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TNF- α levels in cancer patients relate to social variables

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Abstract

Tumor necrosis factor- α (TNF- α) is an important cytokine associated with tumor regression and increased survival time for cancer patients. Research evidence relates immune factors (e.g., natural killer (NK) cell counts, NK cell lysis, lymphocyte profile, and lymphocyte proliferation) to the frequency and quality of social relations among cancer patients. We hypothesized that disruptions in social relations would be associated with lower TNF- α responses, and conversely, that reports of positive changes in social relations correlate with stronger responses. A prospective design measured changes in social activity and relationship satisfaction with a partner in 44 breast cancer patients at the time of cancer diagnosis, and initial surgery and 12 months later. Results indicated that patients reporting increased social activities or satisfaction exhibited stronger stimulated TNF- α responses. This is the first study to link changes in patient social relations with a cancer-relevant immune variable.

Keywords

Tumor necrosis factor; Social adjustment; Social support; Dyadic adjustment; Psychoneuroimmunology

1. Introduction

In the psychoneuroimmunology literature, social variables have been reliably, and positively, associated with immunity (Uchino et al., 1996). In healthy samples, immune functioning has been linked to the number of social relationships and interactions, and perceptions of and satisfaction with support (Gerits and De Brabander, 1999). Similar data come from two studies of cancer patients. Levy et al. (1990) found natural killer (NK) cell activity to be positively associated with quality of emotional support from a spouse, and Lekander et al. (1996) related white blood cell count to the adequacy of social attachments assessed following chemotherapy.

Like NK cells, cytokines are important immune factors. These soluble mediator molecules induce, enhance, or effect immune responses (Dranoff, 2004). Tumor necrosis factor- α (TNF- α) in particular is a potent pro-inflammatory cytokine associated with tumor regression and increased survival time for cancer patients (Nakamoto et al., 2000). Its tumoricidal mechanisms range from the activating host cellular immunity to directly killing tumor cells. At the tumor site, TNF- α induces cell apoptosis within the angiogenic vasculature, leading to hemorrhagic

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necrosis (reviewed in Anderson et al., 2004). By inducing vascular permeability of the tumor, TNF- α facilitates uptake of chemotherapeutic drugs such as doxorubicin (reviewed in Eggermont et al., 2003).

TNF- α has well-known cytotoxic effects on human breast cancer cells (Weitsman et al., 2003, 2004). Unfortunately, the blood cells of breast cancer patients have impaired ability to produce TNF- α (Zielinski et al., 1990, 2003). The potential relevance of TNF- α production to the course of breast cancer (Zielinski et al., 2003) fuels interest in correlates of TNF- α production responses. In short, TNF- α would be a relevant outcome for psychoneuroimmunology studies with cancer patients.

Cancer is, of course, a life-changing event (Gotay and Muraoka, 1998), particularly with regard to social variables. During the months following diagnosis and surgery, family, social, and leisure activities change. Some activities are disrupted, and others are engaged in more frequently. Intimate partnerships may be enhanced or weakened. The nature of this change is not well understood and varies by individual.

We hypothesized that disruptions in social activities or relationships would be associated with lower stimulated TNF- α responses, and conversely, that cancer patients maintaining or increasing social activity and partner satisfaction would have stronger post-treatment TNF- α responses. A prospective research design enabled the testing of these relationships. Newly diagnosed cancer patients were assessed at the time of cancer diagnosis and surgical treatment, and followed for 12 months. Changes in social variables across this period were used to predict changes from baseline to 12-month follow-up in mitogen stimulated TNF- α responses.

2. Method

2.1. Subjects and procedures

Women newly diagnosed with Stage II or III breast cancer were enrolled during their post-operative clinic visits in a randomized clinical trial of a psychological intervention. Complete descriptions of eligibility criteria, accrual, general procedures, and sample description have been reported (Andersen et al., 1998, 2004). Prior to beginning adjuvant therapy, patients completed questionnaires, a medical interview and assessment, and a 60 mL blood draw. Patients were then randomized to Intervention or Assessment-only study arms, and 12 months later, cancer therapies were completed and the 24 intervention sessions had ended. The intervention resulted in reduced stress, improved health behaviors, and stabilized or enhanced T cell blastogenesis at 4 (Andersen et al., 2004).

Patients eligible for this substudy were those who had completed all cancer therapies at least 2 months previously, remained disease free, and completed the 12-month assessment. Measures of social activity, relationship satisfaction with partner, and stimulated TNF- α were assessed at the time of cancer diagnosis and initial surgery and 12 months later. As most patients (85%) were treated with chemotherapy, there were some difficulties with 12-month blood draws (e.g., collapsed veins, low cell count). Samples were unavailable or inadequate for 16 patients. The resulting sample size was $N = 44$, $n = 29$ of whom had a cohabitating romantic partner (see Fig. 1 for flow diagram).

2.2. Measures

2.2.1. Family, social, and leisure activities—A modified version of the Katz Social Adjustment Scales (Andersen et al., 1989; Katz and Lyerly, 1963) indexed social activities involving children, household, relatives, and leisure. Behavioral frequency ratings (0 = “did not occur” to 9 = “occurred more than four times a day”) for the 15 items were summed; scores

ranged from 0 to 135. Internal consistency was .76. Twelve-month test–retest reliability was .50.

2.2.2. Partner satisfaction—The Dyadic Satisfaction subscale of the Dyadic Adjustment Scale (DAS; Spanier, 1976) was used. Items were summed and a score ranged from 0 to 35. Internal consistency was .89. Twelve-month test–retest reliability was .67.

2.2.3. Functional status—A nurse provided Karnofsky Performance Status (KPS; Karnofsky and Burchenal, 1949) ratings, ranging from 0 to 100, following patient interview, physician consultation, and medical chart review. Inter-rater reliability ranges from .70 to .97 (Mor et al., 1984; Yates et al., 1980).

2.2.4. Cancer treatment toxicity—The frequency and severity of general signs/symptoms, and cancer treatment toxicities (e.g., nausea/vomiting) were nurse rated using the Southwest Oncology Group criteria (SWOG; Moinpour et al., 1989). Items were summed and averaged for a total score ranging from 0 (none) to 4 (life threatening). Internal consistency was .76. Twelve-month test–retest reliability was .51.

2.2.5. TNF- α response—Heparinized whole blood was diluted with an equal volume of saline, treated with 1 $\mu\text{g/mL}$ of *Salmonella typhimurium* lipopolysaccharide (Sigma, St. Louis, MO) and incubated overnight at 37 °C in 5% carbon dioxide. The plasma was then harvested by centrifugation and stored at –80 °C until analyzed by ELISA. Triplicate plasma samples were assessed for TNF- α using a commercially available ELISA protocol (Biosource, Camarillo, CA). Sufficient plasma remained from 33 patients and was used to explore IL-6 and IL-1 β responses. These measures were uncorrelated with social variables, and are not reported further. A complete blood count and differential determined the absolute number of monocytes. Data are expressed as ng/mL TNF- α /10⁶ monocytes.

3. Results

Patients with complete ($N = 44$) and incomplete ($N = 26$) data were compared and found to be similar ($ps > .11$) on all demographic, and disease variables examined (see below), study arm, and chemotherapies received. However, study patients were more likely to have received radiation therapy (70.5 vs. 34.8%, $p < .05$).

3.1. Sample ($N = 44$) description

Sociodemographic characteristics are the following: age ($M = 52.05$; $SD = 10.18$); racial group (Caucasian = 95.5%; African American = 4.5%); education ($M = 14.77$ years, $SD = 2.89$), and household income (<\$30k = 23%; \$30–49k = 11%; \$50–79k = 25%; >\$80k = 32%; omit = 9%). Initially, women were approximately 5 weeks post-surgery ($M = 39$ days; $SD = 23$) from segmental mastectomy (48%) or modified radical mastectomy (52%). Initial KPS ratings ($M = 85.91$, $SD = 6.22$) indicated some symptoms/signs that required effort for normal activity. SWOG ratings were low ($M = .25$; $SD = .13$).

3.2. Clinical detail

TNF- α production expressed as ng/mL TNF- α /10⁶monocytes averaged .04 ($SD = .03$) at initial, and .05 ($SD = .03$) at 12 months, with no overall change between assessments [$t(43) = 1.68$, $p > .05$]. As noted in Section 1, there were differences among individuals in the direction of change for social variables. Social activity scores indicated multiple activities per week ($M = 52.61$, $SD = 16.62$ initial; $M = 50.88$, $SD = 13.54$, 12 months), and the level of activity was equivalent across time [$t(43) = 0.72$, $p > .10$]. However, 43% of patients increased and 55% decreased their social activities, with only 2% exhibiting no change. For the patients with a

partner, their satisfaction with the relationship was equivalent across time [$t(28) = 0.60, p > .10$], above the midpoint initially ($M = 26.24, SD = 4.95$) and 12 months later ($M = 27.76, SD = 5.54$). Still, individuals changed, with 41% of women reporting increased and 38% decreased satisfaction with their relationship; 21% reported no change.

3.3. Correlations among variables

Correlations between TNF- α and patient characteristics were calculated. TNF- α was not significantly ($p > .10$) related to sociodemographic, tumor grade, cancer treatment (surgery, chemotherapy, and radiation), or days since surgery variables, initial KPS, and SWOG scores, or study arm. TNF- α was related only to cancer stage (II vs. III; $r = .34, p < .10$), so stage was included as a control variable.

3.4. Hierarchical multiple regression analyses

We tested change in social variables as predictors for subsequent TNF- α responses at 12 months. Two hierarchical multiple regression (HMR) models each employed three steps, entering baseline TNF- α in step 1, cancer stage as a control variable in step 2, and change in social variables in step 3. For the latter, change was measured by subtracting patients' initial scores from their 12-month scores. Next, we covaried the initial scores out of the change scores to form residualized change scores that were uncorrelated with initial level (Zimmerman and Williams, 1982). These residualized change scores for social variables were used as step 3 predictors.

Regression analyses are summarized in Table 1. For the first analysis, the addition of change in social activity as a predictor (step 3) resulted in a significant ($p < .05$) increment in variance explained (9.4%) in 12-month TNF- α . The second analysis included the 29 patients who had partners. In this model, step 3 added both social variables, change in social activities and change in partner satisfaction. Again, social variables explained a significant ($p < .05$) increment of variance (17.2%) in 12-month TNF- α . With regard to the individual predictors, change in social activities was not significant in the final model. In contrast, change in partner satisfaction was significant ($p < .05$), explaining 12.9% of the variance in 12-month TNF- α .

3.5. Follow-up analyses

Four analyses were conducted to address any possible contribution of other variables to these findings. First, because patients with complete data were more likely to have received radiation therapy ($p < .05$) than patients with incomplete data, both HMR models were re-estimated with radiation therapy as a control. The pattern of results was unchanged; radiation was not a significant predictor in either model ($p > .3$). Second, though TNF- α was not correlated with study arm, HMR models were re-estimated including study arm as a control, and again, the pattern of results was unchanged ($p > .4$). Third, we tested for interaction effects between radiation or study arm and the social variables in predicting TNF- α ; all results were unchanged ($ps > .2$). Finally, we replicated the analyses using residualized KPS change scores as a control, to test whether changes in social variables were predictive of TNF- α over and above change in general health. As expected, change in health was a significant ($p < .05$) predictor of 12-month TNF- α in this model. Controlling for this effect, social variables (step 3) again explained a significant ($p < .05$) increment of variance in 12-month TNF- α . Although, neither of the predictors was individually significant in this model ($p \geq .05$ for social activities, $p = .095$ for partner satisfaction), the significance of step 3 overall indicates that change in social variables explained a significant amount of variance beyond that explained by change in general health.

4. Discussion

Stimulated TNF- α production of individual cancer patients was associated with changes in social functioning, an association not attributable to changes in general health. Cancer patients who increased their leisure, home, and social activities with friends and family exhibited stronger TNF- α responses than those who decreased involvement. For women who were partnered, their increases of satisfaction in the partner relationship appeared to be more important to TNF- α than social activity, per se. This may indicate that, for partnered women, the most important component of “social activity” is that with their partner.

We consider these findings in the context of results from the clinical trial ($N = 227$) in which these patients participated. There, intervention patients reported significant increases in support from family measured at 4 months, the end of the intensive phase of the intervention (Andersen et al., 2004). Improvements in T cell blastogenesis were also observed at 4 months (Andersen et al., 2004). Although no effect of study arm was found in this small subset of patients, the positive relationships between social variables and TNF- α responses are consistent with positive social and immune effects found experimentally within the trial.

These pilot data suggest a possible relationship between positive changes in social functioning and TNF- α . This is a modest demonstration of a finding novel to the psychoneuroimmunology literature. The ability of social variables to buffer people against immunologic consequences of chronic stressors (see Miller et al., 2002) has not previously been demonstrated with regard to TNF- α . However, impaired LPS stimulated TNF- α production in vivo has been observed in piglets in chronic social isolation (Tuchscherer et al., 2004) and mice subject to chronic social disruption (Bartolomucci et al., 2003). Both studies indicate that these social variables impacted the hypothalamic–pituitary–adrenal (HPA) axis, a potential pathway from social variables to TNF- α . In response to threat, the hypothalamus emits corticotropin-releasing hormone, leading to systemic secretion of glucocorticoids and catecholamines, which inhibit leukocyte production of TNF- α (reviewed in Elenkov and Chrousos, 2002). If social disruption can activate a biological stress response which impairs TNF- α production, then conversely, increasing quality and frequency of social relations might ameliorate biological stress responses during cancer diagnosis and treatment. This speculative interpretation merits further investigation. Additionally, we used LPS stimulation of whole blood as an ex vivo measure of the ability of monocytes to produce a TNF- α response. In future research, one step would be to determine whether monocytes from breast cancer patients with improved social functioning are more effective in killing target cells.

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Fig. 1.

Study design and flow diagram. Twenty-five (57%) of the patients with complete data were from the assessment-only arm of the larger randomized study, and 19 (43%) were from the Intervention arm.

Table 1

HMR results predicting TNF- α

Step and predictor	Total R^2	R^2 change	β	t	sr^2
<i>Predictor: social activities (N = 44)</i>					
1. Initial TNF- α	.228	.228**	.423	3.134**	.158
2. Cancer stage (II vs. III)	.263	.035	.194	1.438	.033
3. Change in social activities	.357	.094*	.307	2.422*	.094
<i>Predictor: social activities or satisfaction with partner relationship (N = 29)</i>					
1. Initial TNF- α	.206	.206*	.645	3.186**	.237
2. Cancer stage	.267	.061	.191	1.146	.031
3. Change in social activities	.439	.172*	.220	1.440	.048
Change in partner satisfaction			.447	2.349*	.129

Note. β (standardized), t , and sr^2 (squared semi-partial correlation) values are final model statistics.

* $p < .05$

** $p < .01$.