Brain, Behavior, and Immunity 26 (2012) 228–233

Contents lists available at SciVerse ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Short Communication

Impact of breast cancer recurrence and cancer-specific stress on spouse health and immune function

Sharla Wells-Di Gregorio [a,1], Kristen M. Carpenter [b,*], Caroline S. Dorfman [b], Hae-Chung Yang [b], Laura E. Simonelli [c], William E. Carson III [d]

[a] Department of Psychiatry, Center for Palliative Care, The Ohio State University, USA
[b] Department of Psychology, The Ohio State University, USA
[c] Helen F. Graham Cancer Center, Christiana Care Health System, USA
[d] Department of Surgery, College of Medicine and Comprehensive Cancer Center, The Ohio State University, USA

ARTICLE INFO

Article history:
Received 18 March 2011
Received in revised form 15 July 2011
Accepted 17 July 2011
Available online 23 July 2011

Keywords:
Cancer recurrence
Stress
Immune function
Spouses
Breast cancer

ABSTRACT

Spouses of cancer patients are at-risk for poor psychological and physical health as they cope with the complex nature of the disease and fears of losing their partner. Moreover, spouses often serve as patients' primary informal caregivers, a group that evidences poor outcomes across a variety of domains. The present study examines the relative contributions of cancer recurrence – a cancer-specific stressful event – and the subjective experience of cancer-specific stress (IES) in a sample of male spouses of breast cancer survivors. We hypothesized that stress would contribute to poorer physical health and compromised immune function. Spouses (recurrence; $n = 16$) of patients who were coping with their first recurrence were matched to spouses of patients with no evidence of disease (disease-free; $n = 16$). Self-reported physical health (physical symptoms and fatigue) and immune function [T-cell blastogenic response to the mitogens Concanavalin A (ConA) and phytohemagglutanin (PHA) and T3 monoclonal antibody (T3 Mab)] were included as outcomes. Results indicated that patient recurrence status was not a significant unique predictor of physical health or immune function; rather, among all spouses, cancer-specific stress symptoms were associated with increased physical symptoms and altered T-cell blastogenesis. These data suggest that the health implications of caregiving for spouses of cancer survivors is more strongly linked to their subjective experience of cancer as stressful, rather than simply the patients' disease status.

1. Introduction

Cancer is a significant source of stress for patients and their families. Spouses, in particular, are at-risk for poor psychological and health outcomes as they attempt to adjust to the complex, multifaceted nature of the disease. Spouses report more worry (Davis-Ali et al., 1993) and distress (Germino et al., 1995; Northouse et al., 2002) than do patients. In addition, spouses often serve as the patient's primary caregiver, a role that is related to a variety of adverse outcomes, including compromised physical health (Northouse et al., 2002; Pinquart and Sorensen, 2003; Vitaliano et al., 2003) and fatigue (Jensen and Given, 1993; Swore Fletcher et al., 2008; Teel and Press, 1999), both of which potentially limit the spouse's ability to provide ongoing care (Buhr et al., 2006).

The stress associated with a spouse's cancer may be compounded by a recurrence. In the case of breast cancer, approximately 20% of patients recur within 10 years (Brewster et al., 2008). When cancer recurs, the stress of initial diagnosis returns (Andersen et al., 2005) and is accompanied by additional distress (Kim and Given, 2008). Recurrent breast cancer carries high symptom burden and poor prognosis (Hanson Frost et al., 2000); thus, spouses of women with recurrence bear the added burden of anticipating the loss of their partner (Lewis and Deal, 1995).

Appraisals of events as stressful, and the resulting emotional distress, contribute to a series of central nervous system and endocrine changes that can impact immunity. There are only limited immune data from spouses of cancer patients, but the available studies suggest compromised cellular immunity (Futterman et al., 1996), poorer inflammatory control (Rohleder et al., 2009), and, in the only study examining immunocompetence among spouses of cancer patients with recurrence, suppressed response to skin test antigens (Mortimer et al., 2005).

While the broader literature has demonstrated that recurrence is a significant, stressful event associated with poor emotional and physical outcomes for spouses (Germino et al., 1995; Northouse

* Corresponding author.
E-mail addresses: sharla.wells@osumc.edu (S. Wells-Di Gregorio), carpenter.292@osu.edu (K.M. Carpenter).
[1] Center for Palliative Care, 246 Atwell Hall, The Ohio State University Columbus, OH 43210–1222, USA. Fax: +1 614 293 0754.

0889-1591/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbi.2011.07.237

et al., 2000), it remains unclear whether the stress of the recurrence event, *per se*, or the chronic stress of cancer survivorship produces immune impairment. Data from relevant literatures (Kiecolt-Glaser et al., 2002) suggest that spouses' subjective experience of stress would be sufficient to compromise immunity. The present study therefore examined the relative contributions of a cancer-specific stressful event (i.e., recurrence) and the subjective experience of stress (self-reported cancer-specific stress) in a sample of male spouses of breast cancer survivors. We hypothesized that the stress associated with patients' cancer would contribute to poorer physical health and compromised immune function for their spouses.

2. Method

2.1. Design

Given the impossibility of random assignment to recurrence, several authors have recommended use of control groups matched on disease characteristics that impact patients' and spouses' outcomes (Given et al., 1997; Schulz et al., 1990); thus, we used a matched-control design, comparing spouses of women with recurrence to a cohort of spouses whose wives were disease-free, but had a history of breast cancer.

2.2. Procedures

This study was completed as a companion study in the context of two larger studies of breast cancer patients. The first was a randomized clinical trial (RCT) for women with newly diagnosed breast cancer (Andersen et al., 2004). Those patients in the clinical trial who experienced disease recurrence were invited into a second, observational study of recurrence. During the same period, additional recurrence patients from the same clinic were approached for the observational study (Andersen et al., 2007). Independent of clinical trial participation, when a married patient in the recurrence study was identified, she was approached during an early clinic visit following diagnosis and, with permission, her spouse was invited to participate in the present study.

The clinical trial database was used to identify a comparison sample. We matched each recurrence patient to two or three married, disease-free patients using original tumor size, nodal status, menopausal status, time since initial diagnosis, and wives' inclusion in the intervention arm of the RCT. These variables were selected to ensure that patients in both groups would have undergone similar treatment and follow-up since initial diagnosis. Spouses for the disease-free group were sequentially contacted until a match agreed to participate. Exclusion criteria for spouses included: diagnosis of dementia or related condition, immune-related condition, or residence >150 miles from the research site. Following informed consent, spouses completed an in-person interview and blood draw. Assessments were conducted in the clinic between 8 and 11 a.m. to control for diurnal variation. Participants were offered $25.

2.3. Participants

During the study interval (2000–2003), 29 women from the clinical trial recurred. Of these, 23 were married. Twenty-two additional patients were approached for the recurrence study; 17 of whom were partnered, yielding a total of 40 married patients with recurrence. Of the 40 spouses identified, 25 were eligible and 16 (64%) were accrued. Participants were assessed, on average, 8 months following their wife's recurrence diagnosis, approximately 5 years after the initial cancer diagnosis.

A total of 42 eligible spouses of disease-free patients were identified using the procedure described above. Overall, 16 of 42 were enrolled (38%). Participants in the disease-free group were assessed approximately 6 years after their wife's initial cancer diagnosis.

2.4. Measures

Descriptive statistics and intercorrelations for the predictor and outcome variables are presented in Table 1.

Table 1
Descriptive statistics for subjective stress, physical health, and immune function.

	Mean (SD)			Correlation					
	Total (n = 32)	Recurrence (n = 16)	Disease-free (n = 16)	1	2	3	4	5	6
Subjective stress									
1. IES**	17.59 (13.98)	26.25 (12.14)	8.94 (9.84)	—					
Physical health									
2. FSI-TDI*	7.34 (8.77)	10.75 (10.32)	3.94 (5.26)	0.42*	—				
3. PSI**	6.88 (5.22)	9.13 (5.23)	4.63 (4.27)	0.71**	0.66**	—			
Immune function									
4. ConA, μg/mL				−0.49*	−0.02	−0.36	—		
10.0	0.16 (0.12)	0.13 (0.12)	0.17 (0.13)						
5.0	0.22 (0.13)	0.17 (0.12)	0.25 (0.14)						
2.5	0.23 (0.14)	0.20 (0.14)	0.25 (0.15)						
5. PHA, μg/mL				−0.32	0.01	−0.09	0.45*	—	
10.0	0.27 (0.12)	0.25 (0.05)	0.28 (0.16)						
5.0	0.29 (0.13)	0.27 (0.10)	0.31 (0.14)						
2.5	0.26 (0.11)	0.25 (0.07)	0.26 (0.14)						
6. T3 Mab (purified)				−0.39	−0.04	−0.15	0.69**	0.53**	—
1:32	0.36 (0.18)	0.35 (0.10)	0.37 (0.22)						
1:64	0.28 (0.18)	0.24 (0.10)	0.31 (0.21)						
1:128	0.24 (0.15)	0.20 (0.10)	0.27 (0.17)						

Notes: *Abbreviations*: IES = Impact of Events Scale; FSI-TDI = Fatigue Symptom Inventory-Total Disruption Index; PSI = Physical Symptom Inventory; ConA = T-cell blastogenic response to concanavalin A; PHA = T-cell blastogenic response to phytohemagglutinin; T3 Mab = T-cell blastogenic response to T3 monoclonal antibody. Reported means for the immune variables are of the raw scores for the serial dilutions of ConA, PHA, and T3 Mab; correlations reported for the immune variables were calculated using composite scores. Significance levels are for correlations and preliminary univariate ANOVAs.

* $p < 0.05$.

** $p < 0.01$.

2.4.1. Stress

Cancer-Specific Stress: The Impact of Events Scale (IES) (Horowitz et al., 1979) was used to assess cancer-specific stress. Instructions were modified such that spouses were to describe their feelings *about their wife's cancer* during the past week. Total scores are obtained by summing the items and range from 0–75; higher scores indicate greater stress. Internal consistency reliability (Cronbach's α) for this sample was 0.89.

2.4.2. Physical health

Fatigue. The Total Disruption Index from the Fatigue Symptom Inventory-Revised (FSI-TDI) (Hann et al., 1998) was used to assess the degree to which fatigue interfered with participants' general level of functioning and activities of daily living. The FSI-TDI assesses interference across seven domains (e.g., ability to conduct normal work activities in/out of the home, ability to concentrate). Scores range from 0 to 70; higher scores indicate greater interference. $\alpha = 0.92$.

Physical symptoms. The Physical Symptoms Inventory (PSI) (Spector and Jex, 1998) assesses 51 common physical symptoms (e.g., headaches, stomach cramps/pain, legs feeling weak, coughing, nausea) experienced in the last month. Because our interest was in physical health as an outcome and we were concerned about overlap with IES items, five mental health items were omitted (e.g., feeling tense/keyed up, nervous/shaky feeling inside). Items are summed and scores range from 0 to 46; higher scores indicate more symptoms. $\alpha = 0.83$.

2.4.3. Immune function

T-cell blastogenic (proliferative) response to the mitogens Concanavalin A (ConA) and phytohemagglutinin (PHA) and T3 monoclonal antibody (Mab) were studied, as we (Andersen et al., 1998; Carson et al., 2004; Thornton et al., 2007) and others [for reviews, see (Herbert and Cohen, 1993; Segerstrom and Miller, 2004; Webster Marketon and Glaser, 2008)] have demonstrated that T-cell proliferative response decreases in response to a variety of stressors, including caregiving stress (Kiecolt-Glaser et al., 1991). Detailed descriptions of our standard laboratory procedures, including blood separation, quantification of cell subsets, and blastogenesis assays have been published (Andersen et al., 2004; Carson et al., 2004; Thornton et al., 2007). Briefly, peripheral blood leukocytes (PBLs) were isolated from 60 mL of venous blood. For lymphocyte subset quantification, PBLs were labeled with florescent-conjugated monoclonal antibodies (Mabs) specific for cell surface markers total T-cells (CD3, fluorescein isothiocyanate), T4 subset (CD4, rhodamine), and T8 subset (CD8, fluorescein isothiocyanate).

Briefly, PBLs resuspended in supplemented RPMI without phenol red were seeded in triplicate, incubated, and pulsed with MTS [3-(4, 5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt] and phenazine methosulfate to measure proliferative response. Amount of proliferation was determined via optical density readings of suspension in the well compared to cells and media alone (Andersen et al., 2004). Serial dilutions for ConA and PHA were 2.5, 5.0, and 10.0 μg/mL, and serial dilutions for T3 Mab were in the ratios of 1:32, 1:64, and 1:128. To reduce the chance of random variability and the likelihood of Type I error, a composite score for each assay was used in the primary analyses. Participants' scores on each dilution were converted to *z*-scores (i.e., standard deviation units from the overall mean). A composite score was calculated as the average of the *z*-scores across the three dilutions, as described (Carson et al., 2004; Thornton et al., 2007). Adequate blood samples were available for 24 participants (recurrence $n = 10$; disease-free $n = 14$).

2.4.4. Potential controls

Three classes of variables related to physical and immune outcomes were considered as controls. To conserve degrees of freedom, we used an empirical selection of controls, i.e., correlations between potential controls and outcomes were obtained, and only variables significantly correlated ($p < 0.05$) with outcomes were retained.

Sociodemographic and disease variables. Variables included age, education (years), race (white/non-white), years partnered, employment status (yes/no), hours worked/week, annual household income, and time elapsed since wives' initial breast cancer diagnosis.

Health behaviors. Alcohol use (drinks/day); smoking (cigarettes/day, smoking history: yes/no, years abstinent); caffeine intake (ounces/day); sleep (hours/night); and physical activity (regular activity: yes/no, strenuous/moderate/mild activity past week: yes/no, overall activity rating) were assessed.

Health status. The Cumulative Illness Rating Scale (CIRS) (Linn et al., 1995) assessed chronic medical conditions (e.g., hypertension) across 12 bodily systems (e.g., musculoskeletal, cardiovascular). Whole systems are rated on a four-point scale. Items are summed for a total score; higher ratings indicate more chronic conditions. Scores range from 0 to 48.

2.5. Analytic strategy

The recurrence and disease-free groups were compared on sociodemographic and patient disease characteristics using χ^2-tests or analysis of variance (ANOVA). Given the small sample size and the high correlations (Table 1) among similar outcome measures, a multivariate analytic strategy was employed for the principle analyses (Weinfurt, 1995), in order to conserve power and reduce the Type I error that would occur had several ANOVAs been employed (Morrison, 2004). Two multivariate analyses of covariance (MANCOVA) were performed to examine the extent to which a cancer-specific stressful event (recurrence vs. disease-free) and self-reported cancer-specific stress (IES scores) influenced physical health and immunity. Because we were interested in the relative contributions of each, both stress variables were included in each of the models. Age, education, drinks/day, and physical activity level were significantly correlated with physical symptoms or fatigue, and were included as covariates in the physical health analysis. None of the controls considered were significantly correlated (all $p > 0.05$) with individual immune outcomes; thus, none were retained in the final MANCOVA. The percentage of lymphocytes that were T3 positive (T3%) was entered as a covariate to avoid confounding the functional responses (i.e., blastogenesis) with enumerative indicators.

3. Results

On average, participants were 58 years old (SD = 10.3), married an average of 26 years (SD = 12.7), Caucasian (94%), and employed (81%), with median family income of $75 K (SD = $80 K). There were no group (recurrence vs. disease-free) differences on sociodemographic characteristics (all p's $\geqslant 0.07$), health behaviors (all p's $\geqslant 0.10$), CIRS ($p = 0.63$), or in wives' disease/treatment characteristics, including initial stage ($p = 0.06$), treatments received (all p's $\geqslant 0.12$), months since initial diagnosis ($p = 0.49$), or participation intervention arm for those in the RCT ($p = 0.65$). Equivalence of the groups indicates a successful matching procedure.

3.1. Physical health

The Wilks' Lambda multivariate test of overall differences among groups was not statistically significant ($F(2,24) = 0.747$;

Table 2
MANCOVA results.

Physical Health						
	Fatigue Symptom Inventory			*Physical Symptom Inventory*		
	$F(6,24) = 1.345$, $p = 0.275$,			$F(6,24) = 5.252$, $p = 0.001$,		
	Adjusted Total $R^2 = 0.063$, partial $\eta^2 = 0.244$			Adjusted Total $R^2 = 0.451$, partial $\eta^2 = 0.558$		
Predictors	*F*	*p*-value	partial η^2 (CI)	*F*	*p*-value	partial η^2 (CI)
Age	0.919	0.347	0.035 (0.000-0.211)	0.560	0.461	0.022 (0.000-0.186)
Education	0.052	0.822	0.002 (0.000-0.111)	1.017	0.323	0.039 (0.000-0.217)
Alcohol (drinks/day)	0.034	0.854	0.001 (0.000-0.100)	0.059	0.809	0.002 (0.000-0.115)
Physical activity	0.036	0.851	0.001 (0.000-0.102)	0.968	0.335	0.037 (0.000-0.214)
IES	0.498	0.487	0.020 (0.000-0.181)	8.168**	0.008**	0.246 (0.016-0.433)**
Group	1.195	0.285	0.046 (0.000-0.227)	0.014	0.908	0.001 (0.000-0.076)
Immune Function	*ConA*			*PHA*		*T3 Mab*
	$F(3,18) = 6.220$, $p = 0.004$,			$F(3,18) = 1.045$, $p = 0.394$,		$F(3,18) = 3.693$, $p = 0.029$,
	Adjusted Total $R^2 = 0.405$, partial $\eta^2 = 0.483$			Adjusted Total $R^2 = 0.006$, partial $\eta^2 = 0.136$		Adjusted Total $R^2 = 0.260$, partial $\eta^2 = 0.356$
Predictors	*F*	*p*-value	partial η^2 (CI)	*F*	*p*-value	partial η^2 (CI)	*F*	*p*-value	partial η^2 (CI)
T3%¶	8.688**	0.008**	0.303 (0.023-0.518)**	0.595	0.450	0.029 (0.000-0.237)	6.100*	0.023*	0.234 (0.002-0.463)*
IES	10.043	0.005**	0.334 (0.036-0.542)**	2.454	0.133	0.109 (0.000-0.346)	5.206*	0.034*	0.207 (0.000-0.440)*
Group	1.431	0.246	0.067 (0.000-0.296)	0.357	0.557	0.018 (0.000-0.212)	0.827	0.374	0.040 (0.000-0.256)

Notes: *Abbreviations*: CI = 95% Confidence Interval; IES = Impact of Events Scale; T3% = percentage of lymphocytes that were T3 positive.
* $p < 0.05$.
** $p < 0.01$.

$p = 0.484$, partial eta-squared = 0.059). See Table 2. Group (recurrence vs. disease-free) was not significantly associated with either fatigue or physical symptoms. IES scores were significantly associated with physical symptoms, but not FSI-TDI scores. These results suggest that spouses reporting greater cancer-specific stress experienced more physical symptoms, regardless of whether their wife had experienced a recurrence. Results also indicate that neither the recurrence event nor cancer-specific stress was significantly associated with interference from fatigue.

3.2. Immune function

The Wilks' Lambda multivariate test of overall differences among groups was not statistically significant ($F(3,18) = 0.476$; $p = 0.703$, partial eta-squared = 0.073). See Table 2. Group was not significantly associated with immune function; however, men with higher IES scores evidenced poorer ConA- and T3 Mab-induced blastogenesis, but not PHA-induced blastogenesis. Thus, spouses reporting greater cancer-specific stress evidenced lower T-cell blastogenesis, regardless of wives' recurrence status, though the effect was not consistent across all three mitogens.

4. Discussion

These results suggest that caring for a patient with cancer has an observable impact on spouses' physical health and immune function. Moreover, they indicate that the subjective experience of cancer-specific stress, more so than the patient's recurrence status, is associated with a greater level of physical symptoms such as backache/headache, indigestion, and shortness of breath, as well as immune dysregulation. These results are important because caregivers demonstrating poorer proliferative response may be more vulnerable to infection and evidence impaired responses to vaccination (Glaser et al., 2000; Redwine et al., 2004; Webster Marketon and Glaser, 2008), which could limit their ability to provide informal care/support to the patient and has broader implications for their own health. Indeed, decreased proliferative response to mitogens has been associated with increased hospitalizations and mortality among older adults (Ferguson et al., 1995; Murasko et al., 1990; Murasko et al., 1988). The only prior study examining spouse immune responses in the context of cancer recurrence is consistent with these findings; Mortimer et al. (2005) found that longer breast cancer duration and greater cancer-specific intrusive thoughts were associated with suppression of delayed-type hypersensitivity responses to skin test antigens.

These data are consistent with what is known to be the experience of cancer patients and their families: the stress associated with cancer is chronic and may extend for years post-diagnosis (Nijboer et al., 1998). In the present study, cancer-specific stress was higher, on average, among spouses of recurrence patients. However, cancer-specific stress was also elevated for a subset of spouses of disease-free patients, most likely because some treatment-related sequelae (e.g., pain, fatigue, neuropathy) persist even among the disease-free, and, regardless of recurrence status, spouses must cope with the physical demands associated with these symptoms. Such sequelae tend to be more common among recurrence patients due to aggressive and ongoing treatments (Hanson Frost et al., 2000), but future studies are needed to clarify patient and spousal factors that contribute to high levels of cancer-specific stress, as well as neuroendocrine correlates of stress and immunity, among spouses faced with recurrence. Nonetheless, our data suggest that the health implications of caregiving for spouses of cancer survivors is more strongly linked to their subjective experience of cancer as stressful; clinically, this would suggest ongoing assessment of caregiver stress that is not necessarily tied

to specific cancer-related events (e.g., near the time of initial diagnosis or diagnosis of recurrence).

Several authors have provided evidence that caregivers experience poorer health than non-caregivers (Pinquart and Sorensen, 2003; Vitaliano et al., 2003); our data provide evidence for a biological mechanism that might underscore previous findings. Specifically, in the present study, men who reported more cancer-specific stress evidenced poorer T-cell blastogenesis, which serves as a broad indicator of cellular immune function. The results for PHA were not significant, consistent with prior research reporting different responses across immune assays in spousal caregivers (Cacioppo et al., 1998). Such assay differences may be attributable to the age of our sample. For instance, Murasko et al. (1990) reported that only 3% of subjects less than 60 years old failed to mount a proliferative response PHA, ConA, or pokeweed mitogen (PWM), whereas 36% of those over age 60 showed no proliferation to at least one mitogen.

The present study has several strengths. First, a focus on male spouses coping with their wives' cancer is uncommon; studies of spouses of cancer patients include predominantly female or mixed gender samples (Futterman et al., 1996; Rohleder et al., 2009), as has the broader caregiving literature (Kiecolt-Glaser et al., 2002). Second, our methods produced a well-matched sample. Studies of spouses have generally not included comparison groups, though some have contrasted spouses of women with recurrence with spouses of newly diagnosed women (Given and Given, 1992; Northouse et al., 1995). Such designs are useful, but do not account for time from diagnosis, which could impact adjustment.

The primary limitation of our study is the small sample. Large effects are observed for several outcomes based on the parameter estimates for partial η^2 (Cohen, 1988; Levine and Hullett, 2002), but the confidence intervals for the effect sizes are wide. Studies with larger samples are warranted, as such studies would improve the precision of estimates of parameters and effect sizes, increase power to detect more subtle effects (including those of relevant control variables), and enhance generalizability (e.g., to spouses of patients living with other cancers). Clearly there is a need for further research focused on factors contributing to chronic spousal stress beyond the immediate post-diagnosis period (e.g., patient symptom burden, functional limitations) and research examining the connections between spouse stress, immunity, and health outcomes.

Conflict of interest

All authors declare that there are no conflicts of interest.

Acknowledgments

This research was supported by the Ann and Herbert Siegel American Cancer Society Postdoctoral Fellowship (PBR-89; PF-01-017-01-PBP) awarded to Dr. Wells-Di Gregorio and the following research awards to Dr. Barbara L. Andersen: the Longaberger Company-American Cancer Society Grant for Breast Cancer Research (PBR-89A; RSGPB-03-248-01-PBP; PF-01-017-01-PBP), the U.S. Army Medical Research Acquisition Activity Grants (DAMD17-94-J-4165, DAMD17-96-1-6294, and DAMD17-97-1-7062), National Institute of Mental Health (R01MH51487), and National Cancer Institute (R01CA92704; K05CA098133). In addition, we would like to acknowledge Dr. Andersen's mentorship and generous contributions of time, space, materials, and personnel needed to complete this study.

References

Andersen, B.L., Carpenter, K.M., Yang, H., Shapiro, C.L., 2007. Sexual well-being among partnered women with breast cancer recurrence. Journal of Clinical Oncology 25, 3151–3157.

Andersen, B.L., Farrar, W.B., Golden-Kreutz, D., Kutz, L.A., MacCallum, R., Courtney, M.E., Glaser, R., 1998. Stress and immune responses after surgical treatment for regional breast cancer. Journal of the National Cancer Institute 90, 30–36.

Andersen, B.L., Farrar, W.B., Golden-Kreutz, D.M., Glaser, R., Emery, C.F., Crespin, T.R., Shapiro, C.L., Carson 3rd, W.E., 2004. Psychological, behavioral, and immune changes after a psychological intervention: a clinical trial. Journal of Clinical Oncology 22, 3570–3580.

Andersen, B.L., Shapiro, C.L., Farrar, W.B., Crespin, T., Wells-Digregorio, S., 2005. Psychological responses to cancer recurrence. Cancer 104, 1540–1547.

Brewster, A.M., Hortobagyi, G.N., Broglio, K.R., Kau, S.W., Santa-Maria, C.A., Arun, B., Buzdar, A.U., Booser, D.J., Valero, V., Bondy, M., Esteva, F.J., 2008. Residual risk of breast cancer recurrence 5 years after adjuvant therapy. Journal of the National Cancer Institute 100, 1179–1183.

Buhr, G.T., Kuchibhatla, M., Clipp, E.C., 2006. Caregivers' reasons for nursing home placement: Clues for improving discussions with families prior to the transition. Gerontologist 46, 52–61.

Cacioppo, J.T., Poehlmann, K.M., Kiecolt-Glaser, J.K., Malarkey, W.B., Burelson, M.H., Berntson, G.G., Glaser, R., 1998. Cellular immune responses to acute stress in female caregivers of dementia patients and matched controls. Health Psychology 17, 182–189.

Carson 3rd, W.E., Shapiro, C.L., Crespin, T.R., Thornton, L.M., Andersen, B.L., 2004. Cellular immunity in breast cancer patients completing taxane treatment. Clin Cancer Res 10, 3401–3409.

Cohen, S., 1988. Psychosocial models of the role of social support in the etiology of physical disease. Health Psychology 7, 269–297.

Davis-Ali, S.H., Chesler, M.A., Chesney, B.K., 1993. Recognizing cancer as a family disease: Worries and support reported by patients and spouses. Social Work in Health Care 19, 45–65.

Ferguson, F.G., Wikby, A., Maxson, P., Olsson, J., Johansson, B., 1995. Immune parameters in a longitudinal study of a very old population of Swedish people: A comparison between survivors and non-survivors. The Journal of Gerontology 50, B378–B382.

Futterman, A.D., Wellisch, D.K., Zighelboim, J., Luna-Raines, M., Weiner, H., 1996. Psychological and immunological reactions of family members to patients undergoing bone marrow transplantation. Psychosomatic Medicine 58, 472–480.

Germino, B.B., Fife, B.L., Funk, S.G., 1995. Cancer and the partner relationship: What is its meaning? Seminars in Oncology Nursing 11, 43–50.

Given, B., Given, C.W., 1992. Patient and family caregiver reaction to new and recurrent breast cancer. J Am Med Womens Assoc 47, 201-206, 212.

Given, B.A., Given, C.W., Helms, E., Stommel, M., DeVoss, D.N., 1997. Determinants of family care giver reaction. New and recurrent cancer. Cancer Practise 5, 17–24.

Glaser, R., Sheridan, J., Malarkey, W.B., MacCallum, R.C., Kiecolt-Glaser, J.K., 2000. Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. Psychosomatic Medicine 62, 804–807.

Hann, D.M., Jacobsen, P.B., Azzarello, L.M., Martin, S.C., Curran, S.L., Fields, K.K., Greenberg, H., Lyman, G., 1998. Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. Quality of Life Research 7, 301–310.

Hanson Frost, M., Suman, V.J., Rummans, T.A., Dose, A.M., Taylor, M., Novotny, P., Johnson, R., Evans, R.E., 2000. Physical, psychological and social well-being of women with breast cancer: the influence of disease phase. Psychooncology 9, 221–231.

Herbert, T.B., Cohen, S., 1993. Stress and immunity in humans: a meta-analytic review. Psychosomatic Medicine 55, 364–379.

Horowitz, M., Wilner, N., Alvarez, W., 1979. Impact of Event Scale: a measure of subjective stress. Psychosomatic Medicine 41, 209–218.

Jensen, S., Given, B., 1993. Fatigue affecting family caregivers of cancer patients. Supportive Care in Cancer 1, 321–325.

Kiecolt-Glaser, J.K., Dura, J.R., Speicher, C.E., Trask, O.J., Glaser, R., 1991. Spousal caregivers of dementia victims: Longitudinal changes in immunity and health. Psychosomatic Medicine 53, 345–362.

Kiecolt-Glaser, J.K., McGuire, L., Robles, T.F., Glaser, R., 2002. Psychoneuroimmunology: psychological influences on immune function and health. Journal of Consulting and Clinical Psychology 70, 537–547.

Kim, Y., Given, B.A., 2008. Quality of life of family caregivers of cancer survivors: Across the trajectory of the illness. Cancer 112, 2556–2568.

Levine, T.R., Hullett, C.R., 2002. Eta squared, partial eta squared, and misreporting of effect size in communication research. Human Communication Research 28.

Lewis, F.M., Deal, L.W., 1995. Balancing our lives: a study of the married couple's experience with breast cancer recurrence. Oncology Nursing Forum 22, 943–953.

Linn, B.S., Linn, M.W., Gurel, L., 1995. Cumulative Illness Rating Scale. Journal of the American Geriatrics Society 16, 622–626.

Morrison, D.F., 2004. Multivariate Statistical Methods, 4th Edition. Cengage Learning, New York.

Mortimer, J.S.B., Sephton, S.E., Kimerling, R., Butler, L., Bernstein, A.S., Spiegel, D., 2005. Chronic stress, depression and immunity in spouses of metastatic breast cancer patients. Clinical Psychologist 9, 5.

Murasko, D.M., Gold, M.J., Hessen, M.T., Kaye, D., 1990. Immune reactivity, morbidity, and mortality of elderly humans. Aging: Immunology and Infectious Disease 2, 171–180.

Murasko, D.M., Weiner, P., Kaye, D., 1988. Association of lack of mitogen-induced lymphocyte proliferation with increased mortality in the elderly. Aging: Immunology and Infectious Disease 1, 1–6.

Nijboer, C., Tempelaar, R., Sanderman, R., Triemstra, M., Spruijt, R.J., van den Bos, G.A., 1998. Cancer and caregiving: The impact on the caregiver's health. Psychooncology 7, 3–13.

Northouse, L.L., Dorris, G., Charron-Moore, C., 1995. Factors affecting couples' adjustment to recurrent breast cancer. Social Science and Medicine 41, 69–76.

Northouse, L.L., Mood, D., Kershaw, T., Schafenacker, A., Mellon, S., Walker, J., Galvin, E., Decker, V., 2002. Quality of life of women with recurrent breast cancer and their family members. Journal of Clinical Oncology 20, 4050–4064.

Northouse, L.L., Mood, D., Templin, T., Mellon, S., George, T.C., 2000. Couples' patterns of adjustment to colon cancer. Social Science and Medicine 50, 271–284.

Pinquart, M., Sorensen, S., 2003. Differences between caregivers and noncaregivers in psychological health and physical health: A meta-analysis. Psychology and Aging 18, 250–267.

Redwine, L., Mills, P.J., Sada, M., Dimsdale, J., Patterson, T., Grant, I., 2004. Differential immune cell chemotaxis responses to acute psychological stress in Alzheimer caregivers compared to non-caregiver controls. Psychosomatic Medicine 66, 770–775.

Rohleder, N., Marin, T.J., Ma, R., Miller, G.E., 2009. Biologic cost of caring for a cancer patient: dysregulation of pro- and anti-inflammatory signaling pathways. Journal of Clinical Oncology 27, 2909–2915.

Schulz, R., Visintainer, P., Williamson, G.M., 1990. Psychiatric and physical morbidity effects of caregiving. J Gerontol 45, P181–191.

Segerstrom, S.C., Miller, G.E., 2004. Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. Psychological Bulletin 130, 601–630.

Spector, P.E., Jex, S.M., 1998. Development of four self-report measures of job stressors and strain: Interpersonal Conflict at Work Scale, Organizational Constraints Scale, Quantitative Workload Inventory, and Physical Symptoms Inventory. J Occup Health Psychol 3, 356–367.

Swore Fletcher, B.A., Dodd, M.J., Schumacher, K.L., Miaskowski, C., 2008. Symptom experience of family caregivers of patients with cancer. Oncology Nursing Forum 35, E23–44.

Teel, C.S., Press, A.N., 1999. Fatigue among elders in caregiving and noncaregiving roles. Western Journal of Nursing Research 21, 498–514.

Thornton, L.M., Andersen, B.L., Crespin, T.R., Carson, W.E., 2007. Individual trajectories in stress covary with immunity during recovery from cancer diagnosis and treatments. Brain, Behavior, and Immunity 21, 185–194.

Vitaliano, P.P., Zhang, J., Scanlan, J.M., 2003. Is caregiving hazardous to one's physical health? A meta-analysis. Psychological Bulletin 129, 946–972.

Webster Marketon, J.I., Glaser, R., 2008. Stress hormones and immune function. Cellular Immunology 252, 16–26.

Weinfurt, K.P., 1995. Multivariate analysis of variance. In: Grimm, L.G., Yarnold, P.R. (Eds.), Reading and understanding multivariate statistics. American Psychological Association, Washington, D.C., pp. 245–276.