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Psychological research documents that the psychosocial burdens following breast cancer are notable in number, severity, and scope. A biobehavioral model of cancer stress and disease course has been proposed (see Andersen, Kiecolt-Glaser, & Glaser, 1994) and provides a conceptual basis for the proposed research. We are testing the model with a clinical trial: 235 women with stage II or III breast cancer who have been diagnosed and recently surgically treated are randomized between two conditions: (1) assessment and intervention, or (2) assessment only (control). In addition to documenting the quality of life benefits of a psychological intervention, this study provides an experimental test of the psychological and behavioral variables which may influence health outcomes directly. Further, we test specific mechanisms--alteration in immune and endocrine functions--to achieve beneficial health effects for women with breast cancer.

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Barbara Andersen 8/15/98

PI - Signature Date

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INTRODUCTION

Purpose and Background of Previous Work

We have proposed a biobehavioral model of cancer stress and disease course (see Andersen, Kiecolt-Glaser, & Glaser, 1994, for a full discussion). The model identifies the psychological and behavioral factors and the biologic mechanisms by which health outcomes and cancer progression might be influenced. This model provides the conceptual basis for the proposed research (**see Fig. 1**). The present study is a randomized clinical trial testing the model.

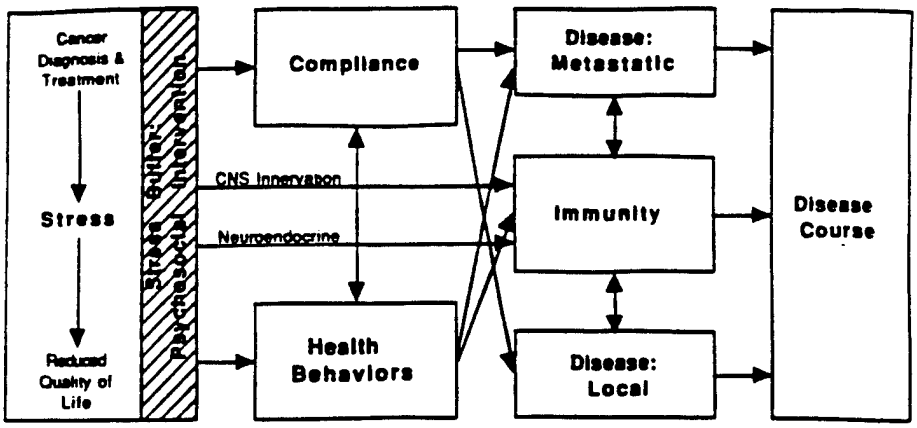

Figure 1: A biobehavioral model of the psychological (Stress and QoL), behavioral (compliance and health behaviors), and biologic pathways from cancer stressors to disease course. (CNS = Central Nervous System).

The cancer stressor and psychological factors: Stress and lowered quality of life. A cancer diagnosis and cancer treatments are objective, negative events. Although negative events do not always produce stress and lowered quality of life, data from many studies, including ours from gynecologic cancer patients (Andersen, Anderson, & deProsse, 1989a), document severe, *acute stress* at diagnosis. However, it is also clear that lengthy cancer treatments and disruptions in major life areas occur, thereby producing *chronic stress.* Emotional distress, in combination with the other life disruptions, can results in a stable, lower quality of life (e.g. Cella & Tross, 1986). Other permanent sequelae from breast cancer treatments, such as sexual problems and/or sterility, impact intimate relationships and social support (Schover, 1994). Unemployment, underemployment, job discrimination, and difficulty in obtaining health insurance can be problems for a substantial minority (Wingard, Curbow, Baker, & Piantadosi, 1991). Thus, many stressors occur for survivors (Andersen, 1994).

Behavioral factors: Health behaviors and compliance. The biobehavioral model suggests that there may be important heath behavior sequelae (see arrow from cancer stress and lowered QoL to health behaviors in Fig. 1), specifically an increase in negative behaviors and/or a decrease in positive ones. There are many manifestations of negative health behaviors. Individuals who are depressed and/or anxious are more likely to self-medicate with alcohol and other drugs, and, in addition, *alcohol abuse* can potentiate distress (Grunberg & Baum, 1985). Distressed individuals often have *appetite disturbances or dietary changes* which are manifested by eating less often or eating meals of lower nutritional value. While there appear to be individual differences in this phenomena (Greeno & Wing, 1994), women may be more vulnerable and women who have undergone changes in their eating habits (e.g. restriction due to cancer treatments) may have hightened vulnerability. On the other hand, a tendency for breast cancer patients receiving adjuvant chemotherapy to *gain weight* has been found (Camoriano, Loprinizi, & Ingle, 1990). Distressed individuals may report *sleep disturbances,* such as early morning

awakening, sleep onset insomnia, and middle night insomnia (Lacks & Morin, 1992). *Cigarette smoking and caffeine use,* which often increase during periods of stress, can intensify the physiologic effects of psychosocial stress, such as increasing catecholamine release (Lane & Williams, 1985; Dews, 1984). Conversely, individuals who are stressed may not begin or abandon previous positive health behaviors, such as regular *physical activity.* Data suggest a positive relationship between physical activity or fitness and psychological health (Dubbert, 1992). In the case of breast cancer patients, positive mood effects as well as increased functional capacity were found for women receiving chemotherapy while participating in a program of aerobic interval training (MacVicar, Winningham & Nichel, 1989).

The model suggests that health behaviors may, in turn, affect immunity (see arrow from health behaviors to immunity in Fig. 1). A covariation of immunity and objective measures of sleep , alcohol intake, smoking, and drug use has been found (Holt, 1987; Irwin, Smith, & Gillin, 1992; Kronfol, Hill, Kroll, Brower, & Greden, 1993). Also, problematic health behaviors interact to produce detrimental immune consequences. For example, substance abuse has direct effects, as well as indirect effects via alterations in nutrition (Jaffe, 1980). Poor nutrition is associated with a variety of immunological impairments (Chandra & Newberne, 1977). Conversely, accumulating evidence suggests that physical activity may have positive consequences both for both the immune and endocrine systems, even among individuals with chronic diseases [e.g. La Perriere et al. (1990) data with HIV-infected men]. In summary, distressed individuals tend toward detrimental health behaviors that may potentiate their stress and, concurrently, negatively affect their immunologic functioning while positive health behaviors, such as exercise, may have the converse effect.

The model suggests that health behaviors may be directly related to disease progression (see arrow from health behaviors to disease: metastatic in Fig. 1). Considering all the health behaviors noted above, the strongest case can be made for the importance of nutrition and diet in breast cancer. A variety of data link nutrition/dietary factors and risk for breast cancer [e.g. epidemiologic data, animal models of high fat diet and tumor growth, obesity and the increase of breast cancer incidence (Howe et al., 1990; Simopoulos, 1987)]. More germane to the proposed research is data suggesting that increased fat intake, obesity at diagnosis, and weight gain may be related to recurrence and survival. The data regarding fat has been sufficiently strong to begin clinical trials of dietary interventions to reduce fat in breast cancer patients; recurrence/survival are the endpoints in these studies. Following two feasibility studies (Nutrition Adjuvant Study, NAS, Chlebowski, 1989; and the Women's Intervention Nutrition Study, WINS, Chlebowski, 1993), a second nationwide WINS study is now underway in which the fat reduction target is a rate of dietary fat of $< 15\%$ of energy. Alternatively, some suggest that fiber, rather than fat, is the critical dietary factor (Howe, Hiroahata, Hislow et al., 1990) in that fiber is postulated to modify serum estrogen levels by increased fecal excretion of estrogens. Finally, related data link weight gain after breast cancer to an increased risk of recurrence (e.g. Holm et al., 1993). Taken together these data suggest that behavioral factors relevant to nutrition, fat/fiber balance, and energy expenditure (vis-a-vis weight gain) may be relevant to disease progression.

The second behavioral factor noted in the model is *treatment (non)compliance* as the available data suggest that psychological factors may be important (see arrow from stress/QoL to compliance in Fig. 1). Compliance problems cross a wide range of diseases, therapies, and individual patient characteristics (e.g. Haynes, Taylor, & Sackett, 1979). In cancer, some patients become discouraged and fail to complete treatment. A general implication of such behaviors is the invalidation of clinical trials, with an eventual adverse effect on overall patient survival (Haynes & Dantes, 1987). For the individual, dosage reductions can compromise his/her survival. A clear demonstration of this effect was data by Bonnadonna and Valagussa (1981) reflecting differential survival rates for women receiving $\geq 85\%$, 65-84%, or $\leq 65\%$ of the recommended dosages of CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) therapy for breast cancer. Surveying the literature we find that non compliance rates range from 8% (Taylor, Lichtman, & Wood, 1984) to 23-25% (Berger, Braverman, Sohn, & Morrow, 1988). Inclusion of "compliance" in the model presumes that a range of treatment regimen characteristics are considered, as the data suggest that different correlates exist for different compliance behaviors (Richardson, Marks, & Levine, 1988;

Lebovits et al., 1990). The model suggest that poor compliance can effect local and/or metastatic control of the disease, and which route is affected depends on the treatment regimen as well as the characteristics of an individual's noncompliance.

The model also specifies that the processes governing compliance and health behaviors may interact (see double headed arrow between compliance and health behaviors in Fig 1) or even may be synergistic. That is, those who are compliant may expect better health outcomes and, thus, comply with diet, exercise, sleep, etc. or other behaviors indicative of "good health." The interaction of these behavioral phenomena may account, in part, for the positive main effect for compliance in randomized clinical trials of drug vs. placebo for coronary heart disease (Epstein, 1984; Coronary Drug Project Research Group, 1980). Despite their importance, health behavior and compliance variables have been understudied in psychological intervention studies, including those with immune outcomes (Kiecolt-Glaser & Glaser, 1992) and those without (Andersen, 1992). Further, changes in health behaviors and/or compliance have been offered as post hoc explanations some of the most notable intervention findings (e.g. survival difference in Spiegel, Bloom, Kraemer, & Gottheil, 1989).

Biological pathways. Stress sets into motion important biological effects involving the autonomic, endocrine, and immune system. Stress may be routed to the immune system by the central nervous system (CNS) via activation of the sympathetic nervous system or through neuroendocrine-immune pathways (see Fig. 1; de la Torre, 1994). In the latter case, a variety of hormones released under stress have been implicated in immune modulation (e.g. catecholamines, cortisol, prolactin, and growth hormone; see Baum, Grunberg, & Singer, 1982; Rabin, Cohen, Ganguli, Lysle, & Cunnick,1989; Sabharwal et al., 1992). Without considering any stress pathway (effect) to immunity, there is evidence for the importance of the immune responses in host resistance against cancer progression, and hence the arrows going in both directions from immunity to local and metastatic disease. Experts in the immunology/cancer area cite the following important findings with regards to the specific importance of NK cell activity: (1) patients with a variety of solid malignancies and large tumor burdens have diminished NK cell activity in the blood; (2) low NK cell activity in cancer patients is significantly associated with the development of distant metastases; and, (c) in patients treated for metastatic disease, the survival time without metastasis correlates with NK cell activity (see Whiteside & Herberman, 1989 for a review). These effects have also emerged for breast cancer patients. Specifically, NK cells have been shown to play an important role in the surviellance of tumor development and the occurrence of metastases (Hanna & Burton, 1986; White, Jones, Cooke, & Kirkham, 1982). Also, the level of NK activity has been correlated with prognostic factors, including tumor burden (Cunningham-Rundles, Fillipa, Braun, Antonelli, & Ashikari, 1981; Wiltschke et al., 1993) and estrogen receptor status (Zielinsky et al., 1989). Moreover, cancers etiologically linked to hormonal stimuli, as is the case for breast cancer, may be more responsive to stress effects (van der Pompe et al., 1994).

Both qualitative (Kiecolt-Glaser & Glaser, 1988; Cohen & Herbert, in press; Weiss, 1992) and quantitative (Herbert & Cohen, 1993 a & b) summaries of the PNI literature conclude that psychological distress and stressors (i.e. negative life events, both acute and chronic) are reliably associated with immune down-regulation in non cancer populations. *Time limited (acute) stressors* can produce immunologic changes in relatively healthy individuals (Glaser et al., 1986, 1987, 1991). *Chronic stressors* are associated with down-regulation rather than adaption, with the largest NK cell effects found for lengthy stressors and/or ones which have interpersonal components (Herbert & Cohen, 1993b for review; Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991 for an example). Many of the qualities of chronic stressors [continued emotional distress, disrupted life tasks (e.g. employment) and social relationships] occur with the decrements in quality of life found in studies of cancer patients. Most relevant are studies with breast cancer patients which provide data linking QoL aspects and immunity. Levy and colleagues (Levy, Herberman, Lee, Whiteside, Kirkwood, & McFeeley, 1990) reported on QoL variables at 3 months post treatment (lumpectomy or mastectomy with or without adjuvant therapy) for 66 women with Stage I or II disease. In addition to estrogen receptor (ER) status predicting NK cell lysis, social support added significantly (+7% of the variance) to the model in predicting higher

NK cell activity. These data are generally in line with data from healthy individuals with "positive" indicators of QoL (e.g. social adjustment) predicting higher NK cell lysis and "negative/distress" indicators (e.g. emotional distress) predicting lower.

There are data on the health (illness) consequences of stress or data linking the two via immunity. One example is that of Cohen et al. (1991). Studying healthy volunteers who were inoculated with either a cold virus or a placebo, they found that rates of both respiratory infection and clinical colds increased in a dose-response manner with increases in psychological stress across five different strains of cold viruses. Data from diagnosed breast cancer groups are relevant. Two studies of extent of disease at initial diagnosis (i.e. number of nodes positive) have been done. Levy (Levy et al., 1985) found self reports of Fatigue (POMS) to be a predictor of nodal status, but there was no effect for Fatigue if NK cell levels were first entered into the regression equation. Levy (Levy, Herberman, Lippman, D'Angelo, & Lee, 1991) examined variables predicting disease free interval (DFI) and recurrence in 90 women with initial Stage I or II breast cancer with data gathered post surgery, and 3 and 15 month follow ups. DFI was predicted by numbers of positive nodes (.-27) and distress (POMS; -.41) at 15 months. Finally, Levy (Levy, Lee, Bagley, & Lippman, 1988) examined time to death following recurrence for 36 women with breast cancer. Along with the medically relevant variables (e.g. DFI), positive affect (Joy) reported at recurrence predicted a longer survival time. In summary, experimental data from stressed but otherwise healthy samples suggest covariation of stress and the incidence of infectious illnesses, and data from cancer samples reveal that conceptually consistent variables are correlated with disease endpoints.

Only three cancer intervention studies have been conducted which have examined immune or health consequences. However, none were, a priori, designed to test disease endpoints, and none included health behaviors in the intervention or the assessment of outcome. The most comprehensive study is that of Fawzy and colleagues (1990 a & b). They studied newly treated Stage I or II melanoma patients randomized to no intervention or a structured short term (10 sessions) group support intervention. Significant psychological and coping outcomes for the intervention subjects were evident by 6 months post treatment; additionally there were increases in the percentage of large granular lymphocytes, the NK cell phenotype, and interferon alpha-augmented NK cell activity. Importantly, the magnitude of the NK changes was frequently greater than 25%. The correlation data was also supportive: interferon-augmented NK cytotoxic activity *increased* with concomitant *reductions* in anxiety (-.37) and depression (-.33). We believe the NK cell data are particularly important because research has shown a reduction in NK cell activity with tumor progression in breast cancer (Akimoto et al, 1986; Takasugi, Ramseyer, & Takasugi, 1977). Also, the intervention effects replicate those of Kiecolt-Glaser et al. (1985) who found relaxation training intervention differences in NK cell lysis for older (primarily female) adults. Six year follow up data on disease endpoints are also available (Fawzy, Fawzy, Hyun, Gutherie, Fahey, & Morton, 1993). Analyses of DFI to death indicate significant group differences, with 29% of controls and 9% of experimental subjects dying in the six year interval. Post hoc analyses indicate that from baseline to the six month assessment, the survivors reported significant decreases in affective distress, increases in active behavioral coping, and increases in CD16 NK cells and interferon alpha augmented NK cell activity (i.e. immune up regulation). In contrast, those who died showed no significant changes on any of these variables, i.e. no QoL improvement or immune enhancement. Data from a relaxation intervention study provide confirmatory evidence as well. Gruber et al. (1993) studied 13 stage I, node negative breast cancer patients who received EMG biofeedback assisted relaxation training. Assessments during the 9-week intervention indicated significant immune differences between the treatment and control groups in the expected direction. Finally, other relevant data come from Spiegel, Bloom, and colleagues (Spiegel, Bloom & Yalom, 1981; Spiegel & Bloom, 1983) who randomized women with metastatic breast disease to no treatment or a group treatment which met weekly for at least one year. The intervention group reported significantly lower emotional distress (POMS) and fewer maladaptive coping responses than the controls. A ten year follow up (Spiegel, Bloom, Kraemer, & Gottheil, 1989) found a striking survival difference between the groups, 18.9 months for the control subjects and 36.6 months for the intervention subjects from study entry until death.

Scope of the Research

Overview. Rationale for a randomized design of treatment vs. no treatment: An experiment is needed to demonstrate cause-effect conclusions for the intervention in demonstrating immune and health effects. While there is an extensive literature documenting the effectiveness of psychological interventions for enhancing QoL outcomes, an extensive data base does not exist on psychological interventions resulting in enhanced immune responses or health outcomes with cancer patients. There are too few data from too few studies (i.e. N = 3; Gruber et al., 1993; Spiegel et al., 1989; and Fawzy et al., 1990 a &b, 1993) to assert that a psychological intervention can *reliably* alter immune function or health consequences. There are enough data to provide encouragement to proceed, but the reliability of the observation needs further documentation. If we were interested only in psychological and/or behavioral variables as outcomes, selection of a factorial design would be in order as the literature has progressed sufficiently to demonstrate the reliability of psychological interventions for quality of life outcomes. In other contexts, we have urged the study of individual differences or the pursuit of factorial designs when psychological responses are the predicted outcomes (Andersen, 1992). From a statistical standpoint, in psychotherapy outcome research effect sizes for comparison of alternative treatments (e.g. a multicomponent intervention vs. information only vs. no treatment) are small to medium when psychological variables are the outcome, and this requires a doubling or tripling of the sample size to detect differences (Kazdin & Bass, 1989). It is unlikely that immune or health variables would be easier to detect with a factorial or treatment comparison design. Finally, we are hard pressed for evidence for a *particular factor* to manipulate to achieve differential immune responses, although the literature does suggest ones as potentially important (e.g. relaxation, coping, social support; Andersen 1992; Kiecolt-Glaser & Glaser, 1992).

Rationale for using prognostic variables for stratification: Randomization will be stratified by four factors: status of axillary lymph nodes and size of primary tumor for women with negative nodes (3 levels: negative nodes but tumor > 2 cm, 1-3 positive nodes, > 4 positive nodes), hormone receptor status (2 levels: positive vs. negative), menopausal status (2 levels: pre and perimenopausal vs. postmenopausal), and support status (2 levels: spouse/spouse equivalent vs. none). These disease stratification variables are the ones which best define the high risk breast cancer patient (Clark & McGuire, 1992), and we have a specific rational for each. *Axillary node involvement* is the most important prognostic criterion in breast cancer, and we have categorized node status using the most common groupings used for subgroup analyses (Gelman, 1992). Women with negative axillary nodes represent a heterogeneous group, but we are only including women with tumors > 2 cm because this defines Stage II disease for the node negative woman (Rosen, Groshe & Kinne, 1989). We are also stratifying by *hormone receptor status and menopausal status* as both factors are used to determine treatment and are related to survival. Receptor negative tumors have higher recurrence rates and shorter survival; women with receptor-positive tumors have treatment determined by menopausal status. Other variables were considered for stratification, such as age (Swanson & Lin, 1994) but menopausal status was chosen instead because it functionally stratifies in much the same way and it also influences treatment selection. Finally, a single psychological variable--*presence of spouse/spouse equivalent*--was chosen because of its documented relationship with survival in individuals with chronic illness (e.g. Berkman & Syme, 1979), lower levels of neuroendocrine parameters (Seeman, Berkman, Blazer, & Rowe, 1994), and ease of determination. There are also parallel data for marital status linked to stage, treatment, and survival in cancer patients (e.g. Goodwin, Hunt, Key, & Samet, 1987; see also Bloom & Kessler, 1994 for the importance of marital status as a predictor of psychological morbidity). This stratification factor is also strongly correlated with other sources of support (e.g. financial resources). These latter benefits would be unlikely if we used another psychological measure (e.g. neuroticism, optimism) for stratification. Due to the number of strata, we will use White and Freedman's (1978) minimization method to allocate patients to the treatment groups. As each new subject is entered, a measure of how this patient will affect the overall balance of the study is computed given the patient's combination of prognostic factors. A biased coin, weighted in favor of the treatment with fewer patients, is used to make the assignment.

We chose prognostic variables rather than cancer treatments for three reasons: 1) the prognostic

variables define treatment selection; 2) treatment philosophies change; and, 3) prognostic factors predict risk of recurrence and/or survival which are endpoints. It is a standard procedure in small cancer therapy trials to stratify on prognostic variables when the effects of the therapy are small relative to the effects of the prognostic factors. We can not stratify on the variety of treatments available for stages II and III, given sample size constraints. Thus, we have chosen 4 variables which by their combinations will equalize prognostic factors across groups and adjust for potential changes in the "state of the art" in breast cancer therapy over the duration of the trial. We have additionally considered the likelihood that the groups, even when stratified and then randomly assigned, will eventually differ on other "nuisance variables" (e.g. cancer treatments recieved). However, data from Hsu (1989) suggest that the probability that the groups will be nonequivalent on at least one nuisance variable with a total sample size of 200 is less than .0006.

Consideration of the effects of cancer therapies on immune function. We have reviewed the literature on the effect of chemotherapy, per se, on immunity. Some chemotherapies will suppress blastogenesis, but more typically, however, the immune-moderating effects of the majority of cytotoxic chemotherapies are unknown. The issue is further complicated by the influence (and interaction of) other factors which effect immunity, such as the following: (1) drug administration parameters--dose, route, time; (2) antigen administration parameters--dose, route, time; and, (3) host parameters--defense mechanisms assessed, time of assessment, capacity to respond (immunocompetence). Nevertheless, we have examined the available evidence on this issue for the most common drugs used for the women in the proposed research: cytoxin (CY), methotrexate (MTX), and 5-FU which are often used in combination (CMF) and Adriamyacin (ADM), used alone. Among these drugs, CY has been the most well studied. Multiple studies indicate CY consistently causes a sharp reduction in circulating peripheral blood lymphocytes, and lymphoproliferative responses to mitogens are impaired, although the effect on antibody production is more variable and suggests immunomodulation rather than suppression (Ehrke et al., 1989). Other data suggest that high doses of CY are immunosuppressive, whereas lower doses frequently are immunopotentiating, and data suggest there is recovery of these functions in 2-3 weeks (Grant, Kaesberg, & Eshler, 1991). On the other hand, CY can potentiate both cellular and humoral immune function in animal models, and the available clinical data from humans suggests that CY can augment immune function to clinically relevant antigens in patients with cancer (Ehrke, Mihich, Ber, & Mastrangelo, 1989). Regarding ADM, the most prominent immunosuppressive effect is that it induces meylosuppression, but data indicate that recovery is complete by one to three weeks (Kempf & Mitchell, 1985). Regarding immunopotentiation, augmentation has been found for both cellular and humoral immune responses in animal models, and clinical studies with cancer patients suggest that cellular immune function may be enhanced but the clinical significance remains to be determined (Ehrke et al., 1989). Regarding MTX, some immunosuppression has been found with intermittent administration. Inhibition of blastogenesis has been found after 3-4 weeks of therapy, but it recovers within days with the cessation of therapy; depressed humoral immunity is the most common immunosuppressive outcome of MTX therapy, with less depression of cell-mediated immunnity (Grant, Kaesberg, & Eshler, 1991). For 5-FU, the available data suggest some suppression of humoral immunity but rapid (one week) recovery after discontinuance of the drug (Kempf & Mitchell, 1985), with less suppression of cellular immunity (Grant, Kaesberg, & Eshler, 1991). Finally, we note that one of the few studies using a repeated measures paradigm, Levy and colleagues (1985) assessed women with Stage I or II breast cancer a week after surgery and three months later following adjuvant chemotherapy plus radiotherapy or radiotherapy alone. They found a persistently low level of NK cell activity that did not change during therapy. At the same time, the mean levels of NK cell activity were significantly lower for the node-positive women at baseline, consistent with the data cited above regarding lower levels of NK activity in patients with greater tumor burden. Thus, immunologists emphasize that it is the tumor burden (stage) which may be more relevant to NK cell activity than any temporary disregulation caused by surgery, radiation, and/or chemotherapy (Whiteside & Herberman, 1990).

Our early data indicated that a 2 to 4 week interval post treatment (surgery) was sufficient for immune recovery for the majority of women. For women in the study receiving chemotherapy, we are finding that the majority (92%) have completed their chemotherapy (usually 4-8 cycles) by the four month assessment. By the 12 month assessment, all women will have been off therapy for at

least two months and potentially for as long as 8 months (with the exception of Tomoxifan). In addition to fully documenting the nature of the regimens for subjects, including radiation and chemotherapy dosages and dosage intensity, we take special care to coordinate blood draws to be as long as possible from the last chemotherapy administration (e.g. 3 weeks), yet not be immediately prior to the next cycle to maximize the likelihood of tapping recovered "baseline" responses yet avoiding acute disregulation with anticipation of (e.g. Jacobsen et al., 1995) or actual drug administration.

Rationale for the repeated measures (0-, 4-, 8-, and 12-months for year 1 and 6- and 12-months for years 2-4): Multiple assessments in year 1 document the effects of both portions of the intervention. For data analyses in which year in study is a factor, the 4 and 8 month assessments in year 1 are averaged to achieve a more stable estimate, as the greatest change is anticipated for year 1. This also achieves uniformity in having 2 assessments for each year when the unit of analysis is year in the study. The repeated assessments determine the short (< 1 year) and long term (2-4 years) effects of the intervention. Immunity data during follow up provides prospective documentation of any differential response patterns among those who do and do not recur.

Hypotheses are tested in three areas. *In Area I, hypotheses involve group differences on psychological, behavioral, immune, and health outcomes.* Specifically, we hypothesize that: (Ia) Intervention subjects will report significantly better psychological outcomes, specifically lowered stress and enhanced quality of life. Intervention subjects will also be less vulnerable to the specific sequelae of breast cancer treatment such as disrupted sexual self concept. (Ib) Intervention subjects will demonstrate significantly improved health behavior outcomes, including higher rates of positive health behaviors (e.g. physical exercise, lower fat intake), lower rates of negative health behaviors (e.g. alcohol intake), and better compliance with cancer therapy and medical follow up. (Ic) Intervention subjects will have significantly better immune function, as assessed with natural killer (NK) cell responses [e.g. NK cell lysis; ability of NK cells to respond to interleukin-2 (IL-2) and gamma interferon (INF-γ)]. (Id) The intervention group will have better health outcomes, lower rates and/or slower cancer progression. In *Area II we will test the relationships among the variables specified in the biobehavioral model,* including the following: (IIa) the prediction of immune function from the psychological variables (e.g. increased stress is significantly correlated with immune changes, such as decreased NK activity); and, (IIb) the role of the immune variables as a mediator linking psychological/behavioral variables to disease outcomes (i.e. stress is related to decreases in functional immunity which are, in turn, related to shorter disease free interval). *In Area III we will examine individual differences.* We will determine change over time for individuals in each group and test for individual differences related to change in immunity or differential health outcomes. Specifically, we hypothesize the following: (IIIa) We will test whether or not differences between women in their level of social support may moderate psychological or immune responses or health outcomes, e.g. women with greater levels of social support may manifest higher levels of NK activity and/or lower rates or slower disease progression; (IIIb) We will test whether or not differences in personality characteristics might influence vulnerability to lowered immunity or illness progression, e.g. individuals high in extraversion, low in neuroticism, high in openness or high in conscientiousness may have better health outcomes; and (IIIc) Finally, we will examine the medical stratification factors (i.e. nodes, ER/PR, menopause) to determine if the effectiveness of the psychological intervention interacts with them.

BODY

Experimental Conditions

Assessment only

Table 1 below displays the schedule for the assessments. Women are paid a modest fee ($20) for their time and effort for each assessment. These reimbursements are also used for the women in the intervention condition.

Table 1: Schematic diagram of the research design for subjects across the 4 years of study participation.

	YEAR 1				YEARS 2-4	
	Dx./Ca. Trt	Follow up (months)			Cont. Follow up (months)	
Grp	0	4	8	12	6	12
1	x----------Inten------x----Maintenance---x--Maintenance--x				x	x
2	x----------None-----x--------None-------x-------None-----x				x	x

Note: *Dx.* = Cancer diagnosis and *Ca.Trt.* = Beginning of initial cancer treatment; Inten(sive) = Weekly (x18) intervention sessions with reliability/validity checks on intervention integrity; Maintenance = Monthly (x8) intervention sessions with reliability/validity checks; *x* = Psychological, health behavior, compliance, and immune and endocrine assessments and disease endpoints.

Assessment and intervention

Conceptualization and content of intervention

The biobehavioral model has been used for targeting of the areas of change. Each construct in the model has been operationalized to correspond to intervention components and assessment measures. Specifically, the intervention includes components to *reduce stress, enhance quality of life (i.e. emotional adjustment, social adjustment and support and breast specific concerns--body image and sexuality), increase positive health behaviors, decrease negative health behaviors, and improve compliance (*see complete description of intervention components is provided below. Briefly, the intervention has two phases. The first phase, the *intensive intervention*, has four parts. Further, we hypothesize that it will be especially important that the psychological intervention produce *long term* behavioral and psychological changes if immune responses and/or disease endpoints are to be affected. Therefore, we include a second phase, a *maintenance intervention,* and the Transtheoretical Model of Behavior Change (Prochaska & DiClemente, 1984, 1986) is used as the guiding theoretical framework for it. This model has been widely used in cancer prevention and screening studies (e.g. smoking cessation, high-fat diets, fruit and vegetable consumption, exercise acquisition, mammography screening; Prochaska et al., 1994). Longitudinal studies of change have found that people pass through five stages of change---precontemplation (no intention to change), contemplation (seriously considering change), preparation (taking steps to change), action (actively involved in meaningful change), and maintenance (maintaining meaningful change)---and further, data suggest that there is a pattern of change in the decisional balance as individuals move through the stages (Prochaska et al., 1994).

Intensive: *Part 1: Stress reduction and enhancing QoL (emotional adjustment)* (Sessions 1, 4-7). There are four components. (a) A simplified version of Gatchel, Baum, and Krantz's (1989) model of stress as a psychophysiological process is offered as a way to conceptualize the cancer stressor. Adaptive coping strategies (e.g. seeking information, positive appraisal) is introduced as skills that can be learned and applied generically. (b) Progressive muscle relaxation (PMR) training (ala Bernstein and Borkovec, 1973 is modified as a skills training effort with group instruction, Carlson & Bernstein, in press) is used as a method for lowering overall body tension. Women are provided with cassette tapes for home use. Instruction begins with 16 muscle group and moves through the steps to relaxation by recall. (c) Cognitive restructuring (Hawton & Kirk, 1989) is used to identify current manifestations of the cancer stressor (e.g. low mood, low energy/fatigue, disrupted relationship with spouse). The A (Activity/Event)--B (Beliefs/Automatic thoughts)--C (Consequences/Feelings and Behaviors) model is offered with examples. (d) Problem solving follows the principles of Goldfried and Davision (1976) and Hawton and Kirk (1989). It consists of five stages: overview of the principles; how to define and formulate target problems, generation of problem solutions; decision making; and, verification of solutions. To learn the principles, women have "hands" on experience by working on solutions for two target problems: fatigue

and time management. This section concludes with women targeting 1-2 other areas for problem solving to enhance generalization.

Intensive: *Part 2: Compliance* (Sessions 2-3, Portions of Session 10). Of the very few studies focused on compliance, the data suggest *information about the disease and treatment* (Richardson et al., 1987; Robinson, 1990), and *enlistment of help of significant others, i.e. social support* (Richardson et al., 1987). There are three components. (a) Disease and treatment information is offered to reduce uncertainty and aid in medical decision making and compliance. Existing educational materials (e.g. the NCI's *Breast Cancer Digest* and American Cancer Society materials) are used. (b) The use of relaxation and distraction in coping with treatments (e.g. chemotherapy side effects) and anxiety vis-a-vis follow up medical examinations is discussed. (c) Assertive communication exercises is conducted to enhance communication with physicians and other health care professionals (see below under Part 3).

Intensive: *Part 3: Improving QoL (social adjustment and breast specific component)* (Sessions 8-13). There are four components. (a) The supportive context of the group intervention is used to direct social comparisons among the group members; as women learn that many of their reactions to the cancer "crisis" are normal and shared by others, problem solving strategies and ways of adaptive coping is fostered (e.g. Taylor's conceptualization of adjustment to threatening events; Taylor, Lichtman, & Wood, 1984). (b) Women's social network is identified by using a concentric circle model (with the patient at the center). We systematically cover five levels of social relationships (e.g. coworkers and friends; physicians; parents/in laws and siblings; children of all ages; and spouse/spouse equivalent) and identify sources of satisfaction and clarify areas of difficulty (Cohen & Wills, 1985). (c) Assertive communication skills, modeled after the work of Jakubowski and Lange (1978) is taught to assist women in expressing their thoughts, feelings, and needs in a manner which facilitates support from and communication with members of their social networks. Four techniques are used: specificity and clarity of one's message; direct communication; "owning" one's message (use of "I," "my" etc. in statements); and, asking for feedback. These skills are practiced across the five levels of social relationships identified in (b) above. (d) Specific breast cancer sequelae of *body changes*, menopausal changes, hormonal changes with Tomoxifan therapy, and impact on sexual self schema (esteem) are discussed as well as coping with sexual changes as discussed in Andersen and Elliot (1993). This session is prefaced by a session focused on social support from the partner.

Intensive: *Part 4: Health behaviors,* (Sessions 14-17). There are three components: diet, exercise, and negative health behaviors. (a) Information on a low fat eating plan is offered to achieve dietary change (dietary fat $\leq$ 25% of energy intake and dietary fiber of 20-30 grams/day from fruits, vegetables, and grains; these are NCI fat and fiber guideline levels). The intervention provides participants with the skills and knowledge to gradually lower their fat and increase their fiber intake, and was adapted from the procedures from the WINS study. The guidelines emphasize the influence of discriminative stimuli for eating, the substitution of low-fat food items for high fat foods, and the setting of step-wise goals for lowing fat intake. The guiding conceptualization is that of health behavior change rather than dieting. We begin and end the dietary intervention with individualized, stage matched reports for dietary change (i.e. fat reduction and specific fiber recommendations based on current eating pattern). Such reports are generated by incorporating the data from the stages of change (Prochaska et al., 1994), Decisional Balance (Janis & Mann, 1977), and the Food Frequency Questionnaire (Kristal, SeLett, Henry, & Fowler, 1990; see below). Recent data demonstrate that messages individually tailored to an individual's stage of change generated a significantly greater reduction in dietary fat intake than non-tailored messages based on NCI Dietary Guidelines (Campbell, DeVellis, Strecher, Zimmerman, DeVellis, & Sandler, in press; Greene, Rossi, Geed, Willey, & Prochaska, in prep). Finally, we note that if the dietary data indicate deficiencies in RDA nutrients based on 2/3 of the 1989 RDAs (Food and Nutrition Board, 1989), women in either group (intervention or control) are provided with appropriate educational materials to increase intake of the deficient nutrient(s). Study subjects are monitored by project dietary resource person from the OSU Clinical Research Center. We attempt to monitor women with significant weight loss, a low albumin, or other indicators of compromised nutritional status to ensure that there is appropriate medical and dietary coverage, and to ensure that the dietary intervention is complimentary to any other dietary care which is needed.

(b) According to the American College of Sports Medicine's (1991) Guidelines for Exercise Testing and Prescription, "exercise therapy is becoming an accepted aspect of rehabilitation in patients with cancer. Regular exercise counteracts the detrimental effects of bed rest and provides psychological benefits " (pg. 178). Available data suggest that resuming or maintaining regular exercise would provide positive health benefits, as recent

controlled trials suggest that even moderate levels of aerobic exercise performed 3-5 times per week for 20-30 minute intervals improve aerobic fitness in middle aged women (King, Haskell, Taylor, Kraemer, & DeBusk, 1991). In the only study that assessed the effect of aerobic activity in breast cancer patients, MacVicar et al (1989) reported that exercising on a stationary bicycle three times per week was associated with a 40% increase in aerobic efficiency and fewer reports of nausea than in non-exercise controls. The exercise intervention is modeled on the home walking protocol of King (1991) et al. which was found effective for older women. An exercise program of this magnitude (producing 50-60% of maximum heart rate) is sufficient to produce positive psychological benefits (King, Taylor, & Haskell, 1993), and low-intensity exercise appears to be beneficial for the immune system in terms of increasing the numbers of natural killer cells and the number of circulating lymphocytes (Newsholme & Parry-Billings, 1994). Didactic information includes how to set realistic goals, schedules for rest, techniques for increasing energy expenditure during activies of daily living, and coping strategies for setbacks. Women who are unable to perform the walking protocol due to treatment complications are provided with alternative activity/rest goals. Co-PI Emery provides guidance on the specific procedures for implementing and monitoring the exercise program.

(c) Information on *controlling negative health behavior*s (i.e. alcohol consumption and smoking) is provided along with specific referral to community/self help group resources. *Disturbed sleep patterns* are addressed with recommendations regarding activity programming, relaxation training, and sleep pattern monitoring.

Maintenance: *Part I: Preparation for maintenance (Session 18, Intensive).* To implement the maintenance plan, immediately prior to the final session of the intensive intervention, each woman completes two measures: 1) Stages of Change: Following the procedures of Prochaska et al. (1994), a 4- or 5- item algorithm for determining the stage of change for the seven target areas which have been the main foci of the intensive intervention: relaxation training, adherence to medical therapy, social support, sexuality/body image, diet, exercise, and control of a negative/problematic health behaviors. For example, the first item on the algorithm asks a woman if she has engaged in the desired positive behavior (e.g. practicing relaxation three times per week for 20 minutes; exercising 20 minutes three times per week; having one-two face to face interactions with a confidant per week). If a woman reports the undesired status or does not intend to change in the next 8 months (the length of the maintenance period), then she is in the precontemplation stage. If she intends to change in the next 8 months, she is in the contemplation stage. Women in the action stage will have reached a particular criterion (e.g. practicing relaxation three times per week) within the past 4 months (the length of the intensive intervention, or the relevant interval since the intervention was conducted during the intensive period). At this first assessment we find that it is unlikely that any women is in the maintenance phase (usually defined by maintaining the criterion behavior for six months).

2) Decisional Balance: Women complete decisional balance measures (Janis & Mann, 1977) for each of seven specific target areas: relaxation training, adherence to medical therapy, social contact with an identified target, sexuality/body image, diet, exercise, and control of a negative/problematic health behavior. These measures are brief (e.g. 8 item) measures which tap the eight categories of decision making in the Janis and Mann model: gains or losses for self, gains or losses for significant others, self-approval or self-disapproval, and approval or disapproval of others. For each measure the item content is specific to the target area. Following the method of Prochaska et al. (1994) a 5 point Likert scale is used that ranges from *not important* (1) to *extremely important* (5) or *strongly disagree* (1) to *strongly agree* (5).

During the first portion of the last intensive therapy session the measures are scored by research assistants. A brief, individualize report is prepared for each woman which summarizes the level of the stage of change (i.e. precontemplation, contemplation, action, etc.) for each of the target areas. The report is further individualized by providing stage-specific and target-specific intervention information for each women, modeled after the work on individualized self-help interventions of Prochaska et al (1993). The session begins by delivery of the reports to the women, with discussion of the stages of change model and its applicability to the intervention targets. The session ends by establishing target goals in each area for each woman.

Maintenance: *Part II: (Sessions 19--26).* The same general format is used for the eight maintenance sessions. Six primary components are included. (a) We review the goals for the month, with each woman rating goal attainment and updating her current progress, vis-a-vis stage of change (e.g. determine whether she has moved from contemplation to action). (b) We emphasize problem solving, social support seeking, and increasing awareness of cues (including self talk) as these general strategies, along with duration of therapist contact in a

maintenance program (e.g. Perri et al., 1988), have been important in the maintenance of change (e.g. Urban, White, et al., 1992). (c) Each session revisits intervention strategies for one of the seven target areas: relaxation training, adherence to medical therapy, social support, sexuality/body image, diet, exercise, and control of a negative/problematic health behavior. However, this additional coverage of target areas is broken down into stage specific interventions, i.e. brief modules on relaxation for precontemplators, relaxation for contemplators; relaxation for maintainers, etc. During the session the women divide into small groups based on their respective stage of change for the target behavior and the interventions are delivered within the small groups and stage appropriate exercises and written material is provided. Given the previous intensive intervention period, we find that the women will fall into only 2 or 3 groups--contemplation, action or maintenance. With two therapists it is possible to assist all the subgroups during this segment. (d) The session closes with goal setting for the next month. e) We prompt the group members to maintain contact with one another between the monthly sessions. For example, women have been comfortable with sharing telephone numbers or some members pair up as "buddies" for bi-weekly contacts. These contacts are for social support and to facilitate maintenance of the behavior change goals. f) Crisis management is needed for particular difficult situations which arise (e.g. local recurrence, death of a family member). The group then needs to process such experiences and provide support to one another as is appropriate.

Therapists and therapy reliability

A single cycle is 26 1.5 hour sessions (18 intensive + 8 maintenance) for a total of 39 therapy hours. At least ten cycles of the intervention (i.e. 100 intervention subjects/8-12 subjects per group) will be conducted. Several steps are taken to insure reliability of the treatment procedures. First, to maximize similarity across cycles, the therapists (two per group) follow a session-by-session written manual (The manual is available on request). To insure reliability within intervention cycles, therapist teams meet weekly to review the previous session, rate the topic coverage, and prepare for the next session. Further, all sessions are videotaped and independent ratings of 50% of the intensive and 100% of the maintenance sessions are done. If there is "drift" in the nature of the intervention, we take corrective action immediately. These tapes also provide an opportunity to quantify the involvement of the subjects in the intervention--a critial component of process research--to generate testable hypotheses of intervention components.

Second, steps are taken to standardize and document the treatment "dose" to the women. 1) Attendance [both in session and "at home," see description below] is monitored. 2) Each woman is given an intervention notebook which provides an easy to read written summary of each session. This facilitates the women keeping focused on the sequence and content of the intervention and, often, women use the session descriptions to prepare for the next week's session. 3) Women are absent on occassion (e.g. women on chemotherapy often have low counts or feel ill) and we have devised procedures for them. When a session is missed, a woman is telephoned by the primary therapist. The therapist provides an update to the woman about the status of the other group members and then together they discuss the session's content as provided in the notebook (The notebooks are written as if a therapist is talking to an individual person). The telephone call is usually 15-20 minutes. This procedure keeps a woman up to date on the group progress, ensures that minimal group time is needed for "catch up, " and reduces the dropout rate as the women stay engaged in the group activities. 4) We assess the womens' perceptions of the group experience with a modified version of the Participant Rating Form from the GROW Project (Roberts et al., 1991). It contains 30 Likert items and asks women to rate the most important aspect of the group experience. 5) For all subjects, we document participation in any therapeutic, counseling or related activities. This brief assessment occurs on an annual basis, and we obtain descriptive data on how involved the woman is/was in these experiences and how supportive she found them, attendance, and the type of group (e.g. breast cancer, cancer general, therapy group, social/recreational, religious group).

We also have procedures in place in the event a woman's disease recurs during study participation. There are at least four circumstances to consider. 1) Some women may be initially regarded as stage II or III disease but are quickly "restaged" following the initial assessment but prior to the four month assessment. The typical scenario for this rapid change is that such women have many positive nodes (e.g. 10+) and further studies are being done for screening prior to bone marrow transplant; during the course of such studies, disseminated disease (e.g. lung, liver or brain mets) may be found. This situation has arisen once in 12 months of recruiting. Our procedure is to provide supportive individual psychosocial monitoring and referral to other psychosocial services when and if the woman has desired such; women in the intervention condition stay in the intervention group if they so desire. 2) If disease recurs for a woman during the course of the intervention interval, either the intensive or the maintenance

phase. When this has occurred for women in the intervention condition, they have continued to come to the intervention sessions as their health has allowed. Whether or not they come, all group members are informed of the situation, and if they feel comfortable doing so, they are urged to contact the woman. Because we anticipated this happening, we have made every effort, and have been successful thus far, to keep the intervention "open" to everyone, regardless of the immendiate disease status. We have found that topics such as stress management, social support, body image, diet, compliance, etc. are important as well for women with recurrent disease. 3) Regardless of when the recurrence happens, we have a modified core assessment battery as women typically wish to limit their participation and/or her energies are limited. Some women want to discontinue their participation entirely upon recurrence, but the majority do not and they are continuing their involvement as long as they feel it reasonable and they are able.

Measures

Stress

Perceived stress. The Perceived Stress Scale measures an individual's appraisal of their life as stressful and includes items for perceptions of daily life as unpredictable, uncontrollable, and overloading. These dimensions are of particular interest for women undergoing difficult, lengthy therapies in the midst of family, home, and job responsibilities. This measure is a predictor of symptomatology beyond that due to depression (Cohen & Williamson, 1988) and norms are available for middle and older age adults.

Traumatic stress. The Impact of Events Scale (Horowitz, Wilner, & William, 1979) examines intrusive and avoidant thinking about the cancer stressor. The 15 item questionnaire has two distinct factors: avoidance and intrusion ($r = .42$); internal consistency is .82 and .78 and two-week test-retest is .79 and .89, respectively. The continuing psychological impact of breast cancer is well documented (e.g. Taylor, Lichtman, & Wood, 1984), and individuals who experience involuntary, distress-related ruminations following traumatic life events are also those who appear to suffer the greatest negative effects.

QoL: Emotional adjustment and coping

Emotional distress. The Profile of Mood States (McNair, Lorr & Droppleman, 1971) is used. It is a 65-item self-report inventory which asks the subject how she has felt during the past week and yields measures of six mood subscales: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. Internal consistency for the scales range from .83-.93. This is one of the best measures of transient mood states. This measure has been widely used in cancer research and been sensitive to immune changes and pre to post treatment differences (e.g. Andersen, Anderson, & deProsse, 1989b).

Mental health is assessed with the Beck Depression Inventory (BDI). This 21 item measure assesses mood, physiological or vegetative signs of depression, and cognitive aspects. Although syndromal depression is expected to be rare among women in the proposed study (Massie & Holland, 1990), depressive symptoms are frequent and clinically important. BDI subscale scores can be calculated for somatic and psychological items. Correspondence between conventional BDI cutoff scores for syndromal diagnoses (i.e. < 11, non depressed; 11-16, mildly depressed; and > 16, moderately to severely depressed) have been excellent in studies that have used RDC criteria, including two studies with ambulatory medical patients (Nielsen & Williams, 1980; Rapp et al., 1988). Thus, the BDI provides an efficient assessment of the severity of depressive symptoms.

Coping. At present the biobehavioral model does not specifically identify a coping construct. However, the literature on breast cancer suggests that coping strategies may moderate emotional adjustment processes (see Carver, Puzo, 1993). For this reason, the 24-item short version of the *COPE* (Carver et al., 1989) is used to provide preliminary data on differential coping responses across time. The COPE is a broad band measure, assessing such strategies as problem focused ones (e.g. active, planning), use of social support, turning to religion, substance use, as well as more problematic efforts (e.g. denial, disengagement). Use of the scale with women with breast cancer indicates satisfactory test-retest reliability (.65 to .90) and specific strategies (e.g. acceptance) predicting emotional distress longitudinally (Carver, Pozo et al., 1993).

QoL: Social adjustment

Social and occupational activities is assessed with a modified version (see Andersen, Anderson, & deProsse, 1989b) of the Katz Social Adjustment Scales. It is a 25-item inventory composed of five factors (73% of the variance): child and home activities (5 items), social contacts with friends (4 items), contacts with relatives (3 items), recreational activities (7 items), and employment involvement (5 items). Rather than perceptions or satisfaction, behavioral frequencies of these activities are obtained. Internal consistencies range .68 to .95 and the measure is sensitive to short (4 months) and long term (12 months) recovery from cancer (Andersen, Anderson, & deProsse, 1989b).

Social Network. The Social Network Index Interview (Cohen, 1991) assesses social integration and is potentially less subject to mood-related biases than perceptions of support. This measure assesses the number of people with whom the individual had contact with on a regular basis and the number of important roles fulfilled by these supports (e.g. spouse, parent, child, employee, friend, neighbor). The number of roles and the number of relationships across roles are predictors of mortality in epidemiologic studies (e.g. Berkman & Syme, 1979; House et al., 1982). Internal consistency is .65.

Social Support. The Interpersonal Support Evaluations List (ISEL; Cohen et al., 1985) contains 40 questions and responses range on a 6 point scale (1 = I agree very much, 6 = I disagree very much). The ISEL measures the perceived availability of the following support resources: (1) appraisal, the availability of some one to talk to about problems, 2) tangible, the availability of material aid, 3) belonging, the availability of people to do things with, and 4) self-esteem, the availability of a positive comparison when comparing the self with other. Cohen et al. (1985) report that the internal consistency of the scales range from .60 to .92, and the scales are not overlapping (.24, ns). A four week test-retest reliability is .87 for the total scale.

QoL: Breast specific component

Sexual activity. The short form of the Sexual Experience Scale assesses the range and frequency of current sexual activity. The inventory includes 12 items which are rated on a 9 point frequency scale. The measure includes five factors: intimate non intercourse activities (two factors), intercourse, anal stimulation, and masturbation. Internal consistency is .84 and 4 month test-retest reliability is .72. Items are worded appropriately to assess both heterosexual and lesbian relationships. The measure is sensitive to change from sexually disruptive breast cancer treatments (e.g. Andersen & Jochimsen, 1985).

Body Satisfaction. The 10-item version of the Body Satisfaction Scale is used to assess satisfaction with the physical body. The short form assesses two satisfaction dimensions: general facial and sexual body (breasts, genitals) and weight and its body correlates for women--hips, thighs, and buttocks (Andersen & LeGrand, 1991). Internal consistency reliability is .76. Data from women with breast and gynecologic cancer indicates that the measure is correlated with conceptually relevant aspects of sexuality, such as sexual desire (Andersen & Jochimsen, 1986; Andersen & LeGrand, 1991).

Health behaviors

Diet

Dietary patterns: The Food Frequency Questionnaire (Kristal, Shattuck, & Henry, 1990) is used as a self report measure of dietary patterns related to selecting a low fat diet. Additional items used by Green, Rossi, Reed, Willey & Prochaska (in press) will be included to assess selection of high fiber foods. The 18 item scale has test retest reliability of .87 and internal consistency of .62, appropriate for a measure which taps four dimensions of dietary behavior (i.e. excluding high-fat ingredients, modifying high fat foods, substituting low fat foods, replacing high fat foods). This measure is used to generate the stages of change individualized reports on dietary change.

Exercise.

Seven-Day Physical Activity Recall Questionnaire (Blair, 1984). This measure was developed as a community health survey as part of a CHD community prevention study (Stanford Heart Disease Prevention Program). It is administered by an interviewer in 10 to 15 minutes, and co-PI Emery provides training of the procedures. Raw data from the interview are used to calculate total energy expenditure, including exercise and

leisure activities. Normative data from age similar women are available.

Self reports. Two questions from Washburn, Adams, & Haile (1987) included to assess: (1) subjects self-rating of activity level compared to peers, and (2) days per week of exercise-induced sweating. Validity for these two items was established by comparing responses to the items with measurements of resting heart rate, triceps skin folds, and self-reported physical activity, suggesting that this simplified approach provides a useful index of physical activity.

The Minnesota Leisure Time Activity (LTA) questionnaire (Taylor et al., 1978) provides an assessment of exercise activity changes during the course of the study. The questionnaire was developed for use in longitudinal studies of coronary heart disease, including the Multiple Risk Factor Intervention Trial (MRFIT; Paul, 1976). The questionnaire is modified to assess only activity between assessments.

Smoking. At baseline we obtain information on lifetime use of tobacco products, including age of onset of use, periods of abstinence of greater than one month, and amount currently used. From these data, quantity and duration of use of each product is calculated. Dose of current use is calculated using the following equivalencies: 1 tobacco unit = 1 cigarette = 0.2 cigars = 0.4 pipefuls.

Alcohol use. An assessment similar to that for smoking is done for alcohol. At intake, subjects are asked about the date of the last alcoholic drink, and single items assess the age of onset of use, current frequency (e.g. days/week and weeks/year), amount (e.g. drinks/day, and ounces/drink), and type (e.g. beer, wine, and or liquor) consumed. Dose is calculated using the following equivalencies: 1 alcohol unit = 1.5 oz. liquor = 12 oz. beer = 6 oz. wine. At baseline, subjects also complete the Mischigan Alcoholism Screening Test (MAST) which is the psychometrically strongest screening measure currently available (Mischke & Venneri, 1987). Internal consistency for the 24 self report items is .84 and the measure is capable of making DSM-IIIR distinctions between a range of problem drinkers (Ross, Gavin, & Skinner, 1990).

Compliance

Reports of oral drug dose. We administer the Morisky et al (1986) brief interview (4 questions) measure of oral medication adherence (e.g. Tomoxifan). Despite its simplicity, this measure is internally consistent (.61), has concurrent validity (e.g. predictive of drug blood levels), and has predictive validity (e.g. predictive of compliance 2 years post assessment).

Calulations of dose intensity. A sensitive measure of cancer (chemo) therapy when different treatment regimens are being compared is dose intensity, which has been defined as the amount of drug delivered per unit time, expressed as mg/m^2/wk, regardless of the schedule or route of adminestration (Hyrniuk, 1988). Relative dose intensity (RDI) is the amount of drug delivered per unit time relative to an arbitrarily chosen standard for a single drug, or, for a combination regimen, with the decimal fraction of the ratio of the test regimen to the standard regimen. To compare the dose intensity of combinations of drugs, the average dose intensity of the combination is calculated as the average amount of drugs delivered per unit time compared to an arbitrarily chosen standard. To calculate average RDI for a regimen containing fewer drugs than the standard regimen, a dose intensity of zero is assigned to the missing drug(s), and the average RDI of the test regimen is divided by the total number of drugs in the standard. The dose intensity of various protocols is compared over whatever time frame the treatment protocal is adminestered. Calculations can be made of intended dose intensity, the dose intensity as described in the treatment protocol, and actual or received dose intensity. Recieved dose intensity reflects the impact of dose reductions and necessary treatment delays imposed in actual practice because of toxicity and is thus the more important data. Since calculations are made on the basis of the amount of drugs given per week regardless of schedule, treatment delays are given equal weight to dose reductions.

These data are important, as a clear-cut relationship between dose intensity and response rate has been demonstrated in breast cancer (e.g. Bonadonna & Valagussa, 1981). Also, these data are needed to document the magnitude of differences, if any, between cancer treatments planned and administered to women in the different arms of the study. They will also be examined to determine if psychological distress, per se, or involvement in the intervention arm may have been correlated with higher levels of therapy (greater dose) actually received when compared to the level of cancer treatment planned.

Appointments for treatment delivery and follow up. The number of missed treatment delivery appointments (e.g. failing to appear for chemotherapy administration or radiotherapy treatments) are recorded (i.e. total number as well as percentage of total appointments). We also record relevant data effecting treatment delivery, such as medically recommended delays (e.g. a radiation therapy "hold" because of skin irritation). We record the number and percentage of follow up visits which were kept. For most physicians, standardized schedules (every three months) exist to facilitate this assessment.

Immune studies and supplementary laboratory studies

Approximately 60cc of blood is obtained from each subject at each assessment. By obtaining four blood samples the first year and two per year thereafter, we monitor the breast cancer patients during the time when risk for recurrence is highest. We sequence study draws with medical follow up draws, but this schedule is often not possible. The blood samples are treated with heparin or EDTA to prevent clotting. Mononuclear cells will be separated using Hypaque-Ficoll density gradients, washed 2 times with Mg and Ca-free buffer, counted in a Coulter Counter, then used as described below. We use fresh cells to perform all the cellular assays and will attempt to control for laboratory variability in the assays by using the same lot of media, the same lot of fetal bovine serum (FBS) or human pooled serum, the same lot of plastic tissue culture plates, etc. and, when possible, the same technicians performing the same assays on an annual basis. These and other standardizing efforts (e.g. single preparation of media, volume purchase of FBS and plastic ware) are routine in the laboratories. While these practices are not the same as performing all assays on one day with all the same reagents, they control for many of the important variables, and these practices have been satisfactory in prior studies from the OSU PNI laboratories.

Other laboratory studies will also be done. *Complete blood cell counts (CBC) and differentials,* performed by the Clinical Immunology Laboratory at the OSU hospital, will be obtained on each blood sample. Lastly, we monitor nutritional status with concurrent *serum albumin.* If this marker is out of the normal range, then the subject's immunological data for that draw is excluded. In the past ten years of PNI studies at OSU we have rarely found subjects who have abnormal levels, but occurrence may be more common with cancer patients.

NK cell numbers. We determine the percentages of CD3+, CD4+, CD8+ lymphocytes and NK cells by flow cytometry using the appropriate monoclonal antibodies (Coulter) and using routine procedures in the FACS Laboratory in the James Cancer Hospital. Having both the CBC and differential data, along with the percentages of these cell populations, we determine the absolute numbers of lymphocytes and NK cells. Quantitative data on the NK cells is needed to aid in the interpretation of the NK cell activity studies (see below); this will enable us to determine whether any difference in activity is a result of function or NK cell numbers.

NK cell lysis. As discussed in the Background section, we study NK numbers and function, and test if NK numbers and their ability to kill target cells is differentially lower in the assessment subjects compared to the intervention subjects. Briefly, cells are prepared to make a 50:1, 25:1, and 12.5:1 effector to target cell ratios and are seeded in triplicate, in 96-well microliter plates. Additional wells containing only target cells (K562) in medium or target cells in a medium containing 1% sodium dodecyl sulfate are used to determine spontaneous and maximum release of radioactivity, respectively. Plates are incubated for 4 hours in a 5% CO_2 incubator at 37°C. Supernatant is harvested using a Titertek Supernatant Collection System and activity is determined by the release of ^{51}Cr into the supernatant. Supernatant is counted using a Beckman 9000 gamma counter.

Ability of NK cells to respond to recombinant IL-2 and recombinant IFN-γ. Of added relevance are studies on the ability of the NK cells to respond to interleukin-2 (IL-2) and gamma interferon (IFN-γ). These studies were chosen because NK cell activity can be enhanced in cancer patients using cytokines like IL-2 to induce LAK cells and IFN-γ. Also, differences exist in the ability of NK cells to respond to IL-2 and IFN-γ in cancer patients managed with different types of therapy, i.e., local radiotherapy alone or radiotherapy plus adjuvant chemotherapy (Akimoto et al., 1986). We might anticipate that if the intervention is effective in lowering stress, then intervention subjects' NK cells might be more responsive to IL-2 and/or IFN-γ than NK cell responsiveness in the control group.

Peripheral blood leukocytes containing NK cells are prepared as described above. Cell suspensions is prepared,

2.8 x 10^6/ml, in complete RPMI 1640 medium supplemented with 10% FBS. The cells are incubated with either media (control) or recombinant IL-2 (60 units/ml) (Genzyme) or IFN-γ (250 units/ml) (Genzyme). The cell suspensions are gently mixed and incubated at 37^0 C for 65 hours. Following incubation, lymphocytes are washed 3 times in RPMI 1640 medium containing 10% FBS in order to remove residual cytokine. An NK cell assay is then be performed as described above.

Health status

Cancer treatment toxicities. The SWOG (Southwest Oncology Group) criteria is used to document the types of and severity of toxicity reactions from any of the cancer treatment regimens, particularly chemotherapy. The standard categories (e.g. blood/bone marrow, gastrointestinal, liver, kidney and bladder, heart, blood pressure, neurologic, fever, metabolic) are included with specific descriptions for each rating (0-4). This assessment is conducted by the project and CRC nurses who are trained and skilled in toxicity assessments.

Functional performance status is assessed using the Karnofsky Performance Status Scale (Karnofsky & Burchenal, 1949) which is the most widely used measure of functional status in cancer studies. The scale ranges from 100 (Normal, no complaints, no evidence of disease) to 0 (Dead) with each decile defined (e.g. 70 = Cares for self, unable to carry on normal activity). Across cancer studies interrater reliability for the scale ranges from .70 to .97, and many studies have demonstrated predictive validity with significant and high correlation with cancer endpoints (e.g. death, treatment toxicities, etc; Ganz et al, 1988). The CRC nurses will do this rating.

Other data/measures

Social desirability is assessed with the 13-item short form version (Reynolds, 1982) of the Marlow-Crowne Social Desirability Scale. High scorers tend to describe themselves in unrealistically positive ways on self-report measures. We administer the short form at the annual assessments as a strategy for examining this bias in the self report data, particularly for emotional distress as there is suggestive evidence for such a bias in older adults (Aneshensel et al., 1987).

Individual differences (personality). The Goldberg (1992) factor markers are used to assess Extraversion, Neuroticm, Openness (Intellect), and Conscientiousness. For each factor, 20 unipolar trait adjectives are used and each is rated on a 9 point scale as to how inaccurate vs accurate the word describes the rater. Extensive psychometric analyses of this measure have been done (Goldberg, 1992) including replications of the factor structure (e.g. coefficients of congruence range from .93 to .99), coefficient alpha reliability (ranging from .88 to .97), and correlations with Costa and McCrae's NEO-PI (ranging from .46 to -.68 with the domain scales). Finally, this measure is easier and quicker for subjects to complete than the NEO-PI.

Results, Statement of Work, and Discussion (DAMD17-96-1-6294)

Army funding in 1996 enabled this large, important effort to continue beyond the pilot phase. Full funding has enabled us to move agressively ahead on subject accrual, complete the backlog of previously unfunded tasks, and, importantly, expand the biologic aspect of the project to include a breast cancer specific immune assay mucin-1 (MUC-1) and an endocrine panel of measures (e.g. serum coritsol, catecholamines, prolactin, growth hormone). Three types of preliminary data are provided, per the statement of work: Task 1 (Recruitment), Task 2 (Intervention Groups), Task 3 and 4 (Data Collection and Analysis).

Task 1: Recruitment and Accrual

Eligible women are newly diagnosed and/or recently treated (i.e. < 3 months post surgery) women with Stage II or III invasive breast cancer who are $\geq$ 20 years of age. Considering accrual thus far, "up front" refusal rates are running 28%, and 12 month dropout rate is extremely low, 6%. The literature suggests that refusal rates in psychosocial intervention studies have ranged from 10 to 25% (Andersen, 1992). In considering the drop out rate, studies of low and moderate risk patients (i.e. Stage I - III: Andersen, 1992) were considered. The literature suggests that dropout rates range from 9% to 27% for the studies which have provided data for initial to 12 month assessments. Thus, the actual rates in this study are extremely good. Also, we have conducted analyses examining the potential for biases between the groups on sociodemographic, disease or health variables, and

current analyses find no significant group differences on any variable at the intial assessment between the study arms.

Below in **Table 2** is an accrual tally for the accrual rate and resulting numbers of psychological/medical/immune assessments for grant years 1-4. This summary is based on an annual projected rate of 60 potential subjects approached for recruitment per year, 45 Ss actually recruited and assessed per year. Per subject, there are 4 assessments during year 1 of participation (45 Ss x 4 = 180) and 2 assessments/year for years 2-4 (assuming 45 Ss x 2 = 90 for years 2 and 3) of participation. Rates designated with an asterisk (*) are projections. There are approximately 150 Ss accrued thus far.

Table 2: Accrual: Actual rate and projections for remainder of grant period.

Grant year	Accrual	Assessments by Accrual Year					Assessment Summary
		Pilot	1	2	3	4	N/year
Pilot	45	180	___	___	___	___	180
1st year	45	90	180	___	___	___	270
2nd year	45	90	90	180	___	___	360*
3rd year	45*	90*	90*	90*	180*	___	450*
4th year	45*	90*	90*	90*	90*	180*	540*

Task 2: Intervention Group

Seven cohorts of intervention groups have been conducted. There is presently a 11% drop out rate in the intervention arm. Because this rate is so low, it is difficult to single out particular reasons for drop out, however clinical data would suggest that women with prior psychiatric histories (e.g. major depression, agorophobia) are at greatest risk, and we are vigorously attending to these conditions to meet the needs of these women and retain them in the study.

Task 3 and 4: Data Collection and Analysis

These tasks have gone extremely well with the added funding. The first major paper from the project, entitled "Stress and immune responses following surgical treatment for regional breast cancer," appeared this year in the *Journal of the National Cancer Institute* and is provided in its entirety in the appendix. This paper provides a complete documentation of the methods, procedures, results, and discussion of the data from the project thus far, and so those areas are not repeated below, however we do provide a brief summary of the findings.

We examined the relationship between stress and several aspects of the cellular immune response in the context of the diagnosis of breast cancer and the post surgery period. Women (N = 116) recently surgically treated for Stage II (70%) or III (30%) invasive breast cancer participated. Prior to beginning adjuvant therapy, all completed a validated questionnaire assessing stress about the cancer experience and provided a 60cc blood sample. A panel of natural killer (NK) cell and T-cell assays were conducted: 1) NK cell lysis; 2) the response of NK cells to recombinant gamma interferon (rIFN-γ) and recombinant interleukin-2 (rIL-2); 3) blastogenic response of peripheral blood leukocytes (PBLs) to phytohemagglutinin A (PHA) and concanavalin A (ConA) and the proliferative response of PBLs to a monoclonal antibody (MAb) to the t-cell receptor (T3).

Multiple regression models were used to test the contribution of psychological stress in predicting immune function. We hypothesized a negative relationship between stress and immunity, and expected this relationship to be replicated between assays and within a single assay [i.e. replicated across effector to target (E:T) cell ratios for

NK cell lysis, for example]. All regression equations controlled for variables which might also be expected to exert short or long term effects on these responses, such as age, stage of disease, and length of time of surgical recovery, and ruled out other potentially confounding variables (e.g. nutritional status) that might also be influential. These controls reduced the plausibly of alternative, rival hypotheses for the findings.

Significant effects were found and replicated between and within assays, including the following: 1) stress significantly ($p < .05$) predicted NK cell lysis; 2) stress significantly ($p < .01$) predicted the response of NK cells to rIFN-γ; 3) stress significantly predicted the response of PBLs to ConA ($p < .05$) and PHA ($p < .05$), and the proliferative response to the T3 MAb ($p < .05$). The cells from 62% of the sample did not respond to rIL-2, but stress was not a factor in predicting the response for the remainder of the sample (38%). The data show that the physiologic effects of stress inhibited a panel of cellular immune responses, cancer relevant NK cell cytotoxicity and T cell responses. Our additional data accrued since the publication of these findings confirm the reliability of these observations.

CONCLUSIONS

To summarize, we view stress, QoL, health behaviors, and compliance as the major factors in a conceptual model of adjustment to the cancer stressor. Also part of the model are the physiological systems--the endocrine and immune systems--which may be important ones for moderating the effects of stress on disease processes. More specifically, we are finding that NK cell function is providing an important "window" on the immune response and a panel of endocrine measures--and growth hormone in particular--are an important stress hormone marker. The literature confirms that QoL benefits accrue from psychological interventions. In contrast, health behaviors and compliance have rarely been an intervention target, although data suggest that such a broadened approach would be effective and provide added power in the examination of stress/endocrine/immunity question.

The context of randomly assigning individuals to conditions that will result in differential psychological and behavioral outcomes (Andersen, 1992) provides one of the necessary conditions for an experimental test of the biobehavioral model. A "simple" experimental design--treatment vs. no treatment--was the strategic next step, as such a design provides cause--effect data for the presence of an intervention producing enhanced psychological and behavioral outcomes, immune responses, and health effects. In addition to the biobehavioral model, the specific design of the intervention, with intensive and maintenance phases, is novel as a maintenance component may be critical to achieve the longterm psychological /behavioral gains necessary to effect endocrine and immune responses and/or disease progression. In sum, the biobehavioral model provides a testable, conceptualization for PNI research in breast cancer and provides an opportunity to test for specific biologic or health consequences of psychological/behavioral interventions for breast cancer patients.

Tasks 1-4 in the Statement of Work have been accomplished. Accrual is proceeding at the projected rate and the refusal rate is in the range projected and the drop out rate is exceedingly low for a study as intensive as the present one. Seven cohorts of intervention groups have been conducted with only a 11% drop out rate. Adequate funding has provided staffing appropriate for the high demand of this project, including the need for psychological/behavioral and medical assessors, a nurse, laboratory technicians, and data management. The additional army grant funds have enabled us to expand the biological assessment to include a critical breast cancer specific immune assay (MUC-1) and an endocrine panel. Finally, our first empirical paper from the project was accepted in a top tier journal, *Journal of the National Cancer Institute*, and the paper recieved national and international coverage in the electronic, print, and radio/television media. It convincingly showed that the physiologic effects of stress inhibited a panel of cellular immune responses, cancer relevant NK cell cytotoxicity and T cell responses. We have conducted followup analyses and know that this is a stable effect. The longitudinal data from this study will be able to determine its health consequences and the biobehavioral mechanisms for any adverse health outcomes.

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REPORTS

Stress and Immune Responses After Surgical Treatment for Regional Breast Cancer

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Background: **Adults who undergo chronic stress, such as the diagnosis and surgical treatment of breast cancer, often experience adjustment difficulties and important biologic effects. This stress can affect the immune system, possibly reducing the ability of individuals with cancer to resist disease progression and metastatic spread. We examined whether stress influences cellular immune responses in patients following breast cancer diagnosis and surgery.** ***Methods:*** **We studied 116 patients recently treated surgically for invasive breast cancer. Before beginning their adjuvant therapy, all subjects completed a validated questionnaire assessing the stress of being cancer patients. A 60-mL blood sample taken from each patient was subjected to a panel of natural killer (NK) cell and T-lymphocyte assays. We then developed multiple regression models to test the contribution of psychologic stress in predicting immune function. All regression equations controlled for variables that might exert short- or long-term effects on these responses, and we also ruled out other potentially confounding variables.** ***Results:*** **We found, reproducibly between and within assays, the following: 1) Stress level significantly predicted lower NK cell lysis, 2) stress level significantly predicted diminished response of NK cells to recombinant interferon gamma, and 3) stress level significantly predicted decreased proliferative response of peripheral blood lymphocytes to plant lectins and to a monoclonal antibody directed against the T-cell receptor.** ***Conclusions:*** **The data show that the physiologic effects of stress inhibit cellular immune responses that are relevant to cancer prognosis, including NK cell toxicity and T-cell responses. Additional, longitudinal studies are needed to determine the duration of these effects, their health consequences, and their biologic and/or behavioral mechanisms. [J Natl Cancer Inst 1998; 90:30–6]**

A diagnosis of cancer and cancer treatments are objective, negative events in an individual's life. Although negative events do not always produce stress and a lowered quality of life, data from many studies document severe, acute stress at cancer diagnosis *(1)* and during recovery *(2)*. The negative psychologic responses of individuals with cancer to the diagnosis and treatment are important in their own right because these responses are targets for cancer control efforts *(3,4)*. In addition, data suggest that stress responses are accompanied by nonrandom (i.e., correlated) negative changes in a broad range of immune responses. This study examines from a biobehavioral perspective whether stress influences cellular immunity in women with breast cancer after diagnosis of breast cancer and during the postsurgical period *(5)*.

Meta-analyses *(6,7)* suggest that psychologic stress and the experience of life stressors are reliably associated with negative immune alterations in noncancer subjects; i.e., "higher" levels of stress (e.g., self-reports of stress or negative affects, such as sadness or clinical diagnoses of depression) are related quantitatively and functionally to "reduced" cellular immune responses, such as lowered natural killer (NK) cell lysis. This effect has been found regularly for individuals in the midst of chronic stressors, and some of the largest responses and changes have been found for lengthy stressors and those that have interpersonal components.

Illustrative data come from Kiecolt-Glaser, Glaser, and colleagues *(8–11)*, who have followed individuals during the long, stressful experience of giving care to a spouse diagnosed with Alzheimer's disease. Not surprisingly, caregivers report high levels of distress and negative affect as they cope with their relative's difficult behavior and mental deterioration *(8)*. Moreover, these researchers have found, for example, that NK cells obtained from caregivers are less responsive to the cytokine recombinant interferon gamma (rIFN γ) and recombinant interleukin 2 (rIL-2) than are cells obtained from matched community control subjects *(9)*. In addition, these highly stressed subjects have a poorer proliferative response to mitogens *(8)*, exhibit substantial deficits in the antibody and virus-specific T-cell responses to an influenza virus vaccine *(10)*, and demonstrate stress-related defects in wound repair *(11)*.

There are fewer data on the relationship between stress and immunity among cancer patients. Levy et al. *(12)* reported on these relationships in 66 women with stage I or II breast cancer 3 months after treatment (lumpectomy or mastectomy with or without adjuvant therapy). In ad-

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See "Notes" following "References."

dition to finding that estrogen receptor status predicted NK cell lysis, these researchers found that social support—a variable hypothesized to *reduce* stress—contributed significantly to a regression model predicting *higher* NK cell activity. These findings suggest that how a person responds to stress may also influence how stress, in turn, influences the immune response.

There is considerable evidence that patients with cancer express abnormal cellular immune responses; these abnormal responses have been found in patients with many different types of cancer *(13–15)*, including breast cancer *(16,17)*. Stressors are not generic, and they would not be expected to have identical physiologic outcomes. So too, the immune response involves a cascade of responses and events that can occur over time. For these reasons, we used a homogeneous breast cancer subject sample and timing of assessment to test the relationship between stress and several components of the cellular immune response, including NK cell and T-cell functions.

Women who had been diagnosed with breast cancer and who had undergone surgery for the breast cancer were studied before they began adjuvant therapy. Since we were interested in the contribution of stress in predicting an immune response above and beyond known correlates, we controlled for naturally occurring factors in our statistical analyses that affect the immune responses—specifically, age, disease stage (lymph node status), and recovery (days since surgery) *(18)*. Because the immune system contains a considerable amount of redundancy, we focused on three components that would each provide important, but complementary, information.

First, we measured NK cell lysis. We chose to measure NK cell lysis because those cells are believed to act early in the immune response and they have been demonstrated to play an important role in immune surveillance against tumors and virally infected cells *(19–21)*. Second, we measured the ability of the NK cells to respond to rIFN γ and rIL-2. It has been shown that lymphokine-activated killer (LAK) cells are highly cytotoxic against a wider variety of tumor cells than those lysed by resting NK cells *(22)*, an effect also observed in patients with breast cancer *(23)*. Finally, to obtain information on the T-cell response, we measured the response of peripheral blood leukocytes (PBLs) to two mitogens—phytohemagglutinin (PHA) and concanavalin A (Con A)—and we induced proliferation by stimulating the T cells with a monoclonal antibody (MAb) to the T-cell receptor.

Subjects and Methods

Patient Eligibility and Data Collection

Participants were 116 women who had been diagnosed with invasive breast cancer and who were surgically treated within the last 4 months but who had not yet begun adjuvant treatment. Women were from 14 to 101 days (mean = 37 days; median = 33 days) after surgery for stage II (70%) or III (30%) invasive breast cancer. We used the American Joint Committee on Cancer and the International Union Against Cancer staging system. The women ranged in age from 31 to 84 years (mean = 52 years). Recruited consecutively from mid-1994 to early 1997, the majority (82%) were being treated at a National Cancer Institute-designated, university-affiliated Comprehensive Cancer Center, and the remainder (18%) were receiving treatment at local community hospitals. All women came to the General Clinical Research Center at the university where psychologic, behavioral, and medical data were collected and a 60-mL blood sample was taken from them. Assessments were conducted between 8:00 AM and 12:00 AM to reduce diurnal variability.

Stress Measure

The Impact of Event Scale (IES) *(24)* is a standardized self-report questionnaire used to examine intrusive thoughts ("I had dreams about being a cancer patient." "Other things kept making me think about cancer") and avoidant thoughts and actions ("I tried not to talk about it." "I was aware that I still had a lot of feelings about cancer, but I didn't deal with them") concerning cancer. Fifteen items are used, and women rate each event or feeling in terms of the frequency of occurrence (i.e., "not at all," "rarely," "sometimes," and "often") during the previous 7 days. Scores range from 0 to 75. For this sample, descriptive statistics were as follows: range, 0–65; mean = 26; median = 25; and standard deviation = 15.2. The scale has satisfactory reliability with internal consistency of .78–.82 and a 2-week test–retest reliability of .79–.89, respectively. The validity of the measure is suggested by data indicating that individuals who experience involuntary, distress-related thoughts following traumatic life events are also those who suffer the greatest negative effects psychologically [e.g., *(2)*].

Immune Assays

Blood cell separation. PBLs were isolated from 60 mL of venous blood by use of Ficoll gradients (Pharmacia Biotech, Inc., Piscataway, NJ). The isolated leukocytes were then washed in calcium- and magnesium-free phosphate-buffered saline and counted on a Coulter counter (Coulter Corp., Miami, FL). Aliquots of 8×10^6 isolated PBLs were suspended again in 0.8 mL of RPMI-1640 medium supplemented with 10% fetal bovine serum, 0.75% sodium bicarbonate, 2 m*M* L-glutamine, and 10 μg/mL of ciprofloxacin.

Quantification of total T lymphocytes, T-cell subsets, and NK cells. Isolated PBLs were absorbed with MAbs conjugated to either fluorescein isothiocyanate or rhodamine according to the cell surface marker being studied: total T cells (CD3, fluorescein isothiocyanate), T4 subset (CD4, rhodamine), T8 subset (CD8, fluorescein isothiocyanate), and NK cells (CD56, rhodamine). All MAbs were purchased from Coulter Corp. Briefly, 0.5×10^6 cells were incubated with the MAb for 15 minutes at room temperature. After the incubation, the cells were fixed, and the red blood cells were lysed with Optilyse C, a buffered solution containing 1.5% formaldehyde, according to the manufacturer's instructions (Coulter Corp.). Samples were analyzed with the use of a Coulter EPICS Profile II flow cytometer as described previously *(8)*.

NK cell cytotoxicity. To determine NK cell activity, a microtiter ^{51}Cr-release cytotoxicity assay was used as described previously *(9,25)*. The target cells used were K-562 cells, an NK cell-sensitive human myeloid cell line. Target cells, labeled overnight for 16 hours with ^{51}Cr, were placed in triplicate wells of 96-well V-bottom plates, and PBLs were added, resulting in effector-to-target (E:T) cell ratios of 100:1, 50:1, 25:1, 12.5:1, and 6.25:1.

NK cell response to cytokines. Procedures for treatment of PBLs with rIFN γ and rIL-2 involved preparing isolated PBLs at a concentration of 3×10^6 cells/mL in complete RPMI-1640 medium and then seeding the cells into three replicate tissue culture tubes (Falcon, Becton Dickinson and Co., Lincoln Park, NJ) at 6×10^6 cells per tube. Cells were incubated in complete RPMI-1640 medium alone or complete medium supplemented with 250 IU/mL rINF γ or 60 IU/mL rIL-2 (Genzyme, Boston, MA). Cell suspensions were gently mixed and then incubated at 37 °C in an atmosphere of 5% CO_2 for 65 hours. For the assay, triplicate aliquots of cell suspensions were placed in wells of V-bottom plates, with E:T cell ratios of 50:1, 25:1, 12.5:1, 6.25:1, or 3.13:1. In addition, six wells with target cells and medium only and target cells with detergent (5% sodium dodecyl sulfate in phosphate-buffered saline) were prepared to determine spontaneously released chromium and maximal lysis, respectively. The plates were centrifuged at 300*g* for 5 minutes at 20 °C to bring the effector and target cells into close contact; they were then incubated at 37 °C in an atmosphere of 5% CO_2 for 5 hours. After this incubation, the plates were centrifuged at 300*g* for 5 minutes at 20 °C, 100 μL of supernatant was collected from each well, and counts per minute were determined by use of a Beckman 9000 gamma counter (Beckman Instruments, Inc., Fullerton, CA) as described previously *(9,26)*.

Blastogenic response to PHA, Con A, and MAb to the T3 receptor. The concentrations for PHA and Con A used were 2.5, 5.0, and 10.0 μg/mL. To measure the blastogenic response to the MAb to the T-cell receptor, we used the following three dilutions of the purified MAb: 32:1, 64:1, and 128:1. For all three assays isolated, PBLs seeded in triplicate at 0.5×10^5 per well were incubated for 68 hours at 37 °C in 96-well flat-bottomed plates and then labeled for 4 hours with MTS, i.e., 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt

(Promega Corp., Madison, WI) to measure proliferative response. Briefly, the MTS procedure is a nonradioactive calorimetric procedure that labels metabolically active cells via reduction of a colored substrate. The amount of proliferation was determined by optical density of the suspension in the well. Optical density determinations were performed by use of a Titertek Multiscan MCC microplate reader (Flow Laboratories, Inc., Finland) at a determination wavelength of 492 nm and a reference wavelength of 690 nm as has been noted *(27,28)*.

Statistical Analyses

Preliminary analyses. Before conducting the principal analyses, we checked the data for the contribution of "nuisance" variables (covariates) that could potentially be related to psychologic stress, immune outcomes, or both [*see (25)* for a discussion]. The variables examined were measures of aspirin, alcohol, caffeine, and nicotine intake; amount of sleep; plasma albumin level (as an indicator of nutritional status); incidence of recent infectious illness; and the Karnofsky performance status rating. We examined the relationships between these variables and each of the three sets of outcome variables: NK cell lysis, ability of NK cells to respond to rIFN γ and rIL-2, and the blastogenic response of PBLs to Con A, PHA, and the T3 MAb. Analysis of variance was used for the categorical independent variables, and simple correlations were used for numerically scaled independent variables.

Screening of these potential covariates involved examination of the relationships between 11 covariates and 20 dependent variables, or a total of 220 bivariate associations. Of these 220 associations, 15 were found to be statistically significant at .05 significance level. This number of significant effects is only slightly more than would be expected by chance alone (i.e., 220 × .05 = 11). Inspection of the significant relationships showed that many of them were attributable to the influence of a few outliers in the data. To be conservative, all of the regression analyses described below were run twice, once including and once excluding those covariates that had significant bivariate associations with the relevant dependent variables. In no case were results of the regression analyses significantly altered by the inclusion of the covariates. Given this fact and the consistently weak relationships of the covariates to the dependent variables, we do not report further results involving the covariates.

Principal analyses. The principal analyses assess the relationship between the IES measure of psychologic stress and the following three sets of outcome measures: 1) NK cell lysis at five E:T ratios, 2) response of NK cells to rIFN γ and rIL-2 stimulation at five E:T ratios each, and 3) the PBL blastogenic response to PHA and Con A and proliferative response to the T3 MAb at three concentrations or dilutions each.

We were interested in the role of stress in predicting these outcomes, over and above the impact of disease and recovery variables on the immune response. Thus, we chose to control for three variables: 1) age, which is associated with downregulation of the immune system; 2) disease stage, which is an indicator of the extent or burden of disease; and 3) days since surgery, which is an indicator of the degree of recovery from surgical stress and related factors (e.g., anesthesia).

Using hierarchical multiple regression *(29)*, we tested the predictive value of psychologic stress for the measured immune outcomes. This procedure enters variables in a specified sequence and, at the final step, provides a test of the variance of the dependent variable (immune outcome) due to the predictor (stress), above and beyond the contribution of the control variables (age, stage, and days since surgery). In these regression analyses, age, days since surgery, and IES were considered as numerical variables. Stage was a categorical variable with two levels: II versus III.

For all of the analyses described below, any missing data were managed by the pairwise deletion technique, wherein each bivariate association is estimated with the use of all subjects for whom measures on both variables are available. This approach allows for more complete usage of available data than do alternative procedures (e.g., listwise deletion). For all of the dependent variables except the response of NK cells to rIFN γ, the quantity of missing data was small—with never more than 10 observations missing for any bivariate association. Effective sample sizes for the regression analyses ranged from 113 for the NK cell lysis ratios to 103 for T3 MAb values. For rIFN γ measures, sample sizes varied from 85 to 49 across the range of concentrations employed.

For each analysis, we provided three regression models: models A, B, and C. Model A includes only the control (independent) variables (i.e., age, stage, and days since surgery) in predicting the immune outcome (e.g., NK cell lysis). Predictors in model A were introduced simultaneously because we had no basis for or a strong interest in investigating their effects in any particular sequence. Model B includes the three control variables as well as the psychologic stress variable (IES) in the prediction of the immune outcome. Of particular interest in this analysis was the increment in the squared multiple correlation (R^2) from model A to model B (i.e., R^2_{B-A}), indicating variance in a dependent variable (e.g., NK cell lysis) attributable to stress (IES) beyond that explained by the control predictors. In addition, the standardized regression beta (β) for the psychologic stress variable (IES) in model B (i.e., β_{Stress}) indicates the magnitude and direction of the influence of this predictor on the dependent variable. The significance of the β weight was also tested. Finally, model C indicates the contribution of psychologic stress as the lone predictor; this third model provides the simple association between psychologic stress and immune function.

Results

Analyses Predicting NK Cell Lysis

Table 1 provides the results from the three models, A, B, and C, predicting NK cell lysis. For model A, in which age, stage, and days since surgery are the independent variables, R^2_A was small and nonsignificant for every E:T ratio (all F ratios were <1.0). Because the percentage of NK cells available would influence the

Table 1. Results of regression analyses for predicting natural killer (NK) cell lysis across six effector-to-target cell (E:T) ratios

	Dependent variable: NK cell lysis at E:T ratios					
	100:1	50:1	25:1	12.5:1	6.25:1	3.125:1
Model A, R^2_A*	.005	.007	.012	.015	.020	.023
Model AA, R^2_{AA}†	.085	.148	.185	.233	.250	.241
Model B‡						
R^2_B	.135	.212	.238	.268	.275	.253
R^2_{B-AA}§	.050	.064	.053	.035	.025	.012
β_{Stress}‖	−.234	−.265	−.240	−.194	−.165	−.115
$t(df = 110)$¶	−2.462	−2.921	−2.672	−2.223	−1.892	−1.280
P	.016	.004	.008	.028	.062	.204
Model C#						
R^2_C	.067	.091	.084	.066	.056	.032
$t(df = 110)$¶	−2.826	−3.338	−3.199	−2.811	−2.558	−1.867
P	.006	.002	.002	.006	.012	.066

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, NK cell lysis. The R^2_A is the total variance in NK cell lysis explained by these three predictors.

†Model AA includes model A variables plus the control predictor percentage of NK cells for the immune outcome, NK cell lysis. The R^2_{AA} is the total variance in NK cell lysis explained by these four predictors.

‡Model B includes model AA control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, NK cell lysis. The R^2_B is the total variance in NK cell lysis explained by the four control predictors and the stress predictor.

§R^2_{B-AA} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the NK cell lysis outcome.

‖β_{Stress} is the standardized regression beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

¶*df* refers to the degrees of freedom in model B.

#Model C includes stress as the only predictor of the immune outcome, NK cell lysis. The R^2_C is the total variance in NK cell lysis explained by stress; this model provides the simple association between psychologic stress and immune function.

total NK cell activity as measured by lysis, we next added the percentage of NK cells, as determined by flow cytometry, into the analyses as an additional, independent control variable as shown (model AA). Across all E:T ratios, the R^2_{AA} values suggested that this variable added significant variance, as predicted, yielding R^2_{AA} values ranging from .085 to .250.

More important was the addition of the stress variable (IES) as a predictor, shown in model B. The value of R^2_B for lysis was noticeably larger than that of R^2_{AA}, and it provided a significant increment in prediction across the E:T ratios. These data indicate that the measure of psychologic stress that was used accounted for significant variance in NK cell lysis above and beyond that explained by age, stage, days since surgery, and percentage of NK cells. Moreover, the sign of the β regression coefficient for IES was negative, as predicted, indicating that an increase in measured stress was associated with a decline in NK cell lysis. The *t* tests for these coefficients were significant at five of the six E:T ratios. Also, no other predictor in model B had a significant regression coefficient.

We also provide the regression results when only IES was used as a predictor, eliminating the control predictors from the model (model C in Table 1). These results showed that the simple association between IES and NK cell lysis was statistically significant at five of the six E:T ratios.

Table 2. Results of regression analyses for predicting natural killer (NK) cell response to recombinant interferon gamma (rIFN γ) across five effector-to-target cell (E:T) ratios

	Dependent variable: NK cell response to rIFN γ at E:T ratios				
	50:1	25:1	12.5:1	6.25:1	3.125:1
Model A, R^2_A*	.025	.097	.080	.138	.124
Model B†					
R^2_B	.041	.151	.197	.257	.208
R^2_{B-A}‡	.016	.054	.117	.119	.084
β_{Stress}§	−.128	−.244	−.358	−.358	−.301
t	−1.104	−2.190	−3.203	−3.084	−2.083
df‖	82	81	74	65	46
P	.274	.032	.002	.004	.044
Model C¶					
R^2_C	.015	.077	.149	.149	.088
t	−1.128	−2.586	−3.581	−3.343	−2.080
df‖	82	81	74	65	46
P	.264	.012	.002	.002	.044

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, NK cell response. The R^2_A is the total variance in NK cell response explained by these three predictors.

†Model B includes model A control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, NK cell response. The R^2_B is the total variance in NK cell response explained by the three control predictors and the stress predictor.

‡R^2_{B-A} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the NK cell response.

§β_{Stress} is the standardized regression beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

‖*df* refers to the degrees of freedom in model B.

¶Model C includes stress as the only predictor of the immune outcome, NK cell response. The R^2_C is the total variance in NK cell response explained by stress; this model provides the simple association between psychologic stress and immune function.

Analyses Predicting Response of NK Cells to Cytokines

Results for the NK cell response to rIFN γ are provided in Table 2 and show a similar pattern. For model A, which used age, stage, and days since surgery as the independent variables, the value of R^2_A was small to moderate, ranging from .025 to .138. When stress (IES) was added to the model B regression, the R^2 values were statistically significant at all but one E:T ratio (50:1). Furthermore, the increments in the prediction due to IES, R^2_{B-A}, were significant and ranged from .054 to .119. This value reflects the proportion of variance in the cell response accounted for by stress (IES) beyond that explained by the control variables. Again, the negative weight of β for IES in model B indicated a negative influence of psychologic stress on the response of the NK cells to rIFN γ. Again, no other predictor in model B had a significant regression coefficient. Finally, the results for model C in Table 2 showed a simple association between IES and the rIFN γ response. These correlations were significant at four of the five E:T ratios; the proportions of variance accounted for were in the range of .077 to .149.

We attempted to calculate a parallel set of regressions for the response of NK cells to rIL-2. However, cells from a large proportion of the patients (62%) had no response to rIL-2. When the regressions were conducted on data obtained from the remaining patients (38%), the addition of stress (IES) in model B produced a significant R^2 value at the 25:1 E:T ratio only. It appeared that the majority of the subjects' NK cells did not respond to treatment with rIL-2.

Analyses Predicting Blastogenic Response of PBLs to Con A, PHA, and the T3 MAb

Table 3 shows regression results for the Con A and PHA blastogenic responses across three concentrations each. Because the findings are similar for both assays, they will be discussed together. For model A, which used age, stage, and days since surgery as the independent variables, the value of R^2_A for Con A ranged from .035 to .054 and was of similar magnitude for PHA, ranging from .022 to .033. Since the number of total T cells available will affect the blastogenesis values, we next added the number of T3-positive cells into the analyses as an additional, independent control variable as shown by the step model AA. Across all concentrations for each mitogen, the value of R^2_{AA} suggested that this variable added variance, yielding the R^2_{AA} values ranging from .105 to .125 for Con A and from .023 to .033 for PHA.

The addition of stress (IES) to the regression for blastogenesis added significant variance, as indicated in model B. All of the R^2 values were statistically significant. Considering the increments in R^2 due to stress (IES), these were significant and ranged from .032 to .061 for Con A and from .047 to .060 for PHA, reflecting the proportion of variance in the blastogenesis accounted for by IES beyond that explained by the control variables. Again, the negative β weights for IES in model B indicated a negative influence of psychologic stress on the blastogenic responses

Table 3. Results of regression analyses for predicting the blastogenic response to concanavalin A (Con A) and phytohemagglutinin A (PHA) across three concentrations each

	Dependent variable: blastogenic response of mitogen					
	Con A			PHA		
	10 μg/mL	5 μg/mL	2.5 μg/mL	10 μg/mL	5 μg/mL	2.5 μg/mL
Model A. R^2_A*	.035	.043	.054	.022	.024	.033
Model AA. R^2_{AA}†	.105	.125	.115	.023	.024	.033
Model B‡						
R^2_B	.166	.174	.147	.083	.074	.080
R^2_{B-AA}§	.061	.049	.032	.060	.050	.047
β_{Stress}‖	−.255	−.229	−.187	−.256	−.234	−.229
$t(df = 103)$¶	−2.668	−2.401	−1.927	−2.521	−2.299	−2.254
P	.010	.018	.058	.014	.024	.026
Model C#						
R^2_C	.053	.065	.053	.070	.054	.052
$t(df = 108)$¶	−2.443	−2.724	−2.443	−2.857	−2.489	−2.441
P	.016	.008	.016	.006	.014	.016

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, blastogenesis. The R^2_A is the total variance in blastogenesis explained by these three predictors.

†Model AA includes model A variables plus the control predictor of number of T cells for the immune outcome, blastogenesis. The R^2_{AA} is the total variance in blastogenesis explained by these four predictors.

‡Model B includes model AA control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, blastogenesis. The R^2_B is the total variance in blastogenesis explained by the four control predictors and the stress predictor.

§R^2_{B-AA} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the blastogenesis outcome.

‖β_{Stress} is the standardized regression beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

¶*df* refers to the degrees of freedom in model B.

#Model C includes stress as the only predictor of the immune outcome, blastogenesis. The R^2_C is the total variance in blastogenesis explained by stress; this model provides the simple association between psychologic stress and immune function.

across concentrations. Moreover, no other predictor in model B had a significant regression coefficient. Finally, results for model C in Table 3 showed a simple association between stress (IES) and the blastogenic response. These correlations were significant for each concentration of Con A and PHA.

Table 4 shows regression results for the proliferative response of T cells to three different dilutions of the T3 MAb. For model A, the control R^2 values were not significant for any dilution. Addition of number of T3-positive cells available as a control increased the variance accounted for as shown by the step model AA. The R^2_{AA} values ranged from .088 to .143. However, increments in R^2 due to the addition of stress (IES), as shown by R^2_{B-AA}, were significant, ranging from .056 to .067. This indicates that about 6% of the variance was accounted for by stress (IES) beyond that explained by the control variables. Once again, no other predictor in model B had a significant regression coefficient. Results for model C again showed the simple, significant association of stress (IES) with the response to the T3 MAb at all dilutions, with R^2_c values of .092 to .102.

Discussion

Any immune response involves a complex cascade of events that occur over time. Studies suggest that the peripheral products of stress can play numerous roles in regulating immunity, and so the effects of stress will, necessarily, be variable. Current research suggests, for example, that the acute stressors, both real stressors [e.g., parachute jumps *(30)*] and artificial stressors [e.g., experimental tasks including speech or math stress *(31)*], are correlated with the mobilization (increase) of NK cells. These changes are thought to be a result of alterations in cell trafficking. In contrast, studies of chronic stressors [e.g., bereavement, caregiving, or divorce *(7,9)*] suggest that stress can have an effect on the ability of NK cells to lyse a target cell, the ability of NK cells to respond to rIFN γ and rIL-2 *in vitro*, and other aspects of the cellular immune response.

Our results suggest that stress, as assessed via a self-report measure of intrusive and avoidant thoughts and behaviors about cancer, was related to a negative effect on NK cell lysis, the ability of NK cells to respond to two cytokines, the blastogenic response of PBLs to two mitogens, and the proliferative response to MAb T-cell receptor. These effects were inhibitory and of similar magnitude (i.e., reliable), both between the assays and within an assay (i.e., across E:T ratios and mitogen concentrations). The analyses controlled for variables that might also be expected to exert short-term or long-term effects on immunity—such as age, stage of disease, and days since surgery—and ruled out other potentially confounding variables (e.g., nutritional status) that might also be influential. These controls reduced the plausibility of alternative, rival hypotheses for these consistent findings.

It is recognized that NK cells mediate natural immunity, but some researchers *(32)* suggest that their role in health generally has been underestimated. For example, there is evidence to suggest that the NK cells participate either directly or indirectly in multiple developmental, regulatory, and communication networks of the immune system. Furthermore, NK cells are efficient effector cells that not only are equipped for cell killing, but also are capable of rapid responses to exogenous or endogenous signals by producing cytokines and other factors involved in interactions between immune and nonimmune cells *(20)*.

The ability to spontaneously lyse a broad range of infected cells or tumor cells is the best known functional attribute of NK cells *(20,22)*. Consistent with previous reports, these data suggest that stress may impair this important process. Our findings highlight the specific effect of cancer stress on immune function, whereas prior data obtained by Levy et al. *(33)* had suggested that women's reports of fatigue were related to lower levels of NK cell lysis. Chronically low levels of NK cell activity occur in patients with cancer, particularly when there are large tumor burdens or disseminated metastases *(32)*. In general, patients with low NK cell activity appear to be at higher risk for infections, to have more prolonged diseases, or to suffer more severe symptoms

Table 4. Results of regression analyses for predicting proliferative response of peripheral blood leukocytes to a monoclonal antibody to T-cell receptor (T3) across three dilutions

	Dependent variable: proliferative response at dilutions		
	128:1	64:1	32:1
Model A. R^2_A*	.026	.052	.064
Model AA. R^2_{AA}†	.088	.104	.143
Model B‡			
R^2_B	.155	.160	.200
R^2_{B-AA}§	.067	.056	.057
β_{Stress}‖	−.273	−.249	−.252
$t(df = 101)$¶	−2.747	−2.514	−2.604
P	.008	.014	.012
Model C#			
R^2_C	.102	.092	.094
$t(df = 101)$¶	−3.452	−3.255	−3.307
P	.002	.002	.002

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, proliferative response. The R^2_A is the total variance in proliferation explained by these three predictors.

†Model AA includes model A variables plus the control predictor of number of T cells for the immune outcome, proliferation. The R^2_{AA} is the total variance in proliferation explained by these four predictors.

‡Model B includes model AA control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, proliferation. The R^2_B is the total variance in proliferation explained by the four control predictors and the stress predictor.

§R^2_{B-AA} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the proliferation outcome.

‖β_{Stress} is the standardized beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

¶df refers to the degrees of freedom in model B.

#Model C includes stress as the only predictor of the immune outcome, proliferation. The R^2_C is the total variance in proliferation explained by stress; this model provides the simple association between psychologic stress and immune function.

than patients whose NK cell activity remains normal *(32,34)*.

A variety of biologic response modifiers are known to increase the activation, proliferation, or cytotoxicity of NK cells *(20)*. Among the best known activators of NK cells are IL-2 and IFN γ. Our data show that the physiologic changes associated with psychologic stress inhibited NK cell lysis. Stress also affected the ability of NK cells to respond to rIFN γ, a finding that is consistent with two previous reports involving another life stressor [i.e., caregiving for a spouse with Alzheimer's disease *(9,26)*]. It is interesting that NK cells from 62% of the women did not respond to rIL-2. In subsequent analyses comparing women who did have an rIL-2 response with those who did not, no stress or disease variable differentiated the two groups. Further studies will need to be performed to explore this result, although it is possible that the lack of responsiveness of NK cells to rIL-2 may be due to an overproduction of prostaglandin E_2 by monocytes. It has been suggested that in breast cancer patients prostaglandin E_2 decreases IL-2 production in effector cell populations, resulting in the down-regulation of the expression of the IL-2 receptor on NK cells *(23)*. Follow-up studies will need to pursue and clarify this difference in cytokine responses.

It has been shown that the ability of PBLs to respond to PHA is reduced, in general, in cancer patients *(35)*; this lowered response is related to tumor burden and declines in the ability of PBLs to respond to PHA with disease progression *(36)*. The negative effect of stress on blastogenesis was replicated in this study across two mitogens, PHA and Con A, as well as in the response of T cells to an MAb against the T-cell receptor. These findings are consistent with correlational and experimental studies indicating that stress impairs the blastogenic response of PBLs to mitogens and virus-specific T-cell responses *(8,10,37–39)*. Mitogen-induced proliferation has been used to indicate the immune system's ability to respond to antigens from pathogens. Chronically stressed, but healthy, individuals showing decrements in the cellular immune response (including NK cell lysis and the response of the PBLs to mitogens) subsequently reported a higher incidence of infectious illnesses *(8)*. If this effect is reliable, these data would suggest that cancer patients who experience high levels of stress, lowered levels of responsive T lymphocytes, and decreased NK cell function may be at greater risk for infectious illnesses as they begin adjuvant therapy.

It is interesting that evidence is accumulating to suggest that psychologic and/or behavioral stress reduction interventions may *enhance* certain aspects of the cellular immune response, including NK cell lysis. In an early investigation, Kiecolt-Glaser et al. *(40)* studied 61 healthy adults living in a retirement home. After receiving 1 month of training in progressive muscle relaxation, the subjects showed evidence of a 30% increase in NK cell lysis in comparison with those who received no treatment or only social contact. Fawzy et al. *(41)* studied 61 patients with melanoma and reported that, 6 months after treatment, subjects receiving intervention had significantly higher levels of IFN alfa-augmented NK cell activity than those who received no treatment. These data suggest that, if behavioral interventions can reduce stress and enhance the cellular immune response, then health outcomes might improve.

In conclusion, these data show a down-regulation of different aspects of the cellular immune response associated with the psychologic stress that accompanies the diagnosis and initial surgical treatment of cancer. We note that these study participants are part of a larger effort testing the biobehavioral aspects of stress, immunity, and disease course *(5)*. It will be important to document the longitudinal nature of these findings, and future studies will provide such data. Moreover, half of the women who participated have been randomly assigned to receive a psychologic/behavioral intervention specifically designed to reduce stress, enhance quality of life, and test for the biologic mechanism—such as immune responses—that may mediate any positive effects of stress reduction on health and disease outcomes.

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tate cancer screening. Arnauld Villers, M.D., Ph.D., a urologist from the Hospital Purpan in Toulouse, France, said he expects the agency to allow general practitioners to recommend PSA testing for men 50 to 75 years of age within the next few months. Prostate cancer gained importance among the French public after former president Francois Mitterrand's diagnosis and subsequent death from the disease in 1996.

Participation rates in the screening trials vary partly due to randomization methods. Some of the trials randomize entire geographic populations. Then men in one area are offered screening. Acceptance of this offer is highest in Finland at 70%; Italy and Sweden are at 60%.

Other trials recruit men prior to randomization and seek to maximize participation so that men in the trial are more typical of the general population. With this approach, the Netherlands has 46% participation.

The study that is based in Antwerp, Belgium, managed to boost its participation rate from 18% to 34% by visiting the homes of men who are eligible to participate. Spain has reached only 23%, and that study's leaders don't expect participation to improve, due to the population's overall fear of detecting illness.

Strength from Diversity

Although the studies follow a core protocol (they must use PSA, employ one of two valid randomization approaches, ascertain prostate cancer mortality in both arms of the study, and apply quality control standards for application of the screening tests), they contain deliberate variations (J Natl Cancer Inst, June 21, 1995;87:868-871). They vary in the number of years between screenings, in the PSA measure that indicates the need for further testing, and in the screening tests provided along with PSA (they may or may not provide digital rectal exam or transrectal ultrasound.). Finally, the treatment options offered depend on each patient's urologist.

This lack of uniformity among the protocols is, technically speaking, an epidemiologists' nightmare. But Freda Alexander, Ph.D., of the University of Edinburgh, Scotland, chair of the ERSPC Epidemiology Committee, used an example to point out its added value. "We could just go with very frequent screenings to get the maximum effect, but that doesn't tell us how well much cheaper screening works." So some centers are using a 1-year screening interval, while others are waiting as long as 4 years between screenings.

Schröder agreed. "There will be a wealth of information coming from [the combined studies] concerning the optimization of the use of screening tests, the types of cancer detected at screening, and prognostic factor analysis that may allow greater selectivity of screening procedures in the future, with proper identification of the type of tumor that may benefit from early treatment."

To avoid contamination of the control group and because the study is looking for differences in mortality, study group members have committed to delay publishing endpoint data until 10-year followup is completed. But, Alexander added, "If evidence accrues that screening might influence shorter-term conditions, the ERSPC management committee could change that policy."

— *Cori Vanchieri*

Stress Reduction: Three Trials Test Its Impact on Breast Cancer Progression

Does psychological stress play a role in cancer progression and can reducing stress slow tumor growth? Some answers could be available soon after the year 2000 to this question, which has intrigued mental health specialists for several decades.

Up to now, the field of psychoneuroimmunology has yielded relatively little data related to cancer. In the area of infectious diseases, particularly colds, researchers have found a variety of links between psychological stress and the immune system. A few investigators have looked specifically at cancer patients and how the stress of diagnosis and treatment may affect immune response. Only a very few have ever designed an intervention to see whether stress reduction can improve immune function and slow cancer progression.


Dr. Barbara Andersen

Now, three such studies are under way, all randomized, controlled trials of support-group interventions with breast cancer patients. None of the trials has data on tumor recurrence or survival yet. But early findings from one of them, reported on page 30, support the hypothesis that cancer-related stress is associated with cellular immune responses that may play a role in tumor growth.

Barbara Andersen, Ph.D., and colleagues at Ohio State University, Columbus, report that baseline measures of stress, specific to the diagnosis of cancer, were linked to levels of natural killer cell activity, T-cell responses, and other cellular responses "relevant to cancer prognosis."

It's still a big step from this finding to the question that Andersen would most like to answer: Can a stress reduction intervention influence cancer progression? But her larger study, plus two others now in progress in the United States and Canada, may help provide that answer over the next 6 years.

Andersen's larger study at Ohio State will involve 235 women with stage II or III breast cancer who are randomized, after surgery and before adjuvant therapy, into two groups, one of which will attend support groups for a year. The group sessions empasize both emotional support and education on, for instance, coping strategies.

All participants are assessed, first at enrollment and then 5 years following randomization to determine stress levels, cellular immune responses, and cancer recurrence. As of Dec. 1, 1997, 160 patients had been accrued. Recruitment should be completed in 1998, Andersen said, and results could be available in about 6 years.

While the step from reducing stress to reducing recurrence rates seems a giant one, the hypothesis has some evidence to back it. In the late 1980s, David Spiegel, M.D., a psychiatrist at Stanford University, discovered that breast cancer patients who received psychosocial support had better survival rates than patients in a control group who received no formal intervention.

Spiegel said he and his colleagues had set out to study the impact of a particular form of support on quality of life. They had not intended to look at survival. But after 10 years, they found that the 50 women in the support group (designed to encourage full "emotional expressiveness" about the cancer and allow patients to confront their feelings about the disease) had survival rates nearly twice those of the 36 patients in the control group. Mean survival for the intervention group was 36.6 months from the time of randomization compared with 18.9 months for the control group.

A few other small studies have had contradictory results. Most frequently cited is a randomized controlled trial at the University of California, Los Angeles, where Fawzy I. Fawzy, M.D., found that a psychosocial intervention was associated with longer survival in melanoma patients.

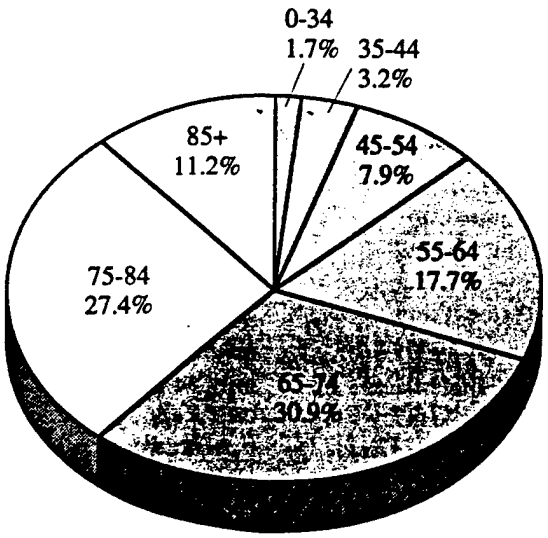
The other U.S. trial looking at stress reduction, immune factors, and cancer

Stat Bite

Age Distribution of Cancer Deaths in the United States

While cancer mortality has begun to decline in the United States, it is estimated that about 560,000 Americans died of the disease in 1997. Because cancer more often occurs in older age groups, more than two-thirds of cancer deaths occur after age 64.

Percent of cancer deaths by age group, all sites, 1990-1994



Source: *SEER Cancer Statistics Review, 1973-1994*/National Center for Health Statistics public use tapes.

progression is under way at Stanford where Spiegel and colleagues are replicating the earlier study with a larger group. Initiated in 1990, the trial has 125 participants who were randomized into two groups, one of which attended support sessions.

Now about three-quarters of the way through a 10-year followup, the investigators are monitoring endocrine and cellular markers of immune function, such as cortisol levels and natural killer cell activity, as well as recurrence and survival rates. Spiegel said they expect to have some preliminary results published later this year, and final results, including survival data, could be ready around the year 2000.

A third trial on stress reduction and cancer progression is taking place in Canada at seven different sites. Led by Pamela Goodwin, M.D. at Mount Sinai Hospital, Toronto, the trial is replicating Speigel's intervention with 235 women. Goodwin said this study should have completed recruitment by the end of 1997 and that results, including survival data, could be available around 2000.

Controversy Continues

A major hypothesis in all three studies — that stress reduction can alter immune function in a way that influences cancer progression — is a controversial one, said Sheldon Cohen, Ph.D. and Bruce Rabin, M.D., University of Pittsburgh, in their editorial on page ___. There is too little known, for one thing, about the type and magnitude of the immune responses that influence cancer progression, they say.

Another problem in studying the role of psychosocial interventions are the number and complexity of factors that might independently influence immune responses and cancer progression. All three trials now in progress are controlling for known prognostic factors, such as the extent of lymph node involvement and whether the tumor cells had estrogen receptors. But numerous other factors could play a role, including the immunosuppressive effects of cancer treatment, the details of which are not completely known.

Another point noted by Cohen and Rabin — and one that turns up repeatedly in the literature on stress reduction and cancer survival — is that a support group could influence disease progression by means other than the stress reduction/immune response mechanism. For instance, supportive interventions might work because they encourage treatment compliance.

Spiegel said that he and colleagues examined this issue in their earlier study by reviewing participants' medical records. They found no difference in treatment that could account for the difference in survival rates. For that trial, "we've pretty much ruled out differences in treatment as an explanation," he said.

However, the impact of intervention on compliance with treatment is still an unknown. One hypothesis being tested in the Canadian study, said Goodwin, is that the psychosocial intervention improves survival by encouraging compliance. The Ohio State researchers are also looking at medical treatment, collecting data not only on prescribed treatment but also on the chemotherapy doses that each patient actually receives.

It is a key issue, Andersen said. "This is something we are looking at very closely."

— Caroline McNeil

To Build a Better Mousetrap, Use Human Parts

Historically disappointing results with mouse-based monoclonal antibodies (MAbs) have biased many clinicians against this approach to treating human diseases. Now, re-engineered antibodies are ready for a comeback, thanks to the persistence of a few researchers who were unwilling to abandon the idea.

One MAb, IDEC-C2B8 or rituximab, recently was approved by the Food and Drug Administration for treatment of a type of non-Hodgkin's lymphoma (see sidebar). Several others, such as HER2 for breast cancer and A33 and anti-EGP40 for colorectal cancer are in clinical trials. And at least two dozen other MAbs are in various stages of clinical testing in the cancer setting.

Such signs of progress have rekindled hope in those researchers who have continued over the past several decades to explore the basic MAb concept — that an antibody injected into a cancer patient could seek out a specific antigen on cancer cells, bind to that antigen, and activate the body's immune system to kill with great specificity only the cancer cells.

Dr. Thomas A.Waldmann

The breakthrough that turned that vision into clinical reality, according to Thomas A. Waldmann, M.D., chief of the metabolism branch at the National Cancer