

Short communication

## TNF- $\alpha$ levels in cancer patients relate to social variables

Phillip T. Marucha <sup>a,1</sup>, Timothy R. Crespin <sup>b</sup>, Rebecca A. Shelby <sup>c</sup>, Barbara L. Andersen <sup>d,\*</sup>

<sup>a</sup> Department of Periodontics, College of Dentistry, University of Illinois at Chicago, USA

<sup>b</sup> Primetrics, Inc., Hilliard, Ohio, USA

<sup>c</sup> Department of Psychology, The Ohio State University, USA

<sup>d</sup> Department of Psychology and Comprehensive Cancer Center, The Ohio State University, USA

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### Abstract

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) 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- $\alpha$  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- $\alpha$  responses. This is the first study to link changes in patient social relations with a cancer-relevant immune variable.

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### 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- $\alpha$  (TNF- $\alpha$ ) 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- $\alpha$  induces cell apoptosis within the angiogenic vasculature, leading to hemorrhagic necrosis (reviewed in Anderson et al., 2004). By inducing vascular permeability of the tumor, TNF- $\alpha$  facilitates uptake of chemotherapeutic drugs such as doxorubicin (reviewed in Eggermont et al., 2003).

TNF- $\alpha$  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- $\alpha$  (Zielinski et al., 1990, 2003). The potential relevance of TNF- $\alpha$  production to

\* Corresponding author. Fax: +1 614 688 8261.

E-mail address: [Andersen.1@osu.edu](mailto:Andersen.1@osu.edu) (B.L. Andersen).

<sup>1</sup> Research conducted while at The Ohio State University College of Dentistry.

the course of breast cancer (Zielinski et al., 2003) fuels interest in correlates of TNF- $\alpha$  production responses. In short, TNF- $\alpha$  would be a relevant outcome for psycho-neuroimmunology 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- $\alpha$  responses, and conversely, that cancer patients maintaining or increasing social activity and partner satisfaction would have stronger post-treatment TNF- $\alpha$  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- $\alpha$  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- $\alpha$  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  $N=44$ ,

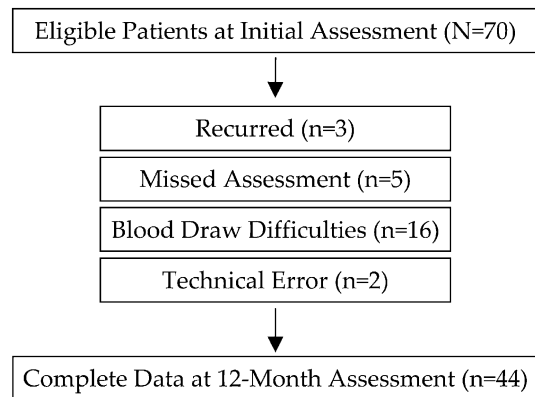


Fig. 1. Study design and flow diagram. Twenty-five (57%) of the patients with complete data were from the assessment-only arm of the larger randomized study, and 19 (43%) were from the Intervention arm.

$n=29$  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.

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