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International Journal of Psychophysiology 54 (2004) 241–249

INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY

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The interaction of social network size and stressful life events predict delayed-type hypersensitivity among women with metastatic breast cancer

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Received 7 October 2003; received in revised form 10 May 2004; accepted 12 May 2004
Available online 4 July 2004

Abstract

This study examined relationships between social support, stressful life events and antigen-specific cell-mediated immunity. Participants were 72 women with documented metastatic breast carcinoma, who completed self-report measures of social support and life stress. Immune response was assessed using the delayed type hypersensitivity (DTH) skin test. Number of positive antigens was significantly related to the interaction of social network size and stressful life events ($p < 0.05$). Number of positive antigens was greater for women who had experienced a high frequency of stressful life events but who reported a larger network of support. However, social network size was inversely related to DTH response among women who had experienced fewer stressful life events. Average induration size was not significantly related to the quality of social support, life stress per se, or their interactions. The relationship between social network size and immune response in women with metastatic breast cancer depends on prior stressful life experience.

Keywords: Social support; Stress; Cancer; Immunity; Hypersensitivity

The central importance of personal relationships in mediating between stress and illness has stimulated considerable research (Uchino et al., 1996). Indeed, social integration is associated with a two-fold reduction in all-cause age-adjusted mortality, an effect comparable to that produced by low serum cholesterol levels or nonsmoking status (House et al., 1988). Similarly, interventions providing psychosocial support have been demonstrated to improve outcome in patients with cancer in five of ten published randomized trials (Linn et al., 1982; Spiegel et al., 1989; Richardson et al., 1990; Fawzy et al., 1993; Ilnyckyj et al., 1994; Cunningham et al., 1998; Kuchler et al., 1999) and in other diseases (Ornish et al., 1990, 1998; Smyth et al., 1999).

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doi:10.1016/j.ijpsycho.2004.05.010

Beneficial health effects of social support have been found to operate via main and buffering effects on stress (Cohen, 1988; Cohen and Hoberman, 1983; Cohen and Wills, 1985; House et al., 1988; Levine et al., 1989; Uchino et al., 1996; Spiegel, 1999, 2001). Evidence for the stress buffering model of support comes from studies of quantitative and functional immune assessments of cell-mediated and antibody mediated immunity (Kiecolt-Glaser and Glaser, 1991). This is important given that chronic stress has been repeatedly reported to have immunosuppressive effects in humans as well as in animal studies (Cohen et al., 1999; Glaser et al., 1998; Herbert and Cohen, 1993; Kiecolt-Glaser et al., 1998; Sheridan et al., 1994, 1998; Sternberg et al., 1992; Vedhara et al., 1999). Examining the effect of social support on NK and T cell function among spouses of cancer patients, a positive relationship between social support and natural killer cell activity and with 1 of 2 measures of in vitro T cell activity has been found. A similar relationship between social support and in vitro T cell activity has been described in several other studies (Kiecolt-Glaser et al., 1991; Linn et al., 1988; Persson et al., 1994; Thomas et al., 1985).

While some researchers have pointed to the multidimensional nature of social support (Uchino et al., 1995, 1996) and tried to identify particular components of social networks that may be most beneficial (Cohen and Wills, 1985; Seeman et al., 1994), others have noted that potentially supportive social interactions can sometimes have negative consequences (Buunk and Hoorens, 1992). Social relations may also generate a paradoxical response. Negative effects could arise from aversive social interactions, from excessive or unwanted advice, or from the stress of trying to maintain social relationships during times of illness. Among the same sample studied here, in patients undergoing stressful life events, larger social network size has been previously found to be associated with reduced mood disturbance, while aversive social support was associated with increased mood disturbance (Koopman et al., 1998).

However, it is pertinent that stress does not always have adverse effects (Dhabhar and McEwen, 1997). For evolutionarily adaptive reasons, physiological reactions to stress may have short-term beneficial effects, including immunoenhancement (Dhabhar and McEwen, 1997). Under conditions of acute stress, in vivo cell-mediated responses in rats have been observed to increase, whereas under conditions of chronic stress, such responses are suppressed (Dhabhar and McEwen, 1997). There is strong evidence to suggest that enhancement and inhibition under differential stress conditions are mediated 'systemically' or 'globally' by the adrenal stress hormones, cortisol and epinephrine (Dhabhar and McEwen, 1999) and mediated 'locally' by the cytokine, interferon (IFN) gamma (Dhabhar et al., 2000). The mechanism proposed by which T cell response to delayed type hypersensitivity (DTH) skin test antigens could be enhanced under conditions of acute stress is via leukocyte redistribution from the blood to skin and lymph nodes (Dhabhar et al., 1996).

Despite these findings and the fact that reduced DTH responses have been described in humans experiencing a range of stressful conditions (Vedhara and Nott, 1996; Mehta et al., 2000), literature including the role of social relationships in humans is limited. Yet studies involving such differential in vivo immune responses may be particularly important in relation to disease progression. To the best of our knowledge, there is only one study to date that examines the relationship between stress, social relations and in vivo cellular immune response as measured by DTH in humans (Cole et al., 1999). This study (Cole et al., 1999) measured DTH responses in a sample of functional bowel disease and fibromyalgia patients, classified according to social inhibition characteristics, comparing conditions of high social engagement with a baseline control condition. They found DTH induration responses to be greater for socially inhibited individuals (Cole et al., 1999). Although this study describes a 'stable predisposition' of social inhibition as being related to heightened immunological responsiveness under conditions of intense social engagement, the results could more generally provide evidence to support the notion that an individual's immunological defense system is affected by engagement in social relationships.

We hypothesized that lower social support (smaller social network or reduced positive support) would be associated with reduced cell-mediated immune function as measured by DTH responses. Secondly, we hypothesized that increases in stressful life events (measured in terms of number of events, recency,

and severity) would be associated with decreased DTH responses. Thirdly, we hypothesized that the greatest DTH responses would be found among women who reported higher social support (larger social network and more positive social support) and less life stress.

1. Method

Using a cross-sectional design, we examined relationships between social support, stressful life events, and an in vivo measure of T cell activity, DTH, in women with metastatic breast cancer. The aim was to examine physiological responses in a population of women for whom social support might be particularly valuable.

1.1. Participants

Participants were drawn from a larger sample of 125 women with documented metastatic breast carcinoma who were recruited into a randomized, prospective study of the effects of supportive/expressive group psychotherapy on cancer survival (Spiegel and Classen, 2000; Spiegel et al., 1989). Women were considered eligible for the study if they had confirmed diagnoses of stage IV metastatic disease, had a physician's Karnofsky rating of 70% or more, had adequate proficiency in English to complete the questionnaires and participate in an English speaking therapy group and lived within San Francisco Bay area. Of the sample of 125 women, 29 did not have complete data on the variables under investigation and were not included in analysis. A further 24 had used steroid medications or drugs that affect endogenous cortisol levels (Megace, inhalant or systemic corticosteroids) within the previous 2 weeks and so were not included in this study due to potential effects on DTH response. The subset of 72 women who had full data on social support, stressful life events and DTH were included in analysis. Demographics and medical variables of the sample are shown in Table 1. After complete description of the study to the participants, written informed consent was obtained.

The only difference between the final sample of 72 women compared to the sample of 53 women who were dropped due to medication use or missing data was that the final sample was significantly ($p < 0.05$) older (mean age = 54.7 years, SD = 10.0) than those women who were dropped from this analysis (mean age = 50.7 years, SD = 9.9).

Table 1
Demographic and medical variables ($N = 72$)

Mean age (SD)	54.9 (11.0)	
Mean years of education (SD)	16.1 (2.7)	
Ethnic background	White	90.3% (65)
	Asian-American	6.9% (5)
	Native American	1.4% (1)
	Black/African American	1.4% (1)
Currently married		51.4% (37)
Income	Less than $20,000	13.9% (10)
	$20,000–99,999	66.7% (48)
	$100,000 and above	19.4% (14)
Disease free interval Mean (SD)	49.5 (35.9) months	
	Chest wall or regional lymph nodes	31.9% (23)
Dominant site of recurrence	Bone	37.5% (27)
	Viscera	30.6% (22)
Treatment received within 2 months of study entry	Chemotherapy	33.3% (24)
	Radiotherapy	16.7% (12)
Prior hormonal treatment		81.9% (59)
Estrogen receptor status	Positive	72.2% (52)
	Negative	19.4% (14)
	Unknown	8.3% (6)

1.2. Psychosocial measures

Patients completed questionnaires at baseline (prior to randomization) to assess demographic and disease status variables and the following:

Social Support. (1) The 29-item Yale social support index (Seeman and Berkman, 1988). This has been used extensively to assess number of contacts (Berkman and Syme, 1979), quality of support (Berkman, 1986) and patient satisfaction with support received (Seeman and Berkman, 1988). In aged populations, this measure has been used successfully to predict physical performance and mortality (Seeman et al., 1993, 1994, 1995). (2) The Single Item Measure of Social Support (SIMSS) (Blake and McKay, 1986). This scale assessed practical support, asking participants: 'How many people do you have near that you can readily count on for real help in times of trouble or difficulty, such as watch over children or pets, give

rides to hospital or store, or help if you are sick?' Response options are '0,' '1,' '2–5,' '6–9,' or '10 or more', ranging from low to high assistance. This measure has been strongly associated with a composite social support index and is predictive of morbidity in women (Blake and McKay, 1986).

Life Event Scale (Horowitz et al., 1977). This 37-item self-report instrument, designed to evaluate cumulative stress from the impact of life events, assesses categories of stressors including deaths, separations, health concerns, threats to self or self-image, and threats to material well being (e.g. 'Death of your mother,' 'Loss of a personally valuable object,' and 'Failing an important examination'). Participants selected the time frame within which each event most recently occurred from; (1) 1 day–1 week ago; (2) 1–6 months ago; (3) 6–12 months ago; (4) 1–2 years ago; (5) over 2 years ago; and (6) never. We used the overall presumptive stress scores recommended by Horowitz et al. (1977). Greater weighting was given to an event if the respondent indicated that it occurred more recently. Test–retest reliability has been found to be moderate for recent events (0.71 after a 6-week interval for the same events) and somewhat better for distant events (0.81 after a 1-year interval).

1.3. Immune measure

Antigen-specific cell-mediated immune response was evaluated in vivo at baseline, prior to randomization, using The Multitest CMI (Pasteur Merieux Connaught, Swiftwater, PA) to measure delayed type hypersensitivity (DTH) response. DTH is a measure of cellular immune response to injected antigen and as such is a localized inflammatory reaction that is initiated by helper T cells that have been previously sensitized to a particular antigen. Upon recognition of the antigen, these T cells secrete cytokines which recruit non-specific inflammatory cells, to the site of the reaction. This test used simultaneous measurement of cutaneous DTH responses to seven commonly encountered antigens (tuberculin, tetanus, diphtheria, Streptococcus, Candida, Trichophyton, and Proteus) in comparison to a vehicle control. Antigens were administered subcutaneously on the volar surface of the forearm and response indicated by induration at the site of administration was measured 48 h later. The Connaught test has the seven antigens (and an eighth control needle) arranged in a standard manner on a single pad, so all subjects receive the same pattern of antigens at the same time. Criteria for a positive reaction were as follows, based on that outlined in previous studies (Hickie et al., 1995; Rosenstreich, 1993). The size of each induration was recorded as the mean of two measurements of the diameter of the induration taken at right angles to one another. Induration exceeding the response to control vehicle by more than 2 mm mean diameter was considered a positive reaction. Responses were scored to indicate the number of positive responses and the sum of the mean diameter measurements. While the measure itself is relatively crude, it has the distinct advantage of being an in vivo measure of actual immune response to antigen, and of the seven different antigens reduces the effect of exposure history and provides evidence regarding the immune system's ability to respond to antigenic challenge.

Eight patients reported having prior adverse reactions to tuberculin administration. For these patients the tuberculin antigen was omitted from the test and their scores were adjusted to account for the fact that fewer antigens were used. The two DTH outcome variables used in analyses were number of positive antigens and average induration size of response to positive antigens.

1.4. Data analysis

Because the items used on the Yale Index of Social Support and the Single Item Measure of Social Support varied between 4- and 5-point response alternatives, we transformed responses into three scales for analysis; size of social network, positive support, and aversive relationships (Koopman et al., 1998). Participants responses to each individual item were then converted into percentile ranks for that item, and for each subject the percentile ranks on the items composing a given scale were averaged (summed and then divided by the number of items on the scale) to determine the score on the scale. To minimize multicolinearity due to interaction terms that were the product of two other independent variables, we used a centering procedure (Glantz and Slinker, 1990).

Associations of the DTH dependent variables with current systemic medical treatment, radiotherapy treatments received within 2 months of baseline data collection, and other current medications (e.g., androgens, antidepressants, and cholesterol-lowering medications) were examined using Spearman rank correlation coefficients. None of these medical variables was significantly correlated with DTH in bivariate correlational analyses and therefore were not included in regression analyses.

Multiple regression analysis using a stepwise forward procedure was used to analyze the relationships between the independent and the dependent variables. The two dependent variables were correlated at $r = 0.25$ and thus analyzed in separate regression models: (1) the number of positive DTH responses and (2) the average diameter of all positive DTH responses. Included in both regression analyses were the four independent variables of primary interest: social network size, positive social support, aversive social support and stressful life events entered in the first block and their interaction terms entered in the second block.

2. Results

Consistent with previous results in patients with disseminated cancer, overall DTH responses in this population were very low. A mean of 1.4 (SD = 1.3) out of seven antigens positive compared to a mean of 3.5 out of seven antigens positive in normal female volunteers. However, plots of the residuals, for number of positive antigens, did not indicate failure of normality in terms of a restricted dependent range, and as such assumptions of multivariate analyses were met (Tabachnick and Fidell, 1996). As a main effect, none of the social support or life stress variables or their interactions was significantly related to the strength of the mechanisms involved in mounting the response to the skin test.

The multiple regression was statistically significant for the number of positive antigens to the skin test as the dependent variable [overall $F(1, 70) = 4.70$, $p < 0.05$, adjusted overall $R^2 = 0.05$], with a significant interaction found between stressful life events and size of social network (Beta = 0.25, $t = 2.16$, $p < 0.05$). As hypothesized, the number of positive antigens to the skin test was greater when the social network was large, however this occurred only among women who had experienced higher stressful life events. For those women who had experienced few stressful life events, the relationship between size of social network and number of positive antigens was reversed (see Fig. 1). No further significant relationships were found between the other psychosocial variables and number of positive antigens on the skin test.

Additional correlational analyses were conducted to assess the relationship between the CMI variable of significance in the regression (number of positive antigens) and cortisol (methods and procedure detailed elsewhere CITE). In line with the original hypotheses it was postulated that the DTH alterations found in response to the interactive effect of life stress and support network may occur via the action of cortisol. Both diurnal salivary cortisol and a morning measure of salivary cortisol (8 am) were assessed. For diurnal cortisol no significant correlations were found with number of positive antigens, however, for the morning measure, a small but significant negative effect was found. In addition, correlations between the relevant significant effects of life stress and negative support were also assessed. A modest but significant positive effect was found between morning cortisol and negative support. The correlation coefficients for number of positive antigens, morning cor-

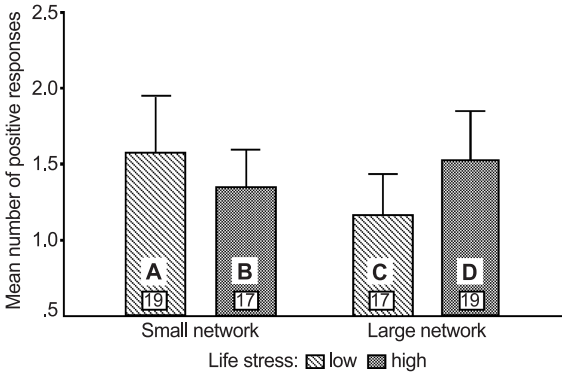

Fig. 1. Number of positive DTH responses for four groups of patients split at median social network size (56.5) and median life stress score (274.5) Grouping performed for illustrative purposes only and analysis was conducted on the entire sample using social network size and life stress as continuous variables in regression analysis.

Table 2
Correlations between number of positive antigens, morning cortisol, social support indices and life stress

	1	2	3	4	5	6
1. Morning cortisol (8 am)	–	0.21*	−0.06	−0.14	−0.17	−0.27*
2. Negative support		–	−0.23*	−0.42**	0.03	−0.02
3. Network size			–	0.56**	−0.043	−0.06
4. Positive support				–	−0.01	−0.16
5. Life stress					–	0.07
6. DTH—number of positive antigens						–

*$p < 0.05$.
**$p < 0.01$ (one-tailed, Spearman's correlations).

tisol, social support indices and life stress are reported in Table 2.

3. Discussion

Evidence in support of the first two hypotheses concerning primary or main effects, was not found. However, the regression analyses yielded a significant effect in support of the secondary effect of the third hypotheses. Social network size was directly related to DTH immune response to antigens only among women with high stress, while the reverse was true for those with low stress. Despite the homogeneity of the sample in regard to having metastatic breast cancer, considerable variation in stress levels was observed between patients. In previous work using data from this group of women we found that positive social support (appraisal, belonging, and tangible support) was associated with lower mean cortisol levels (Turner-Cobb et al., 2000). Thus in the current analysis of this data, we theorized that if social support was found to predict DTH responses then the underlying mechanism by which this may be occurring was via the pathway of endogenous cortisol production. Subsequent data analysis provides preliminary support for this interpretation. The 8 am cortsiol measure was negatively related to number of antigens and positively related to negative support. The importance of the 8 am sample in detecting immune correlates of psychosocial stress needs further exploration in conjunction with recent evidence of the importance of awakening cortisol responses (Edwards et al., 2003).

Since no evidence was found in support of main effects of the size of the social network or stressful life events on DTH response, the secondary interaction effect found needs to be treated with caution at this point. However, this interaction effect reflects an important relationship between social network size and stressful life events with number of positive antigens. When illustrated heuristically using median splits, it can be seen that the highest DTH responses were found in two groups; (1) in women with small social networks who had experienced less stressful life events (Fig. 1A), and (2) in women with larger social networks who had experienced more stressful life events (Fig. 1D). This interaction is best conceptualized by comparing the relationships between groups A–C and groups B–D (Fig. 1). Contrary to that predicted, under lower stress conditions, immune response is greatest when there are fewer individuals in the social network (Fig. 1A) and poorest when there are a greater number of social contacts (Fig. 1C). Similarly, under higher life stress, DTH responses are poorer when network size is smaller (Fig. 1B) and DTH responses greater when more social contacts are available (Fig. 1D).

Thus the hypothesis that social support acts as a buffer of the negative physiological effects of stressful events was found under conditions of greater life stress only. The unanticipated finding to emerge from these analyses was the comparatively low DTH response among patients with lower life stress and many social contacts. This is consistent with other findings, for example, that reported in a male HIV sample (Miller et al., 1997). These authors also found evidence for social relationships having possible deleterious effects since lower levels of loneliness predicted a greater decline in CD4 levels longitudinally (Miller et al., 1997). Furthermore, evidence that the relationship between social support and immune response in women with metastatic breast cancer depends on prior stressful life experiences could be interpreted within the stress-allostasis paradigm (McEwen, 1998). Hence

under high stress, more social support contacts available may have an immunoenhancing effect, while under low stress conditions the social network may itself be experienced as stressful, a source of obligations rather than support. It has been suggested that maintaining a large social network could itself be a chronic stressor (Buunk and Hoorens, 1992). However, this interpretation is tempered by the fact that we found no relationship between our measure of aversive social relationships and DTH response in this population.

Future work incorporating the role of individual differences would add an important dimension to further understanding such relationships (Cole et al., 1999). In relation to chronic stress, these counter-intuitive findings are paralleled by evidence suggesting that the immune response in humans and in animals is higher under acute stress conditions (Dhabhar and McEwen, 1996; Naliboff et al., 1991). As with DTH testing in any population in humans, it is also possible that acute stress was experienced by a subsample of patients in direct response to the anticipation of the test administration. However, clinical observations by those carrying out the DTH testing do not warrant this conclusion.

Other methodological limitations of this study include the absence of a healthy control group and the cross-sectional nature of these analyses. The larger ongoing intervention study from which these baseline data are drawn may in due course be able to provide further insight into the underlying mechanisms linking psychosocial and immune function variables. This larger study does include a control group of women with metastatic breast cancer who are not attending group therapy, however, it is acknowledged that the inclusion of a disease free control group would be a recommendation for future studies.

Despite its limitations, the current study does provide evidence suggesting that at least one measure of immune response (DTH) may be higher among patients experiencing high levels of prior life stress if they have a large social support network, confirming prior observations of stress buffering by social support. These results were found after addressing the possibility of confounding by relevant medication and medically related variables. The results of this study link the DTH response with psychosocial factors in physical illness and as such are important since they help place DTH measurement within the human literature. Over interpretation is cautioned however, until further work can support these findings and explore main effects, which were not found here, in greater detail. Future research on the balance of stress and support among cancer patients may help to elucidate endocrine and immune variables that may account for some of the variance in disease progression.

4. Uncited reference

Cohen et al., 1985

Acknowledgements

This research was supported by Grant MH47226 from the National Institute of Mental Health. Robert W. Carlson, M.D. consulted on medical aspects of recruiting and assessing patients, Daniel P. Stites, MD and Ronald Levy, MD on immunological measures and DTH testing, and Helena Kraemer, PhD on statistical analyses. We also appreciated the contributions of research staff Elaine A. Miller, Julie Seplaki, Jane Benson, Sue Dimiceli, Greg Schaal and Mike Schaal, and all of the women who participated in this research.

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