effective for treating women with early stages of breast cancer. Massage therapy may then be offered as an adjunct therapy to attenuate the psychological, biochemical and immune changes associated with the disease. Moreover, massage therapy has little or no side effects, and is a safe and apparently positive treatment for women with breast cancer in that women in the treatment group continued with the massages on their own accord after the study period. Moreover, that we are finding positive effects of the relaxation therapy is encouraging as this cost-effective intervention can be conducted via an audiotape by women who cannot afford to participate in other more expensive or time-consuming therapies.

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Table 1. Means (standard deviations in parentheses) for the massage therapy, relaxation therapy and control group.

Variables	Massage		Relaxation		Control	
	FIRST Pre/Post	LAST Pre/Post	FIRST Pre/Post	LAST Pre/post	FIRST Pre/post	LAST Pre/post
Self-reports †						
Anxiety (STAI)	$36(13)_a/27(12)_b$**	$35(10)_a/25(8)_b$**	$35(15)_a/30(11)_b$*	$36(12)_a/32(13)_a$	$29(9)_a/30(6)_a$	$35(13)_a/32(9)_a$
Mood (POMS)	$11(11)_a/5(9)_b$**	$7(6)_b$*$/4(7)_b$*	$13(15)_a/8(13)_b$*	$11(16)_a/17(33)_a$	$5(9)_b/3(5)_b$	$8(10)_b/7(10)_b$
Biochemical						
Cortisol †	$156(49)_a$	$169(64)_a$			$224(154)_a$	$179(72)_a$
5HIAA ‡	$2157(1377)_a$	$3153(2235)_b$*			$3718(2847)_a$	$4055(3605)_a$
Dopamine ‡	$270(128)_a$	$312(83)_b$*			$230(139)_a$	$266(104)_a$
Immune Measures ‡						
NK Cell	$231(125)_a$	$259(93)_b$*	$313(121)_a$	$323(230)_a$	$254(90)_a$	$236(67)_b$*
NK Activity	$27(13)_a$	$28(13)_a$	$29(9)_a$	$32(14)_a$	$29(13)_a$	$30(16)_a$
Lymphocytes	$29(4)_a$	$32(7)_b$*	$28(7)_a$	$30(8)_b$*	$30(8)_a$	$31(8)_a$

† Lower scores are optimal; ‡ Higher scores are optimal. Different letter subscripts indicate signficant differences between adjacent means at the * $p < .05$, ** $p < .01$.