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13. ABSTRACT *(Maximum 200*

The Breast Research Initiative for DeterminiG Effective Skills for coping with Cancer (BRIDGES) consists of a prospective, randomized intervention trial with sixty women in each of three arms: 1) the UMASS mindfulness meditation-based Stress Reduction and Relaxation Program (SR&RP); 2) a nutrition education program (NEP) developed specifically for BRIDGES; and 3) a usual care control group. The 180 women under age 65 with Stage I or Stage II breast cancer enrolling into this randomized trial are being evaluated for: 1) psychological and behavioral indices of function and coping; 2) Quality of Life (QOL) measures: 3) compliance with the interventions and with medical treatment regimes; and 4) biochemical/immunological measures consisting of cytokines and melatonin. Analyses will be conducted to test hypotheses related to the three specific aims of the study: SR&RP effect on QOL; SR&RP & NEP effets on immune parameters; and durability/decay of intervention-related effects. As of 30 September 1996 the study had closely adhered to the Statement of Work agreed upon at the time the grant was awarded. Recruitment has maintained close to targeted levels. An additional sixth, and final cycle of the intervention will begin in January 1997. Most subjects (94%) who have been randomized and begun the study have been retained. All data have been collected as per protocol stipulations.

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Date

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INTRODUCTION

An increasing body of research literature has shown that psychological states have clear impact on recovery and quality of life in women with breast cancer. Psychosocial variables such as emotional expression, coping styles, and factors related to social support appear to have the most promise for improving quality of life and increasing the probability of prolonged survival. There also is a small body of evidence indicating that women with breast cancer receiving psychosocial interventions may derive a beneficial effect in respect to improved response and disease-free survival. Psychological distress seems to be particularly acute in younger women with breast cancer, a population that seems particularly amenable to psychosocial interventions. This is due, in part, to the fact that breast cancer tends to be a more aggressive disease of young ages and younger women have more concern with issues related to body image and major disruptions to typically very busy lives.

In light of these findings, there is an important need for the development of cost-effective psychosocial interventions for women with breast cancer. A successful intervention will be one that can reduce emotional distress, promote effective coping with diagnosis and treatment for breast cancer, and be useful and adaptable to the diverse population of younger women with breast cancer. The current study seeks to adapt the University of Massachusetts Medical Center's Stress Reduction and Relaxation Program (SR&RP) for younger women with breast cancer. The SR&RP is a well-established intervention program with demonstrated effectiveness in improving emotional status and quality of life in individuals with a variety of serious medical problems. The program is educationally based. Currently, it functions in inner city health clinics with diverse populations.

Our research addresses aspects of two of the fundamental research issues in psychosocial effects of breast cancer and the role of our well-recognized (but hitherto untested in this population of patients) SR&RP intervention in quality of life and status of immune parameters that may themselves be important in determining disease prognosis. Specifically, this research is designed to: 1) examine the psychosocial impact of breast cancer; and 2) identify techniques for delivering cost-effective care to facilitate recovery, improve immunological response, and improve quality of life after treatment for breast cancer.

Overall Goal

The primary goal of this proposal is to test the efficacy of the well-established, short-duration mindfulness meditation-based Stress Reduction and Relaxation Program (SR&RP) in women under 65 years old with newly diagnosed Stage I and Stage II breast cancer. The SR&RP intervention aims to influence a number of well-defined psychosocial factors which are suggested by a growing body of evidence as critically important for: adjustment to a potentially life-threatening diagnosis; enhancement of quality of life; and potentially, for enhancement of resistance to disease progression and survival in women with breast cancer. The study will

consist of a prospective randomized three-arm design with 60 women enrolled into each arm: 1) the SR&RP intervention, tailored to focus on issues specific to this population; 2) a nutrition education program (NEP) which will serve as an inactive attention control with regard to the psychosocial outcome measures and as a potentially active intervention with regard to effect on immune parameters (see Specific Aim 2); and 3) a usual care control group.

Specific Aim 1: To test the effect of SR&RP on Quality of Life (QOL), emotional awareness and expression, coping strategies and related perceptual and behavioral factors, and compliance with the intervention and with medical recommendations in women (under 65 years old) with newly diagnosed Stage I and II breast cancer. Because the SR&RP and NEP groups will have an equally intense group session component and the NEP group will receive none of the essential components of the SR&RP, the test between the two groups, SR&RP and NEP, will distinguish between the effect of the SR&RP intervention and non-specific group/therapist factors.

Primary Hypothesis: The SR&RP intervention will result in improved QOL and ability to cope, compared either to the NEP or to usual care alone.

Secondary Hypothesis: The SR&RP intervention will result in: a) improved perception of self and self in relationship to the world, as measured by increased self-esteem, sense of coherence, and decreased loneliness; b) a corresponding reduction in mood disturbance (e.g., anxiety and depression); c) increased use of active-behavioral and active-cognitive coping strategies, as measured by the Dealing with Illness Coping Inventory; and d) increased compliance with treatment regimens as compared to usual care alone.

Specific Aim 2: To test the relative effect of the SR&RP versus NEP and usual care on immune parameters specifically related to cytokines that activate Natural Killer (NK) cells and melatonin levels that may in turn affect response to breast cancer [Massion, 1995 #1390]. Because NK activity may be related to recurrence [Levy, 1991 #134] we have previously shown that low-fat diets enhance NK activity [Hebert, 1990 #313] and we have preliminary data that meditation may affect melatonin levels in women, we are particularly interested in relative differences between the two test groups, SR&RP and NEP, compared to usual care alone.

Specific Hypothesis: Relative to usual care, the SR&RP intervention will increase the immune responsiveness of Stage I and II breast cancer patients. This will result in an increase in the production of cytokines, e.g., Interleukins 2 and 4 (IL-2,4), which activate NK cells, and interferon (IFN) γ, which activates macrophages.

Specific Aim 3: To determine if the study effects (described in Aims 1 and 2), along with maintenance of the intervention practices, persist over 1-2 years of follow-up.

Specific Hypothesis: Psychosocial and immunological changes will be maintained over time and related to on-going practice of the SR&RP and NEP dietary practices, self-regulatory

strategies and behaviors.

WORK ACCOMPLISHED

It is important to note that when the grant was written, we stated that women who were under fifty years of age would be entered into our study. We have extended this criterion to include any women who is under sixty-five years old at time of diagnosis with breast cancer. The reasons for extending the age requirement are as follows: 1) typically women work until they are sixty-five years old, which means they lead lives as busy as those of women under age fifty in fact, we find they often are busier in respect to career development; 2) we found that these women also have concerns with issues related to body image; and 3) we had no reason to believe that these women would not obtain the same benefits from the interventions. The age of 65 years provides a natural and culturally widely appreciated demarcation between early middle age, and its concomitant demands and pressures, and late middle age, with its progressive decline in terms of life pressures.

Because the Statement of Work contained in effect at the time the grant was awarded, provides the framework for all activities undertaken since that time, we employ it here as the outline of all progress.

Task 1: Run-in Phase. Months 1-3

a. Additional focus groups and preliminary data will be gathered as needed.

   Weekly meetings were held for the first 6 months of the study. These were always attended by the four site coordinators and two Co-Principal Investigators from the University of Massachusetts. In the first 3 months, other investigators (mainly oncologists and surgeons) also attended the meetings. At these sessions, recruiting protocols were developed and patient communication and other issues were discussed and resolved. It was determined that sufficient preliminary data were collected prior to the grant application process in order to guide planning of the recruitment protocols and data collection instruments. Therefore, additional focus groups were not held.

b. Based on focus group and preliminary studies, introductory and booster (therapy) sessions will be developed so that the content of the program will be most useful to younger women with early stage breast cancer.

   Introductory and booster sessions were developed. We determined that there would be two introductory sessions for the SR&RP intervention. At these sessions, women discuss their experience with breast cancer and start learning about mindfulness-meditation. There are an average of twelve women in each of these classes. The size of the groups allows them to support one another's experiences and enables them to bond so that when they attend the SR&RP classes they are likely to know someone in their class. These sessions gives the

women a chance to meet and talk with other women who are experiencing the same illness. It also allows them to ask questions or talk about whatever is important to them. There are four booster sessions which are held after the standard SR&RP classes. At these sessions, women learn more about meditation and yoga, discuss their experiences in the SR&RP and continue to discuss their experiences with breast cancer. These sessions serve to review and reinforce what they have learned in the SR&RP and give the women a chance to talk about issues of personal concern to them.

c. The Nutrition Education Program will be developed using the recently funded Women's Health Initiative as an appropriate low-fat model.

The Nutrition Education Program (NEP) was to be developed using the recently funded Women's Health Initiative (WHI) as an appropriate low-fat model. It was decided that we could design and implement a low-fat intervention superior to that of the WHI. Therefore, we invested the necessary resources and developed a program specific to BRIDGES. The NEP consists of an overview of diet and health with an emphasis on how change in diet can affect well-being and how it broadens rather than narrows dietary options. The program is held at a location close to the University of Massachusetts Medical School in Worcester and consists of 14 weekly sessions each ninety minutes long. There is an additional session on a Saturday or Sunday which lasts six hours. The participants are asked to do various homework (cooking and nutrition) assignments which helps them to incorporate the program information into their daily life. At these classes the women do hands-on preparation and tasting of low-fat, high-fiber foods. They are taught alternative methods of creating and enhancing flavors including the use of spices and herbs. The transition to low-fat eating also entails increased consumption of vitamins and minerals. The role of these nutrients plus various spices in health is discussed. The individuals assigned to this intervention develop personal eating plans and dietary goals so that they reduce the amount of fat in their diet to less than twenty percent of the calories that they eat.

d. Instrument material will be piloted and finalized, where appropriate. Reliability tests will be conducted when necessary.

Because all instruments had been validated and checked for reliability in previous studies it was not necessary to conduct separate reliability tests for BRIDGES. All instrument materials were piloted and finalized as stipulated in the protocol. Most of the instruments are being used in our other studies and all have performed well in previous tests of validity and reliability. We omitted the interviewer-administered questionnaires (i.e., the Hamilton Anxiety and Depression Scales) because they were redundant to other self-assessment data. Copies of these instruments were included in the appendix of the original submission and modified forms currently in use in the study were included in the appendix of last year's annual report. Below is a list of instruments being utilized.

Baseline questionnaire Measures include: Background and Demographic Data: age; sex; marital status; education; number of children; number and dates of pregnancies; breast feeding history: (months for each child); and menopausal status (including surgical menopause). Personal Health History: present medical/psychiatric history and treatment (including history of exposure to estrogens, oral contraceptives, unusual menstrual problems). Family Health History: history of breast cancer; history of other cancers. General Self Care: sleep; exercise frequency; and smoking status.

Besides data collected on the baseline instrument we also administer these other questionnaires:

Beck Anxiety Inventory
Beck Depression Inventory
Sense of Coherence
Revised UCLA Loneliness Scale
Rosenberg Self-Esteem Scale
Functional Assessment of Cancer Therapy (FACT)
Mini-Mac Scale
Dealing with Illness
Marlowe-Crowe Social Desirability (MCSD) scale (Personal Reaction Inventory)
Symptom Check List
Social Readjustment Rating Scale
Social Approval
Seven Day Dietary Recall (7DDR)

e. An introductory video tape (to be used for recruitment) will be produced.

Dr. Ockene directed this task. During the weekly meetings (which were discussed in 1a) the purpose of the video, along with the content of the script, was discussed. The Project Coordinator and a representative from each site were videotaped. The video is five minutes long. It includes information about the funding source, why the study is important, and how the study is designed. It is shown to most of the women who are interested in joining the study. The video tape and script were included in the appendix of last year's annual report.

f. The Project Coordinator will be hired and trained in conducting phone and in-person interviews by Drs. Clemow and Massion.

The Project Coordinator, Susan Druker, was hired. Due to her skills in conducting interviews, the training session was not needed. Also, as noted above, we decided not to include in the battery of psychosocial instruments the Hamilton Anxiety Scale and the Hamilton Depression Scale. Both of those scales are administered verbally. Ms. Druker

worked with the three other site coordinators in developing numerous study protocols including ones for periodic interviewing.

g. A database to be used in the will be constructed.

This task has been completed. The biostatistician along with a research fellow developed a plan for our database. A research assistant, Jay Fowke, has been hired to work part time. He is at the University of Massachusetts pursuing a Ph.D. in Public Health.

h. Analysis of available run-in phase data will be done by Drs Hebert and Massion.
We have conducted process-related analyses (to assure data collection steps have occurred) and performed simple univariate analyses. Thus far all data are completed, within range, and have good internal logic. Jay's role is to develop a formal data management plan for BRIDGES. After identifying all the sources of data we are collecting, he created the data entry programs for all data not collected via optically scanned instruments. Along with the biostatistician he determined the location of data entry-files, the choice of data entry personnel, the timetable for data entry, quality assurance steps, and timing and the backup and archiving of the analytic data entry steps.

Task 2: Recruitment. Months 4-21:

a. 180 women (age <65 years) with Stage 1 or 2 breast cancer from Worcester, Ma and Providence RI will be recruited as participants for the study.

Currently, 161 individuals have been enrolled into the study. As discussed previously, we extended the age eligibility to women who were diagnosed with Stage 1 or 2 breast cancer at age 65 or less. We will finish recruiting women on 31 December 1996. It is anticipated that we will achieve our goal of 180 women. A patient brochure was developed along with a letter that is signed by one of their physicians in order to assist with recruitment.

b. Baseline measures will be taken on all study parameters as stated in the protocol.

A baseline questionnaire was developed as described in last year's report. The following anthropometric measures continue to be taken at baseline: height; weight; sitting height; and waist and hip circumference. Blood also was drawn and a twenty-four hour urine was collected. The medical questionnaire continues to be used to collect information on: date of first positive cytology or positive biopsy; if individual had radiation, when and if there were major complications; what type of surgery was performed (i.e. lumpectomy alone, mastectomy, etc); histology; tumor size; tumor grade; tumor diffentiation; axillary nodes samples; estrogen/progesterone receptor concentrations; stage of breast cancer and information about their chemotherapy treatment. A nutritional assessment is completed by all

participants. For this, we are using a seven-day diet recall(7DDR).

c. Study subjects will be randomized into one of the three arms of the study 1) Stress Reduction and Relaxation (SR&RP); 2) Nutrition Education Program (NEP), and 3) Usual supportive care(UC).

Study subjects are randomized into one of the three arms of the study 1) the Stress Reduction and Relaxation (SR&RP); 2) the Nutrition Education Program (NEP), and 3) Usual supportive care (UC). We call the UC arm, the Individual Approach Condition and state in our patient brochures that they choose whatever strategy to cope that they think is best for them. An eligibility requirement form that was developed continues to be used. Of the 161 subjects randomized 53 are in SR&RP, 56 are in NEP and 52 are in UC.

Task 3: Intervention. months 6-27;

a. Participants will become involved in the intervention arm to which they are randomized. The SR&RP and NEP will be given four times per year at UMMC.

The interventions are given three-times per year. Five interventions have been offered, all lasting 14 weeks. One more intervention will be offered next year. We decided to add another interention in order to achieve our goal of recruiting 180 women. This decision was reached due to two of the participating institutions falling short of their recruiting goals. Each institution was to recruit 45 women. One institution, because of the distance to the University of Massachusetts Medical Center, only recruited 16 patients. The other institution which fell short of their goal recruited 30 patients. The women involved in SR&RP and NEP give rave reviews of the interventions. We contact them on a monthly basis to obtain feedback and, without exception, everyone states very positive things about being involved in the study.

b. Just prior to the interventions (or time-controlled for the women randomized to usual care) all parameters (except immuno-endocrine measures and diet) assessed at baseline will be reassessed.

Because of budgetary restrictions prior to final approval, we reduced measurements from five to four times over the period of each woman's involvement. To make best use of these data, we decided that all baseline measures (see 2b) would be taken just prior to the interventions. Therefore, there was no need to reassess these measures prior to the interventions. We have collected 152 baseline measures, 123 four month measures, and 98 one year measures.

c. The SR&RP group will receive the standard SR&RP segment plus additional therapy sessions for a total of fifteen sessions.

The SP&RP group receive the standard SR&RP segment plus additional therapy sessions for a total of fifteen sessions. As stated previously, two introductory sessions plus four booster sessions are required for all women who enter the SR&RP arm of the study. For more information see 1b.

d. The NEP group will receive their intervention on approximately the same schedule as women in the SR&RP arm of the study.

The NEP group receives their intervention at the same time as the women in SR&RP. Nutrition classes and SR&RP classes last for fourteen weeks and begin and end at the same time.

Task 4: Follow-up months 8-46;

a. All participants will be assessed just after the intervention (or time adjusted for all women in the UC) and at twelve months and twenty four months after recruitment. Assessment will include all the psychological and quality of life measurements, as well as immuno-endocrine parameters and the nutritional assessments. At twelve months melatonin will be assessed. Nutrition assessments will be made only at the twelve month and twenty four-month post recruitment points in order to account for seasonal differences in dietary intake.

All participants are assessed just after the intervention (or time adjusted for all women in the UC) and at twelve months and twenty-four months after baseline. Assessment includes all the psychological and quality of life measurements, as well as immuno-endocrine parameters and the nutritional assessments. At four and twenty-four months, melatonin is assessed. Nutrition assessments also are made at four months, twelve months, and twenty-four months after baseline. We decided to do the nutritional assessment at four months because the information gathered provides us with data as to whether women have changed their diet immediately subsequent to the intervention. Monthly phone calls also are utilized to gather data. It is during these phone calls that we check for compliance with the SR&RP protocol.

Eleven (6%) individuals have dropped out of our study. We estimated that our retention rate would be 80%. Our high retention rate is due to the positive response of our patients to this study.

b. Ongoing data collection, review for completeness, and preliminary testing of study hypotheses will occur.

All site coordinators review the questionnaires which are returned for completeness. The process of entering the data is ongoing. Much of the data are optically scanned. If there are any unanswered questions in the baseline instrument or medical questionnaire, we ask the individuals to answer these questions over the phone.

Task 5: Final Data Analysis, Months 47-51

a. Perform all exploratory analyses to test for adherence to model assumptions.
b. Perform all data simplification tasks (e.g. principal components analysis).
c. Test study hypotheses.
d. Conduct post-hoc analysis of study data.
e. Prepare manuscripts.

In our first annual report we stated that except for e., where we are preparing manuscripts, based on preliminary data [Clemow, 1995 #1319; Massion, 1995 #1390] or theoretical considerations [Hebert, 1996 #1391], there has been no activity because we are in month 24 of the project.

In the second year two book chapters have been written where BRIDGES is discussed. The first book chapter is in the Textbook of Psycho-oncology (Kabat-Zinn J, Massion AO, Hebert JR, and Rosenbaum E. In press 1997). The book chapter describes the SR&RP intervention and its application in oncology. BRIDGES is mentioned as an ongoing study. No data is provided from the BRIDGES study; it is mainly descriptive.

The second book chapter is in Melatonin in Psychiatric and Neoplastic Disorders (Massion AO, Teas J, Hebert JR. In press 1997). The book chapter discusses our hypotheses about melatonin and meditation. BRIDGES is discussed and preliminary data are provided.

We also may be presenting an abstract at the Society for Behavioral medicine meeting in March, 1997. This would be a preliminary report (n = 75) of baseline and four month scores on psychosocial measures.

James Hebert was invited by the editor of Advances to provide comments to an article written by Keith Block. Dr. Block runs an alternative cancer treatment center in Illinois. Dr. Hebert provides an epidemiologist's view of Block's challenge by discussing his role as a reviewer of Department of Defense breast cancer grant applications and the grant application review process. BRIDGES is briefly mentioned (Hebert, In press 1997).

CONCLUSIONS

In summary, progress in the second year of this grant has been excellent. All of the deliverables that were promised have been completed successfully, recruitment figures are on track, and retention is excellent. Governance for the study has worked very well with most executive decision making happening in a small working group consisting of Drs. Hebert and Massion and Ms. Susan Druker. In some instances our decisions are provisional on their being broadcast to investigators at UMMC and other sites for final approval. Day-to-day operational issues have been decided mainly in the site coordinator's working group which is chaired by the Project Coordinator/UMASS Site Coordinator, Ms. Susan Druker. Because Susan Druker is a member of both of the functioning working groups, communications within UMMC site and across the four sites have been extraordinarily smooth and efficient. The overall Steering Committee Meeting has occurred twice in the second year. Occasionally, an executive decision has come out of these meetings. However, it has transpired that its main purpose is to provide information to investigators at the other sites and to rekindle enthusiasm in the study. Although there was no place to mention this above, it should be noted that the enthusiasm level for study and the dedication about which people feel regarding their own involvement and involvement in their patients has never been higher in any study with which I have been involved.

One of our major concerns in designing this study concerned issues around the asymmetry of intervention conditions where blinding is not possible. In the years of meetings before we formally proposed this study, we spent more time on this issue than anything else. Our concern was that an obvious imbalance between the intervention conditions would either lead to a low recruitment rate or there would be large differential dropout after women were randomized. With about 90% of total recruitment currently completed and having begun the fifth cycle of interventions, we can confidently say that this has not been a problem. Currently, we are working on a manuscript that discusses issues around behavioral interventions that cannot be blinded. We feel that the experience of the BRIDGES Study provides practical lessons in how to deal with this ubiquitous, very obvious, and little attended to problem.

We hope that the extraordinary successes of the first year of the BRIDGES Study will continue for the remaining three years. I appreciate the opportunity to convey the excellent progress that we have had to date.

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