

Biologic Cost of Caring for a Cancer Patient: Dysregulation of Pro- and Anti-Inflammatory Signaling Pathways

Nicolas Rohleder, Teresa J. Marin, Roy Ma, and Gregory E. Miller

ABSTRACT

Purpose

Caring for a family member with cancer is a psychologically demanding experience. However, it remains unclear whether the distress that caregiving provokes also takes a physiologic toll on the body. This study observed familial caregivers of patients with brain cancer for a year after diagnosis and tracked changes in neurohormonal and inflammatory processes.

Patients and Methods

Eighteen caregivers (age 50.4 ± 3.5 years) and 19 controls (age 50.2 ± 2.6 years) were assessed four times during a year (before and after radiotherapy, as well as 6 weeks and 4 months thereafter). Salivary biomarkers of hypothalamus-pituitary-adrenal axis and sympathetic nervous system (SNS) activity were collected, and blood was drawn for assessment of the systemic inflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6). Blood was also used to monitor in vitro IL-6 production by endotoxin-stimulated leukocytes and expression of mRNA for pro- and anti-inflammatory signaling molecules.

Results

Caregivers showed marked changes over time in diurnal output of salivary amylase, a marker of SNS activity, whereas secretions in controls were stable during follow-up. Cortisol output was similar in caregivers and controls. During the year, caregivers showed a profound linear increase in systemic inflammation, as indexed by CRP. At the same time, they displayed a linear decline in mRNA for anti-inflammatory signaling molecules and diminished in vitro glucocorticoid sensitivity.

Conclusion

These preliminary data show that familial caregivers of patients with cancer experience marked changes in neurohormonal and inflammatory processes in the year after diagnosis. These changes may place them at risk for morbidity and mortality from diseases fostered by excessive inflammation.

J Clin Oncol 27. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Caring for a family member who has cancer is a psychologically demanding experience. In addition to concerns about the family member's welfare, caregivers report high levels of fatigue, depressive symptoms, and poor quality of life.¹⁻⁵ However, it remains unclear whether this distress also takes a toll on the body. Studies have identified a broad array of physiologic alterations in caregivers of patients with dementia,⁶ including altered diurnal output of stress hormones,⁷ blunted immune responses to vaccination,⁸ and increased concentrations of biomarkers of systemic inflammation and platelet aggregation.^{9,10} Long-term studies have also shown that risks of morbidity and mortality are increased in caregivers of disabled family members and in persons whose spouses have been hospitalized recently for major illness.¹¹⁻¹³

However, to our knowledge, research has not explored whether caregiving exacts a similar toll on the bodies of those caring for a family member with cancer, who are typically younger and healthier than caregivers of patients with disabilities or dementia. Therefore, we recruited a sample of familial caregivers of patients with brain cancer and healthy matched controls. Caregivers of patients face a number of special challenges that include anticipatory grieving about the patient's impending death, the need to provide emotional support and assistance with daily living, and the transformation of the relationship from equal to dependent.

Caregivers were assessed four times during the course of each patient's first year of treatment with a focus on psychological distress, salivary output of the stress-related biomarkers cortisol and amylase, and processes that mediate inflammation. Controls were assessed at matched time points. We expected

From the Department of Psychology, Brandeis University, Waltham, MA; and Department of Psychology, University of British Columbia; and British Columbia Cancer Agency, Vancouver Centre, Vancouver, British Columbia, Canada.

Submitted June 19, 2008; accepted January 26, 2009; published online ahead of print at www.jco.org on May 11, 2009.

Supported by Grant No. 89736 from the Canadian Institutes of Health Research, Grant No. CL-SCH-58 from the Michael Smith Foundation for Health Research (G.E.M., N.R.), and Grant No. RO 2353/4-1 from the German Research Foundation (Deutsche Forschungsgemeinschaft).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Nicolas Rohleder, PhD, Brandeis University, Department of Psychology, MS 062, PO Box 549110, Waltham, MA 02454; rohleder@brandeis.edu.

© 2009 by American Society of Clinical Oncology

0732-183X/09/2799-1/\$20.00

DOI: 10.1200/JCO.2008.18.7435

that, during the course of treatment, caregivers would show greater output of cortisol and amylase as well as increasing concentrations of the inflammatory biomarkers C-reactive protein (CRP) and interleukin-6 (IL-6). On the basis of past work, we expected that the latter changes would be enabled by a decline in glucocorticoid inhibition of the inflammatory response¹⁴ and by altered gene expression of proteins involved in the intracellular signaling cascade that orchestrates inflammation.¹⁵ Specifically, we expected upregulation of the major pro-inflammatory signaling proteins from the nuclear factor- κ B (NF- κ B) family and downregulation of the major anti-inflammatory signaling proteins inhibitory κ B (I- κ B) and glucocorticoid receptor (GR).¹⁶

PATIENTS AND METHODS

Patients and Procedure

Caregivers were recruited from the central nervous system tumor clinics at the British Columbia Cancer Agency, Vancouver Centre, between January 2005 and December 2007. All were primary familial caregivers for patients being treated for glioblastoma multiforme, the most common and most aggressive primary brain tumor, which has 5-year survival rates of approximately 10% to 20%.¹⁷ Families were approached about the study by their treating physicians before the initiation of radiotherapy; those who expressed interest in participating were put in contact with the project coordinator. Controls were recruited from Vancouver, British Columbia by using newspapers advertisements. To be eligible, the control had to match an enrolled caregiver on age (± 5 years), sex, ethnicity, and marital status and had to be free of major stressors, such as divorce, bereavement, unemployment, and family illness, during the past year. All participants were free of serious medical illness at study entry. The project was approved by the Research Ethics Boards of the University of British Columbia and the British Columbia Cancer Agency, and all participants provided written informed consent before participating. Caregivers were assessed four times during the course of the patients' treatment. Assessments were conducted before onset and at conclusion of radiotherapy as well as 6 weeks and 4 months thereafter. Control participants were assessed at matched time points. Participants received \$50 for each assessment.

Endocrine System

Basal hypothalamus-pituitary-adrenal axis and SNS activity were assessed by measuring cortisol and α -amylase in saliva obtained on three consecutive days after each study visit. Samples were collected at waking and 0.5, 1, 4, 9, and 14 hours later. Daily output and diurnal rhythms of cortisol and amylase were computed (Appendix, online only).

Systemic Inflammation

Systemic inflammation was assessed through serum levels of CRP and IL-6, which were measured by standard high-sensitivity techniques that had detection limits of 0.20 mg/L and 0.039 pg/mL, respectively¹⁸ (Appendix, online only).

Pro- and Anti-Inflammatory Signaling Pathways

Leukocyte expression of pro-inflammatory (NF- κ B subunits p65 and p105) and anti-inflammatory (I- κ B, GR- α , GR- β) signaling molecules was quantified through real-time reverse transcriptase (RT) polymerase chain reaction. Assays were conducted on a Prism 7000 Sequence Detection System (Applied Biosystems, Foster City, CA) by using commercially available one-step assays (Appendix, online only).

In Vitro Regulation of Inflammation

To index the glucocorticoid sensitivity of leukocytes, whole blood was incubated with lipopolysaccharide and different concentrations of hydrocortisone (HC) for 6 hours.^{14,19} Supernatant concentrations of IL-6 were mea-

sured by enzyme-linked immunosorbent assay, and the 50% inhibitory concentration (IC₅₀) was calculated for each dose-response curve. The IC₅₀ reflects the concentration of HC needed for 50% inhibition of cytokine production and is, therefore, inversely related to glucocorticoid sensitivity (Appendix, online only).

Psychological Distress

Psychological distress was assessed with widely used, standardized questionnaires. The Perceived Stress Scale (PSS)²⁰ captured how stressed and overwhelmed respondents felt during the prior week, and the short form of the Center for Epidemiologic Studies Depression Scale (CES-D)²¹ assessed the frequency of depressive symptoms during the same time frame. These instruments showed excellent psychometrics and had a Cronbach's α coefficient greater than 0.89.

Statistical Analyses

To determine whether caregivers and controls showed differing patterns during the year, we estimated a series of growth curve models that utilized HLM 6.06 (Scientific Software International, Inc., Lincolnwood, IL). In the within-person (ie, level-1) models, outcomes were estimated as a function of time since study entry (coded in weeks; to test for linear effects) and time since study entry squared (coded in weeks squared; to test for curvilinear effects). These models yielded person-specific intercepts that reflected the values of outcome variables at study entry (β_{0i}) and the rates of linear (β_{1i}) and curvilinear (β_{2i}) change during follow-up. In the between-person (ie, level-2) models, we estimated β_{0i} values for each participant as a function of the group, and we included the covariates of cigarette smoking, body mass, and oral contraceptives. We also estimated between-person models, in which β_{1i} and β_{2i} values for each participant were predicted as functions of the group. The critical parameters reported were γ_{01} , which reflected group differences at baseline, γ_{11} , which reflected group differences in rate of linear change, and γ_{21} , which reflected group differences in rate of curvilinear change (Appendix, online only). Study entry means for all variables are reported in Appendix Table A1 (online only).

RESULTS

Sample Characteristics

As summarized in Table 1, groups were statistically indistinguishable on demographic, lifestyle, and biomedical characteristics at baseline (all $P > .17$) and remained similar during follow-up (all $P > .12$). Patients had received their diagnoses 13.4 weeks (standard deviation [SD], ± 4.6 weeks) before study entry, and the initial surgical intervention was performed at an average of 11 weeks (SD, ± 15.43) before study entry. Most caregivers ($n = 15$) were spouses of patients with cancer; the others included a son, father, and brother.

Psychological Distress

At study entry, caregivers reported more perceived stress (PSS mean \pm SD, 18.4 ± 8.6) than controls (mean \pm SD, 11.8 ± 5.9 ; γ_{01} , -4.844389 ; standard error [SE], 1.980377 ; $P = .020$). Caregivers' levels of perceived stress were about 1 SD greater than is typical of American people age 45 to 54 years old, which is the 80th percentile of the population distribution.²² Caregivers also reported more depressed mood (CES-D mean \pm SD, 12.0 ± 7.0) than controls (CES-D mean \pm SD, 6.1 ± 4.6 ; γ_{01} , -5.014511 ; SE, 1.521561 ; $P = .003$). At baseline, 66.5% of them had short-form CES-D scores of 10 or greater, which in many settings is used as a screening cutoff for clinical depression.²³ These psychological disparities persisted at a similar magnitude throughout follow-up (PSS: γ_{11} , 0.012350 ; SE, 0.036341 ; $P = .736$;

Table 1. Demographic, Behavioral, and Biomedical Characteristics of Caregivers and Controls at Study Entry and During Follow-Up

Patient Demographics and Clinical Characteristics	Group		Group Differences											
			At Study Entry			With Time			Curvatures					
	Caregivers (n = 18)	Controls (n = 19)	t	χ^2	df	P	Trajectories							
							γ_{11}	SE	P	γ_{21}	SE	P		
Age, years			1.417		35	.17								
Mean	50.4	50.2												
SEM	3.5	2.6												
Sex, % female	61.1	68.4		0.22	1	.642								
Ethnicity, % white	83.3	63.2		1.91	1	.167								
Education, % with university degree	38.9	57.9		1.34	1	.248								
Personal history of cardiovascular disease, %	22.2	21.1		0.01	1	.931								
No. of cigarettes per day	3.17	2.11	0.483		35	.632	-0.147326	0.091136	.115	0.011531	0.007297	.123		
Exercise, minutes per week			-0.277		35	.784	-0.441740	0.921058	.634	0.128388	0.081683	.125		
Mean	134.17	145.53												
SD	28.58	29.41												
Alcohol consumption, drinks per week			0.386		35	.701	0.067252	0.102688	.517	-0.003716	0.003512	.298		
Mean	6.38	5.32												
SD	2.25	1.66												
Body mass index, kg/m ²			0.046		35	.96	-0.010797	0.008470	.211	-0.000918	0.000663	.175		
Mean	26.66	24.89												
SD	0.97	0.79												

Abbreviation: SD, standard deviation.

CES-D: γ_{11} , 0.027244; SE, 0.045038; $P = .549$; Appendix Fig A1, online only).

Endocrine System

HLM analyses of endocrine parameters indicated that the diurnal rhythm of salivary α -amylase did not differ significantly between caregivers and controls at study entry (γ_{01} , 0.0018; SE, 0.0048; $P = .704$). However, the groups' trajectories diverged significantly over time (γ_{11} , 0.0013; SE, 0.0006; $P = .028$), and so did their curvatures (γ_{21} , -0.000038; SE, 0.000013; $P = .007$). As Figure 1A shows, the diurnal rhythm of amylase secretion declined (ie, became flatter and less pronounced) during the first half of the follow-up in caregivers. It reached a nadir about 18 weeks after study entry, when most patients had completed radiotherapy, and gradually became more prominent after that. Amylase diurnal rhythm was stable over time among controls.

To illustrate how these disparities played out diurnally, Figure 1B presents average amylase concentrations over 3 days during weeks 14 to 21 of follow-up, which is the time when disparities between caregivers and controls were most pronounced. As the figure illustrates, caregivers' amylase secretions show a less pronounced increase in the late morning and lower levels during the afternoon.

Total daily output of amylase was not different between caregivers and controls at study entry (γ_{01} , -0.123114; SE, 1.606075; $P = .939$), but differences in groups' trajectories and curvatures were marginally significant (γ_{11} , 0.330024; SE, 0.149698; $P = .034$; γ_{21} , -0.00702; SE, 0.003543; $P = .055$). As Figure 1C shows, both groups began the study with similar amylase levels, but output of controls increased gradually over time, whereas output of caregivers was rela-

tively stable. None of the covariates were significant predictors of amylase diurnal rhythm or daily output (all $P > .09$).

The diurnal rhythm of salivary cortisol did not differ between groups at study entry (γ_{01} , 0.002375; SE, 0.005712; $P = .678$), and no differences in trajectories or curvatures were observed (γ_{11} , 0.000249; SE, 0.000519; $P = .634$; γ_{21} , -0.000011; SE, 0.000015; $P = .435$). Daily cortisol output also did not differ between groups at study entry (γ_{01} , 0.635725; SE, 0.804012; $P = .431$), and no differences in groups' trajectories and curvatures were found (γ_{11} , 0.008461; SE, 0.104394; $P = .936$; γ_{21} , 0.000124; SE, 0.002871; $P = .966$; Appendix Fig A2, online only). Smokers had higher daily cortisol outputs at study entry than nonsmokers ($P = .002$); none of the other covariates were significant predictors of cortisol indices.

Systemic Inflammation

HLM analyses indicated that groups had similar quantities of the inflammatory marker CRP at study entry (γ_{01} , -0.044436; SE, 0.079286; $P = .576$). However, the groups' trajectories diverged significantly over time (γ_{11} , -0.005285; SE, 0.001668; $P = .004$), as caregivers' concentrations increased markedly and controls declined slightly (Fig 2A). Smokers had higher CRP levels at study entry ($P = .019$); none of the other covariates were significant predictors.

Plasma concentrations of IL-6 did not differ between groups at study entry (Fig 2B; γ_{01} , -0.00811; SE, 0.037876; $P = .831$), and the groups' trajectories and curvatures were similar (γ_{11} , 0.000201; SE, 0.002056; $P = .923$; γ_{21} , -0.000043; SE, 0.000039; $P = .283$). Smoking and body mass index were associated with higher IL-6 levels ($P = .007$ and $P = .04$, respectively), but none of the other covariates were.

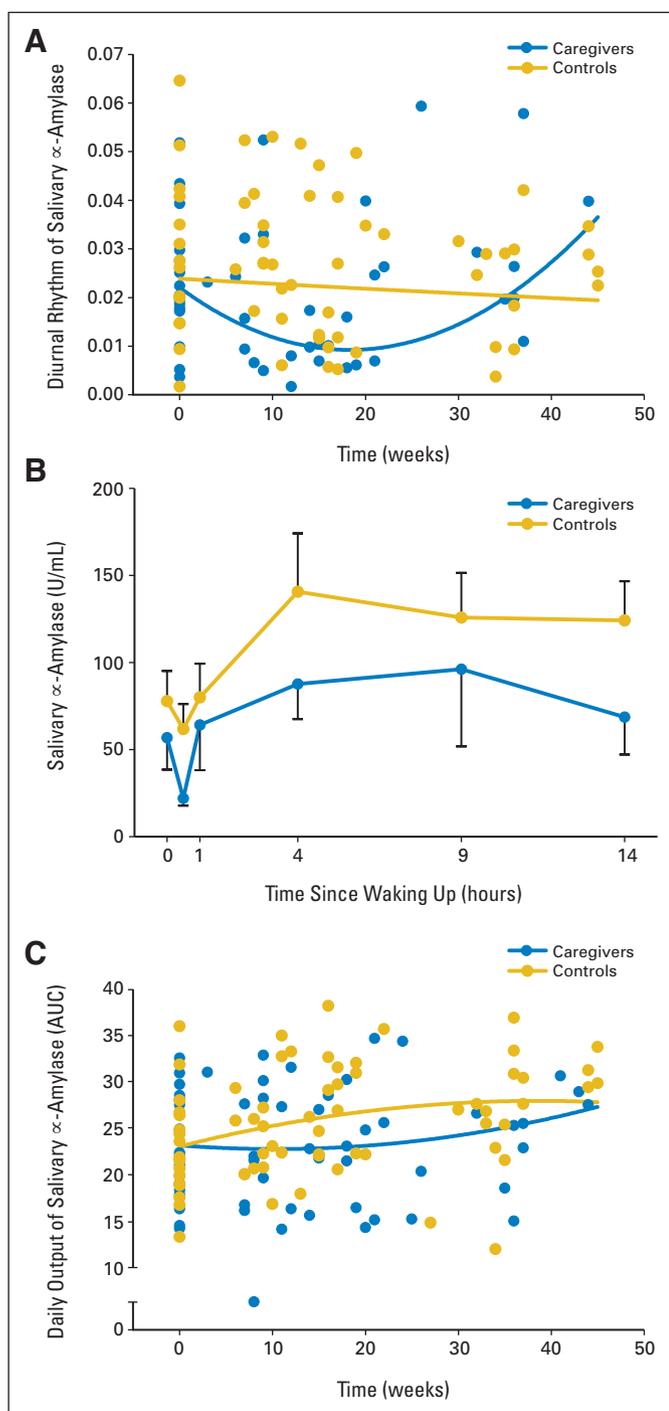


Fig 1. (A) Changes over time of diurnal rhythm of salivary α -amylase; (B) diurnal profile of salivary α -amylase secretion in caregivers and controls at the nadir of the diurnal rhythm (weeks 14 to 21 after study entry); and (C) changes over time of daily output of salivary α -amylase (area under curve [AUC]).

Pro-Inflammatory Signaling Pathways

To examine whether development of low-grade systemic inflammation in caregivers was associated with changes in pro-inflammatory signaling pathways, we measured expression of mRNA for two major proteins of the NF- κ B complex (ie, NF- κ B p65 and p105). HLM analyses showed no significant group differences at study entry (p65: γ_{01} , -0.048341 ; SE, 0.249504 ; $P = .848$; p105: γ_{01} , -0.40313 ; SE,

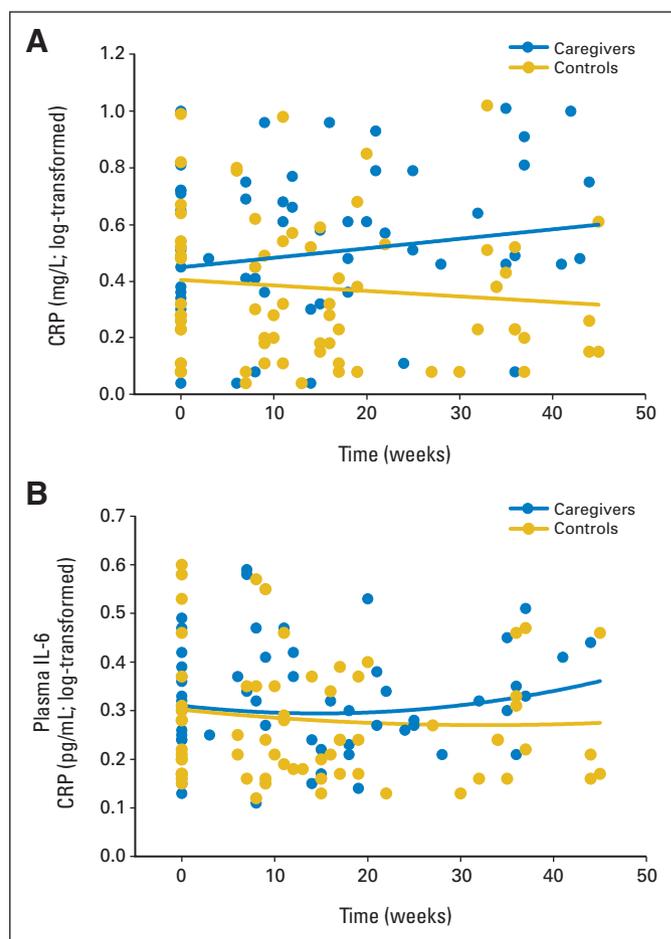


Fig 2. Plasma concentrations of (A) C-reactive protein (CRP) and (B) interleukin-6 (IL-6) during follow-up in caregivers and controls.

0.281935 ; $P = .162$). However, trajectories differed significantly between caregivers and controls (p65: γ_{11} , 0.035163 ; SE, 0.013227 ; $P = .012$; p105: γ_{11} , 0.03634 ; SE, 0.011383 ; $P = .003$). Expression of NF- κ B p105 and p65 increased during the follow-up period in controls, whereas it decreased in caregivers (Fig 3; Appendix Fig A3, online only). Expression of NF- κ B p65 was associated with body mass index ($P = .034$); none of the other covariates were significant predictors.

Anti-Inflammatory Signaling Pathways

To examine whether the development of low-grade systemic inflammation was associated with changes in anti-inflammatory signaling pathways, we assessed mRNA for the active isoform of the GR (ie, GR- α) relative to expression of the inactive isoform (ie, GR- β) on the basis of the hypothesis that the GR- α :GR- β ratio is indicative of the ability of GR to exert its anti-inflammatory effects.^{24,25} We additionally measured mRNA for I- κ B, which neutralizes the activities of NF- κ B.

HLM analyses revealed significant differences in the GR- α :GR- β ratio between caregivers and controls at study entry (γ_{01} , -0.05116 ; SE, 0.018702 ; $P = .008$) as well as significant differences in group trajectories (γ_{11} , 0.009849 ; SE, 0.002743 ; $P = .001$) and curvatures (γ_{21} , -0.000226 ; SE, 0.000077 ; $P = .006$). Specifically, the GR- α :GR- β ratio was higher in caregivers at study entry, but it declined

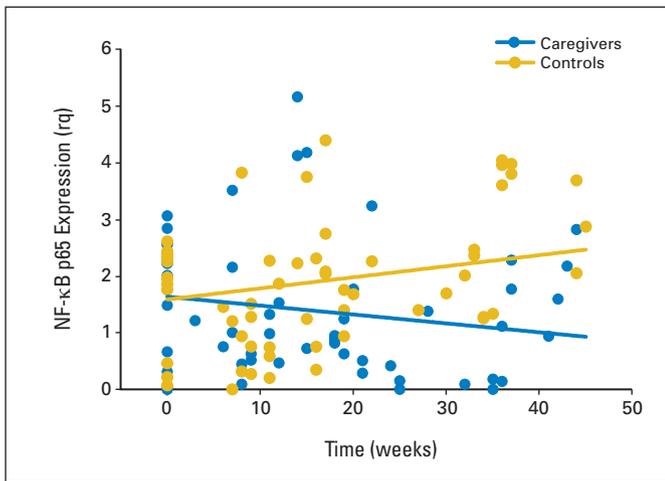


Fig 3. Expression of the pro-inflammatory nuclear factor (NF)-κB p65 during follow-up in caregivers and controls.

during the next 4 months until it reached a nadir about at about 18 to 20 weeks, which is the same time that amylase reached nadir. The ratio then began to increase again (Fig 4A). None of the covariates were significant predictors.

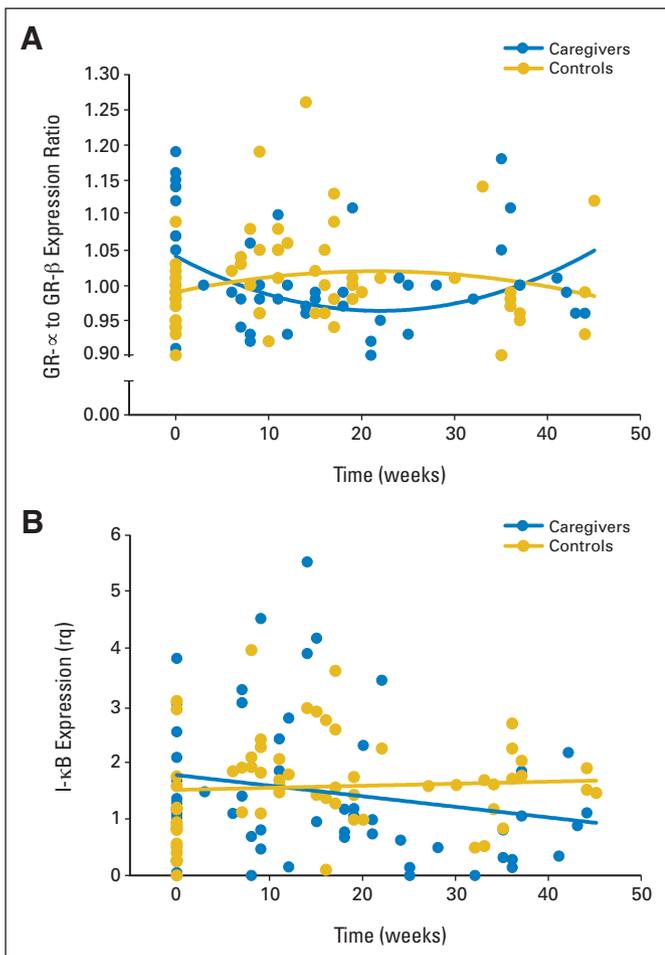


Fig 4. (A) Ratio of glucocorticoid receptor (GR) –α relative to GR-β expression, and (B) expression of inhibitory κB (I-κB) during follow-up in caregivers and controls.

When isoforms were analyzed separately, there were no significant group differences at study entry (GR-α: γ_{01} , 0.528989; SE, 0.350508; $P = .141$; GR-β: γ_{01} , 0.760363; SE, 0.42563; $P = .083$) or in trajectories or curvatures during follow-up (GR-α: γ_{11} , -0.00692; SE, 0.034427; $P = .842$; γ_{21} , 0.00035; SE, 0.00074; $P = .639$; GR-β: γ_{11} , -0.04696; SE, 0.043926; $P = .293$; γ_{21} , 0.00106; SE, 0.000963; $P = .279$; Appendix Fig A4, online only).

HLM analyses showed no group differences in expression of the anti-inflammatory I-κB at study entry (γ_{01} , -0.260031; SE, 0.217535; $P = .241$), but there were significant disparities in trajectories over time (γ_{11} , 0.022277; SE, 0.008781; $P = .016$). Figure 4B shows that I-κB expression decreased over time in caregivers, whereas it remained stable in controls. Expression of I-κB was higher in users of oral contraceptives ($P = .029$); none of the other covariates were significant predictors.

In Vitro Regulation of Inflammation

Finally, to test whether the disparities in signaling molecule expression translated into alterations in functioning physiologic systems, we measured in vitro glucocorticoid sensitivity of leukocyte IL-6 production. HLM analyses indicated a marginally significant difference in glucocorticoid sensitivity between caregivers and controls at study entry (γ_{01} , 0.117958; SE, 0.060249; $P = .052$). Specifically, IC_{50} tended to be lower among caregivers, which indicated that their leukocytes were more sensitive to glucocorticoid inhibition than leukocytes in controls. This pattern changed directions over time (γ_{11} , -0.010599; SE, 0.006167; $P = .094$). As Figure 5 shows, caregiver IC_{50} increased over time, which means the glucocorticoid sensitivity of their leukocytes declined, whereas the IC_{50} of controls remained relatively stable. The groups' curvatures were not significantly different (γ_{21} , 0.00018; SE, 0.000158; $P = .264$). None of the covariates were significant predictors.

DISCUSSION

These data indicate that caring for a family member with glioblastoma is associated with significant psychological distress that is similar in

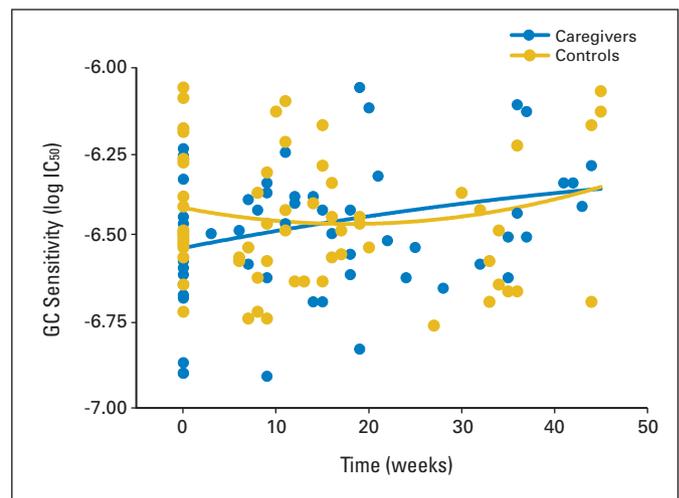


Fig 5. Glucocorticoid sensitivity in caregivers and controls during follow-up. The log 50% inhibitory concentration (IC_{50}) of hydrocortisone inhibition of lipopolysaccharide-stimulated IL-6 production is shown. The log IC_{50} is inversely related to glucocorticoid sensitivity.

magnitude to what various groups of patients with cancer themselves experience.²⁶⁻²⁸ Moreover, these data show that caring exacts a physiologic toll on the body. Caregivers showed marked changes in a broad array of neurohormonal and inflammatory parameters in the year after diagnosis. The most striking changes were in systemic inflammation. By about 20 weeks after study entry, nine of 18 caregivers had CRP concentrations greater than 3 mg/L compared with two of 19 of the controls. According to current guidelines, concentrations in this range suggest high risk for coronary heart disease.²⁹ Hence, these data suggest the possibility that caring for a family member with brain cancer may heighten vulnerability to coronary disease, as well as other metabolic, autoimmune, and psychiatric conditions that are sensitive to inflammation.³⁰⁻³²

The study found that, at the same time that CRP increased in caregivers, expression of anti-inflammatory signaling molecules and leukocyte responsiveness to glucocorticoid inhibition declined. However, the latter decrease was relative, because caregivers began the study with more glucocorticoid-sensitive cells. These findings are consistent with the hypothesis that, over time, caregiving induces a relative resistance to the anti-inflammatory properties of glucocorticoids, a process which is thought over the long-term to lead to low-grade chronic inflammation.¹⁴ Differential cortisol output does not appear to underlie these changes in tissue sensitivity, as caregivers and controls had similar patterns of diurnal secretion throughout the study. It is possible that SNS outflow was more central in driving these effects, because catecholamines are able to regulate both GR dynamics and pro-inflammatory signaling.³³ Indeed, differential SNS activity could have modulatory influences on several biologic systems important to the caregiver health (eg, immune, metabolic, cardiovascular), even in circumstances in which cortisol output was normal.

The study also yielded some puzzling findings. For example, it is not clear why controls showed greater output of amylase over time, or why caregivers showed declining NF- κ B expression over time. The latter finding is particularly difficult to reconcile with the marked CRP increase observed in caregivers, unless one assumes that it is declining levels of inhibitory control over NF- κ B, as reflected in I- κ B decreases, that are primarily responsible for the increase in systemic inflammation. Even if this is the case, it is still difficult to explain why NF- κ B would decline in caregivers. One possibility is that this pattern reflects the immune system's efforts to counter-regulate inflammation, but these data do not allow testing of this hypothesis. It is also difficult to understand why systemic IL-6 did not increase alongside CRP in caregivers, because the former molecule is the primary stimulus for the latter to be released from the liver. This discrepancy might be explained by IL-6 release by multiple tissues, response to acute changes in mood and diet, and likelihood to randomly fluctuate more than CRP.^{18,34}

We observed significant temporal variability in biologic outcomes among caregivers. Although three of the outcomes changed in a linear fashion over time, another three followed u-shaped functions that had nadirs at about 18 to 20 weeks after study entry.

It is not clear why trajectories shifted at this juncture. Regardless, the temporal variability in outcomes has important methodological, theoretical, and clinical implications. Methodologically, the variability highlights the importance of conducting multiwave longitudinal assessments. These designs are rare in the literature about caregivers but are of utmost importance, because single-time point assessments can generate misleading conclusions about which direction a process changes, depending on when assessments are conducted. Theoretically, the observed patterns indicate that different biologic systems respond to caregiving with unique, but interrelated, temporal dynamics. These patterns are consistent with recent theories about the dynamic nature of biologic responses to life stress. According to these models, biologic systems are up- or downregulated with differing temporal patterns after the onset of and during the course of chronic stress. This is partly a result of changing psychological demands over the course of the stressor, but it also stems from the interaction of changes in psychological demands with changes in biologic responses.³⁵⁻³⁸ Clinically, these patterns have important implications for understanding vulnerability of caregivers of cancer patients to disease over time. Specifically, they suggest that caregivers may be relatively protected early in treatment. However, as time passes and systemic inflammation increases, the caregivers may be at risk for flare-ups of existing autoimmune diseases, progression of atherosclerosis, worsening of glucose control, and symptoms of psychiatric disorders.³⁰⁻³²

This study has several limitations, including a small sample size, which might be another reason for some of the puzzling findings; a limited set of biologic outcomes; and no morbidity and mortality data. Nonetheless, it reveals that caring for a family member with cancer is associated with a highly dynamic pattern of neurohormonal and inflammatory adaptations that, if sustained, could have important implications for caregivers themselves about susceptibility to life-threatening diseases.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Roy Ma, Gregory E. Miller

Financial support: Gregory E. Miller

Administrative support: Teresa J. Marin, Roy Ma, Gregory E. Miller

Provision of study materials or patients: Roy Ma, Gregory E. Miller

Collection and assembly of data: Nicolas Rohleder, Teresa J. Marin

Data analysis and interpretation: Nicolas Rohleder, Teresa J. Marin, Gregory E. Miller

Manuscript writing: Nicolas Rohleder, Teresa J. Marin

Final approval of manuscript: Nicolas Rohleder, Teresa J. Marin, Roy Ma, Gregory E. Miller

REFERENCES

1. Kim Y, Schulz R: Family caregivers' strains: Comparative analysis of cancer caregiving with dementia, diabetes, and frail elderly caregiving. *J Aging Health* 20:483-503, 2008

2. Kim Y, Given BA: Quality of life of family caregivers of cancer survivors: Across the trajectory of the illness. *Cancer* 112:2556-2568, 2008 (suppl)

3. Northouse LL, Mood DW, Montie JE, et al: Living with prostate cancer: Patients' and spouses' psychosocial status and quality of life. *J Clin Oncol* 25:4171-4177, 2007

4. Braun M, Mikulincer M, Rydall A, Walsh A, Rodin G: Hidden morbidity in cancer: Spouse caregivers. *J Clin Oncol* 25:4829-4834, 2007

5. Fletcher BS, Paul SM, Dodd MJ, et al: Prevalence, severity, and impact of symptoms on female family caregivers of patients at the initiation of radiation therapy for prostate cancer. *J Clin Oncol*

26:599-605, 2008

6. Vitaliano PP, Zhang J, Scanlan JM: Is caregiving hazardous to one's physical health? A meta-analysis. *Psychol Bull* 129:946-972, 2003

7. Gallagher-Thompson D, Shurgot GR, Rider K, et al: Ethnicity, stress, and cortisol function in Hispanic and non-Hispanic white women: A preliminary study of family dementia caregivers and noncaregivers. *Am J Geriatr Psychiatry* 14:334-342, 2006

8. Vedhara K, Cox NK, Wilcock GK, et al: Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. *Lancet* 353:627-631, 1999

9. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, et al: Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci U S A* 100:9090-9095, 2003

10. von Känel R, Dimsdale JE, Mills PJ, et al: Effect of Alzheimer caregiving stress and age on frailty markers interleukin-6, C-reactive protein, and D-dimer. *J Gerontol A Biol Sci Med Sci* 61:963-969, 2006

11. Schulz R, Beach SR: Caregiving as a risk factor for mortality: The Caregiver Health Effects Study. *JAMA* 282:2215-2219, 1999

12. Lee S, Colditz GA, Berkman LF, et al: Caregiving and risk of coronary heart disease in US women: A prospective study. *Am J Prev Med* 24:113-119, 2003

13. Christakis NA, Allison PD: Mortality after the hospitalization of a spouse. *N Engl J Med* 354:719-730, 2006

14. Miller GE, Cohen S, Ritchey AK: Chronic psychological stress and the regulation of proinflammatory cytokines: A glucocorticoid-resistance model. *Health Psychol* 21:531-541, 2002

15. Miller GE, Chen E, Sze J, et al: A functional genomic fingerprint of chronic stress in humans: Blunted glucocorticoid and increased NF- κ B signaling. *Biol Psychiatry* 64:266-272, 2008

16. McKay LI, Cidlowski JA: Molecular control of immune/inflammatory responses: Interactions between nuclear factor- κ B and steroid receptor-signaling pathways. *Endocr Rev* 20:435-459, 1999

17. Thapa K, Laws ER: Tumors of the central nervous system, in Murphy GP, Lawrence W,

Lenhard RE (eds): *Textbook of Clinical Oncology*. Atlanta, GA, American Cancer Society, 1995, pp 378-410

18. Rohleder N, Miller GE: Acute deviations from long-term trait depressive symptoms predict systemic inflammatory activity. *Brain Behav Immun* 22:709-716, 2008

19. Rohleder N, Wolf JM, Kirschbaum C: Glucocorticoid sensitivity in humans—interindividual differences and acute stress effects. *Stress* 6:207-222, 2003

20. Cohen S, Kamarck T, Mermelstein R: A global measure of perceived stress. *J Health Soc Behav* 24:385-396, 1983

21. Radloff LS: The CES-D scale: A self report depression scale for research in the general population. *Applied Psychological Measurement* 1:385-401, 1977

22. Cohen S, Williamson G: Perceived stress in a probability sample of the United States, in Spacapan S, Oskamp S (eds): *The Social Psychology of Health: Claremont Symposium on Applied Social Psychology*. Newbury Park, CA, Sage, 1988

23. Andresen EM, Malmgren JA, Carter WB, et al: Screening for depression in well older adults: Evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med* 10:77-84, 1994

24. Bamberger CM, Bamberger AM, De Castro M, et al: Glucocorticoid receptor beta, a potential endogenous inhibitor of glucocorticoid action in humans. *J Clin Invest* 95:2435-2441, 1995

25. Oakley RH, Jewell CM, Yudit MR, et al: The dominant negative activity of the human glucocorticoid receptor β isoform: Specificity and mechanisms of action. *J Biol Chem* 274:27857-27866, 1999

26. Lutgendorf SK, Weinrib AZ, Penedo F, et al: Interleukin-6, cortisol, and depressive symptoms in ovarian cancer patients. *J Clin Oncol* 26:4820-4827, 2008

27. Thornton LM, Andersen BL, Crespino TR, et al: Individual trajectories in stress covary with immunity during recovery from cancer diagnosis and treatments. *Brain Behav Immun* 21:185-194, 2007

28. Keir ST, Guill AB, Carter KE, et al: Stress and intervention preferences of patients with brain tumors. *Support Care Cancer* 14:1213-1219, 2006

29. Pearson TA, Mensah GA, Alexander RW, et al: Markers of inflammation and cardiovascular disease: Application to clinical and public health practice—A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 107:499-511, 2003

30. Ridker PM, Cushman M, Stampfer MJ, et al: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 336:973-979, 1997

31. Pradhan AD, Manson JE, Rifai N, et al: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 286:327-334, 2001

32. Dantzer R, O'Connor JC, Freund GG, et al: From inflammation to sickness and depression: When the immune system subjugates the brain. *Nat Rev Neurosci* 9:46-56, 2008

33. Bierhaus A, Wolf J, Andrassy M, et al: A mechanism converting psychosocial stress into mononuclear cell activation. *Proc Natl Acad Sci U S A* 100:1920-1925, 2003

34. Steptoe A, Hamer M, Chida Y: The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain Behav Immun* 21:901-912, 2007

35. McEwen BS, Stellar E: Stress and the individual: Mechanisms leading to disease. *Arch Intern Med* 153:2093-2101, 1993

36. Mohr DC, Pelletier D: A temporal framework for understanding the effects of stressful life events on inflammation in patients with multiple sclerosis. *Brain Behav Immun* 20:27-36, 2006

37. Miller GE, Chen E, Zhou ES: If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychol Bull* 133:25-45, 2007

38. Miller GE, Chen E, Cole SW: Health psychology: Developing biologically plausible models linking the social world and physical health. *Annu Rev Psychol* 60:501-524, 2009

Appendix

Methods: participants and procedure. Caregivers were recruited from the central nervous system tumor clinics at the British Columbia Cancer Agency, Vancouver Centre, between January 2005 and December 2007. All were primary familial caregivers for patients being treated for glioblastoma multiforme, the most common and most aggressive primary brain tumor, for which 5-year survival rates are approximately 10% to 20%.¹⁷ Families were approached about the study by their treating physicians before the initiation of radiotherapy; those who expressed interest in participating were put in contact with the project coordinator. Controls were recruited from the broader community of Vancouver, British Columbia by using advertisements in newspapers. To be eligible, they had to match an enrolled caregiver on age (± 5 years), sex, ethnicity, and marital status and had to be free of major stressors, such as divorce, bereavement, unemployment, and family illness during the past year. To participate, all participants had to be free of infectious disease in the 2 weeks before evaluation, as evidenced by a normal complete blood count, and had to be free of serious and chronic illnesses, including cancers, coronary heart disease, stroke, HIV/AIDS, hepatitis, autoimmune diseases, chronic obstructive pulmonary disorder, schizophrenia, bipolar disorder, and dementia. None of the caregivers initially approached had to be excluded as a result of any of these criteria. The project was approved by the Research Ethics Boards of the University of British Columbia and the British Columbia Cancer Agency, and all participants provided written informed consent before participating. Caregivers were assessed four times during the course of the patients' treatment. Assessments were conducted before onset and at conclusion of radiotherapy, as well as 6 weeks and 4 months thereafter. Control participants were assessed at matched time points. Participants received \$50 for each assessment.

Measures: endocrine system. Basal activity of the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system was assessed by salivary biomarkers. Salivary cortisol is an established noninvasive marker of activity of the hypothalamus-pituitary-adrenal axis (Kirschbaum C, et al: *Psychoneuroendocrinology* 19:313-333, 1994), and α -amylase is increasingly used as a marker of SNS activity. Secretion of salivary α -amylase is activated by acute psychosocial stress in a pattern similar to that of norepinephrine (Rohleder N, et al: *Ann N Y Acad Sci*

1032:258-263, 2004; Rohleder N, et al: *Psychophysiology* 43:645-652, 2006). These stress responses can be eliminated by β blockade (van Stegeren A, et al: *Psychoneuroendocrinology* 31:137-141, 2006) and can be pharmacologically induced by the SNS-activating substance yohimbine (Ehlert U, et al: *J Clin Endocrinol Metab* 91:5130-5133, 2006). α -amylase displays a reproducible diurnal rhythm; daily output and secretion pattern covary with chronic psychosocial stress and depression (Rohleder N, et al: *Health Psychol* 27:534-532, 2008; Nater UM, et al: *Psychoneuroendocrinology* 32:392-401, 2007).

After each of the four assessments, participants collected saliva as they went about 3 days of normal activities. Collections were scheduled at waking and 0.5, 1, 4, 9, and 14 hours later. To facilitate the collection process and to enhance compliance, we lent participants a handheld computer (Palm Zire 21, Palm Inc, Sunnyvale, CA), which signaled them to collect saliva at the specified sampling times. Specifically, when participants woke up, they took the first saliva sample and activated a customized software application on the Palm. The handheld would then sound alarms at the appropriate times for the rest of the day's samples. To collect the saliva samples, participants chewed lightly on a cotton dental roll (Salivette; Sarstedt, Nümbrecht, Germany) for 1 minute so that it became saturated in saliva. Participants were instructed to avoid taking saliva samples immediately after tooth brushing and food intake. The dental roll then was placed in a plastic container and was stored in the refrigerator until the end of the ambulatory monitoring period. To ensure compliance with the saliva sample protocol, the computer flashed a three-digit code each time the alarm sounded. Participants recorded the code on the plastic container, and a research assistant later matched these codes with individual samples to generate real sampling times for each saliva sample.

Cortisol was measured by utilizing a commercial chemiluminescent assay (IBL-Hamburg; Hamburg, Germany). Salivary α -amylase was measured by utilizing an enzyme kinetic method, as previously described (Rohleder N, et al: *Psychophysiology* 43:645-652, 2006). Intra- and interassay coefficients of variation were less than 12%. After log transformation of cortisol and amylase values, indices for the diurnal rhythm were calculated by linear regression of hormone concentrations onto time since waking (excluding the wake-up response). For cortisol, negatively-signed rhythm values were considered normative, because they reflected the usual pattern of declining hormone output during the day. The opposite is the case for amylase. To index total daily output, we calculated area under the curve for each hormone across 3 days of sampling by using the trapezoidal method, with actual sample collection times on the x axis.

Systemic inflammation. To assess systemic inflammatory activity, venous blood was drawn from an antecubital vein into serum separator Vacutainer tubes (Becton Dickinson, Mississauga, Canada). Blood was allowed to clot for 30 minutes and then was centrifuged for 10 minutes at $1200 \times g$. Plasma was divided into aliquots and was stored at -30°C until additional analysis was performed. Interleukin-6 (IL-6) concentrations were quantified in duplicates by using commercial high-sensitivity enzyme-linked immunosorbent assay kits (Quantikine HS human IL-6; R&D Systems, Minneapolis, MO) that had a minimum detectable concentration of 0.039 pg/mL. Inter- and intra-assay variabilities were less than 10%. C-reactive protein was measured by the Clinical Chemistry Laboratory of St. Pauls Hospital (Vancouver, Canada) by using a high-sensitivity chemiluminescence technique on an Immulite 2000 instrument (Diagnostic Products Corporation, Los Angeles, CA). This assay has an intra-assay variability of 2.2% and a detection threshold of 0.20 mg/L.

Pro- and anti-inflammatory signaling pathways. Expression of pro- and anti-inflammatory signaling molecules was quantified through real-time reverse transcriptase polymerase chain reaction. We assessed expression of nuclear factor κB (NF- κB) p65 and p105 as major pro-inflammatory signaling pathways, and we assessed inhibitory κB (I- κB) expression and the glucocorticoid receptor (GR) $-\alpha$:GR- β expression ratio as major anti-inflammatory signaling pathways. We used the GR- α :GR- β ratio because GR- β inhibits transcriptional activity of GR- α , which leads to more glucocorticoid resistance in individuals with higher relative expression of the β isoform.^{24,25} Higher GR- β has been found, for example, in patients with autoimmune diseases (Piotrowski P, et al: *Folia Histochem Cytobiol* 45:339-342, 2007).

Total RNA was extracted from leukocytes by using PAXgene Blood RNA kits (Pre-Analytix, Hombrechtikon, Switzerland). Reverse transcriptase polymerase chain reactions were carried out on a Prism 7000 Sequence Detection System (Applied Biosystems, Foster City, CA), by using commercially available one-step assays that were based on 5' nuclease activity of FAM-labeled TaqMan probes (Applied Biosystems). For NF- κB p65 and p105 and for I- κB , commercially available assays were used (#Hs00153294_m1, #HS00765730_m1, and #HS00153283_m1; Applied Biosystems). For the GR isoforms, we developed a new TaqMan assay in collaboration with Applied Biosystems. The primer sequences were 5'-AGTGGTTGAAAATCTCCTTAAGTATTGCT-3' (forward) and 5'-GGTATCTGATTGGTGATGATTTTCAGCTA-3' (reverse) for GR- α and 5'-AGAAGATTATGTGCACCTCGTTGTC-3' (forward) and 5'-GGCACAGCTTCTTTTCCCATTTAAT-3' (reverse) for GR- β . All assays used a standard thermal cycling protocol recommended by the manufacturer. As an internal control, 18S mRNA (for GR isoforms) or β -actin mRNA (for NF- κB and I- κB) were quantified in parallel with target genes. The data were normalized by using the ΔC_T method ($\Delta\text{C}_\text{T} = \text{C}_\text{T}$ target - C_T control). Results were expressed as relative quantities of each target, which were calculated by subtracting each participant's ΔC_T from the highest ΔC_T in the distribution. Thus, higher relative quantities indicate greater expression of target genes.

In vitro regulation of inflammation. To assess the sensitivity of the inflammatory response towards glucocorticoid suppression, 10 mL of venous blood were drawn from an antecubital vein into Vacutainer tubes (Becton Dickinson) with lithium heparin as an anticoagulant. Within 30 minutes, blood was transferred to the laboratory and was processed in sterile conditions. Blood was diluted 10:1 with saline (0.9% NaCl; Braun, Scarborough, Canada), and five aliquots of 1.6 mL were transferred to a six-well culture plate (Sarstedt, Montreal, Canada). All five aliquots were coincubated with 200 μL of lipopolysaccharide (LPS; Sigma Chemicals, St. Louis, MO) at a final concentration of 50 ng/mL and with five different concentrations of hydrocortisone (final concentrations: 0, 2.76×10^{-5} , 2.76×10^{-6} , 2.76×10^{-7} , 2.76×10^{-8} mol/L; Sigma Chemicals; St. Louis, MO, USA). After 6 hours of incubation at 37°C and 5% carbon dioxide, each aliquot was centrifuged at $16,110 \times g$ for 5 minutes. The resulting plasma supernatant was stored at -30°C until additional analysis was performed. IL-6 concentrations were quantified in duplicates by using commercial enzyme-linked immunosorbent assay kits (Quantikine human IL-6; R&D Systems) that had minimum detectable concentrations of 0.7 pg/mL. Inter- and intra-assay variabilities were less than 10%. As an index for glucocorticoid sensitivity, the 50% inhibitory concentration (IC_{50}) was calculated for each individual dose-response curve by using GraphPad Prism, version 4.00c for Macintosh (GraphPad

Software, San Diego, CA). The IC₅₀ reflected the specific concentration of hydrocortisone needed for 50% inhibition of cytokine production and was, therefore, inversely related to glucocorticoid sensitivity.

Psychological distress. Psychological distress was assessed with two widely used, standardized questionnaires. The Perceived Stress Scale²⁰ captured how stressed and overwhelmed respondents felt during the prior week, and the 10-item short form of the Center for Epidemiologic Studies Depression Scale (CES-D)²¹ assessed the frequency of depressive symptoms during the same time frame. These instruments showed excellent psychometrics in our sample and had a Cronbach's α coefficient greater than 0.89.

Statistical analyses. To determine how biologic outcomes changed over time in caregivers and controls, we estimated a series of growth curve models by utilizing HLM 6.06 (Scientific Software International, Lincolnwood, IL). In the within-person (ie, level-1) models, we estimated each biologic outcome as a function of time since study entry (coded in weeks; to test for linear effects) and of time since study entry squared (coded in weeks squared; to test for curvilinear effects). These models yielded a series of person-specific intercepts that reflected the value of the biologic outcome at study entry (β_{0i}) and person-specific trajectories that reflected the rates of linear (β_{1i}) and curvilinear (β_{2i}) changes during the follow-up. In the between-person (ie, level-2) models, we estimated β_{0i} values for each participant as a function of the group, and we included the covariates of cigarette smoking, body mass index, and oral contraceptive use. We also estimated between-person models, in which β_{1i} and β_{2i} values for each participant were predicted as functions of the group status (caregiver v control). In general, we started with equations that included both linear and quadratic terms. For cases in which the quadratic term was significant, we inferred a curvilinear effect for time and interpreted the data accordingly. When the quadratic term was nonsignificant, we dropped it from the model and tested the linear effect for time. All models included random variables that specified the amounts by which each participant deviated from the sample's average β_{1i} and β_{2i} . The critical parameters were the coefficients γ_{01} (which reflected group differences at baseline), γ_{11} (which reflected group differences in rate of linear change), and γ_{21} (which reflected group differences in rate of curvilinear change). All other analyses were performed by using SPSS 13 for Mac OSX (SPSS Inc, Chicago, IL).

Table A1. Means and SEMs of All Variables in Caregivers Versus Controls at Study Entry

Variable	Data per Treatment Group at Study Entry			
	Caregivers (n = 18)		Controls (n = 19)	
	Mean	SEM	Mean	SEM
Diurnal slope of salivary α -amylase	0.023	0.004	0.021	0.005
Daily output of salivary α -amylase, AUC	23.32	1.36	23.15	1.29
Diurnal slope of salivary cortisol	-0.047	0.004	-0.044	0.005
Daily output of salivary cortisol, AUC	9.61	.622	9.67	0.661
CRP, log-transformed	0.479	0.063	0.380	0.061
IL-6, log-transformed	0.294	0.026	0.297	0.035
NF-kB p105 relative expression	1.66	0.237	0.913	0.201
NF-kB p65 relative expression	1.81	0.252	1.81	0.219
GR- α /GR- β ratio	1.05	0.020	0.971	0.012
GR- α relative expression	1.63	0.279	2.17	0.264
GR- β relative expression	1.42	0.342	2.46	0.283
I-kB relative expression	1.53	0.221	1.02	0.214
in vitro glucocorticoid sensitivity, IC ₅₀	-6.54	0.051	-6.39	0.050

Abbreviations: AUC, area under the concentration-time curve; CRP, C-reactive protein; IL-6, interleukin-6; NF, nuclear factor; GR, glucocorticoid receptor; IC₅₀, 50% inhibitory concentration.

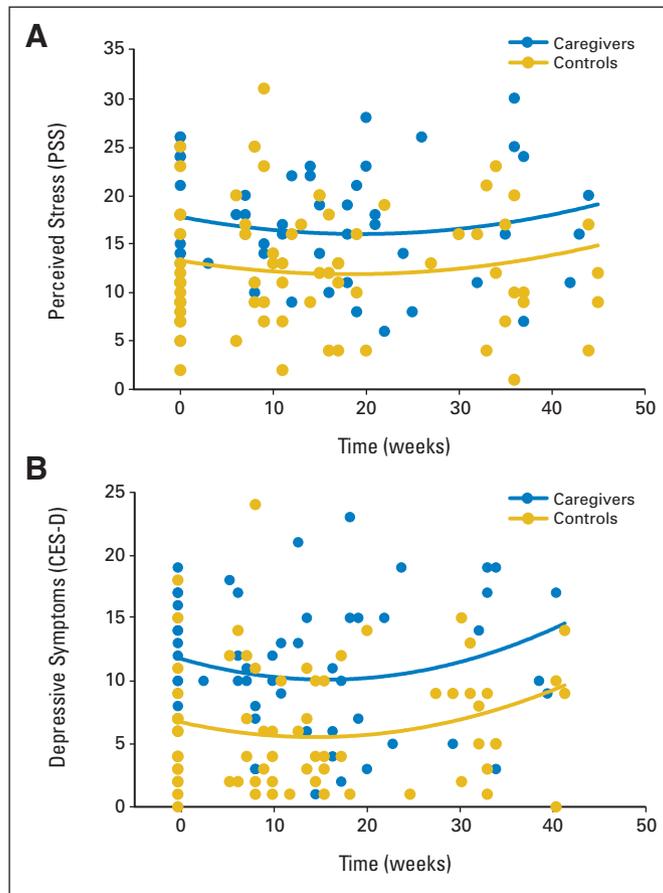


Fig A1. Changes over time of (A) perceived stress (PSS) or (B) depressive symptoms (according to Center for Epidemiologic Studies Depression Scale [CES-D]) in caregivers and controls.

Biologic Dysregulation in Caregivers of Cancer Patients

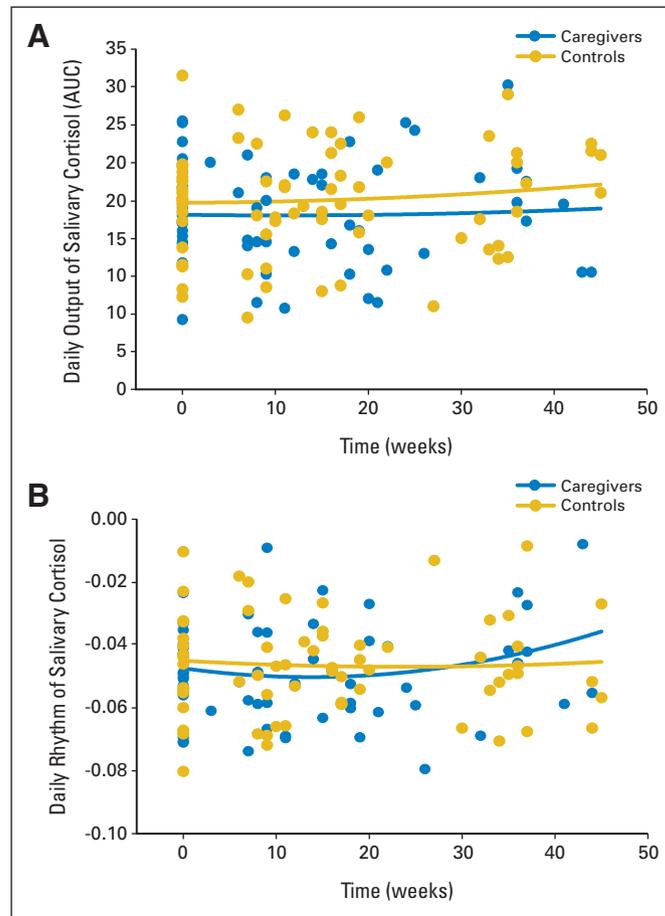


Fig A2. Changes over time of (A) diurnal rhythm of salivary cortisol and (B) daily output of salivary cortisol (area under curve [AUC]) in caregivers and controls.

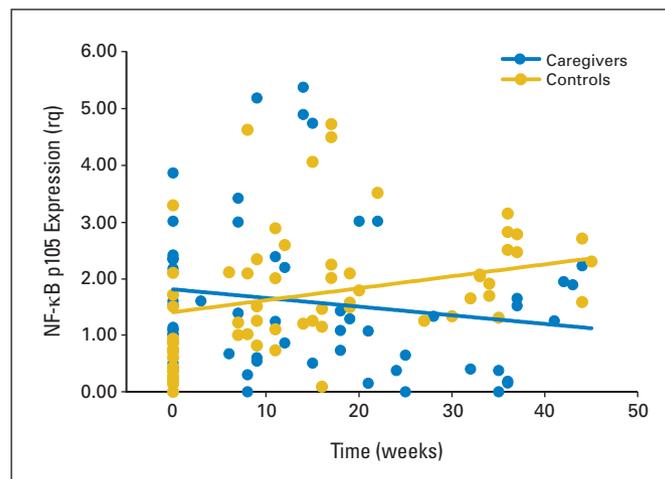


Fig A3. Expression of the pro-inflammatory nuclear factor (NF)-κB p105 during follow-up in caregivers and controls.

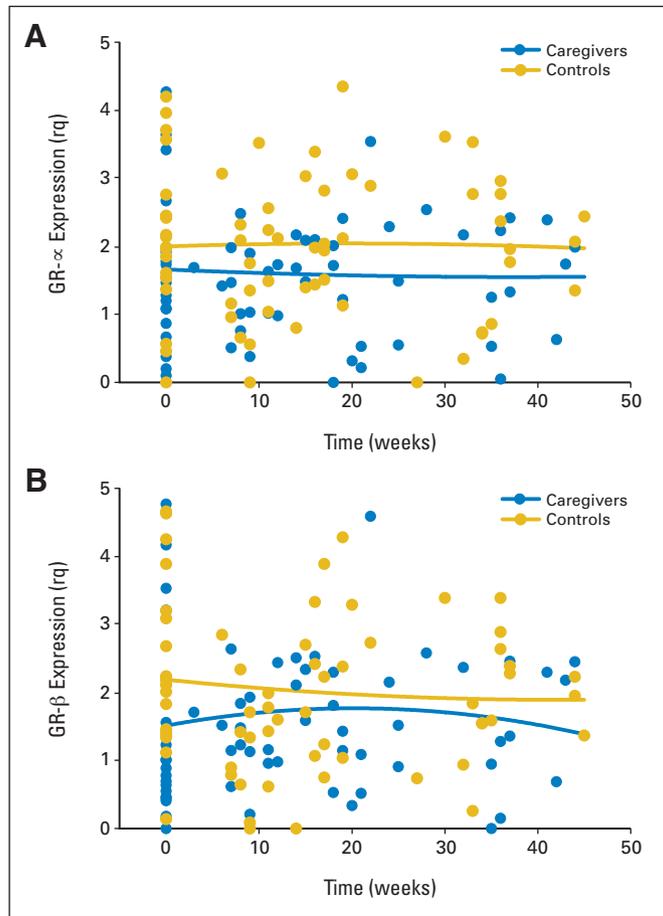


Fig A4. Expression of the (A) α - and the (B) β -isoform of the glucocorticoid receptor (GR) during follow-up in caregivers and controls.

Care of the Caregiver: Stress and Dysregulation of Inflammatory Control in Cancer Caregivers

Susan K. Lutgendorf, *University of Iowa, Iowa City, IA*

Mark L. Laudenslager, *University of Colorado Denver School of Medicine, Aurora, CO*

Substantial research has examined the psychosocial distress experienced by cancer patients; however, much less attention has been paid to the experiences of caregivers, who provide much of the social support and home-based outpatient care for patients. The article by Rohleder et al¹ in this issue of *Journal of Clinical Oncology* highlights these topics and also addresses the question of whether the distress from caregiving for a cancer patient takes a biologic toll on the caregiver.

A 2004 survey by the National Alliance for Caregiving and AARP estimated that there are 44.4 million unpaid caregivers in the United States, of whom approximately 8% provide care to someone with cancer.^{2,3} Among the terminally ill, 96% of caregivers are family members.⁴ Cancer caregiving involves a variety of challenges. These include many practical concerns related to the physical day-to-day needs of the patient, such as managing symptoms and adverse effects, transporting the patient to medical appointments, administering medication, handling insurance, and communication with health care providers. As most caregivers (59%) are working either full- or part-time, caregiving may add an additional burden,³ and many caregivers have to contend with lost time at work or career disruption along with the financial burdens of the patient's treatment. Often caregivers must also manage child care or care of aging parents. Emotionally, effects may include personal distress concerning the diagnosis or effects of treatment in a loved one, concerns regarding disability or the potential loss of the loved one, and the challenge of emotionally supporting the patient despite the caregiver's own distress.⁵ Caregivers may have less time to spend with friends who might otherwise provide important emotional support. Caregivers often report exhaustion and fatigue, and feel captive in their role, particularly when the patient has high levels of physical or emotional demands.⁶ Depression is a common problem⁷ and is underdiagnosed in caregivers.⁸ A meta-analysis found equivalent levels of distress in caregivers as in the patients themselves.⁵ These issues may be more profound among caregivers with low socioeconomic status or less education because of limited resources and/or flexibility.^{7,9,10}

Not only does caregiving entail a psychological burden, but the stress of caregiving often has a biologic impact also, as shown by Rohleder et al.¹ Most previous studies examining biologic effects of caregiving have studied caregivers of dementia and Alzheimer's patients. Caregiving for Alzheimer's patients has been associated with wide-ranging effects on physiology, including poorer cellular immune function,¹¹⁻¹³ cytokine dysregulation,^{14,15} slower wound healing,¹⁶

greater autonomic and neuroendocrine dysregulation,¹⁷ and poorer response to influenza vaccine,^{11,18,19} with the impact of caregiving worsening with increased distress. Caregiving for children with chronic illnesses has also been shown to have significant effects on telomere length and aging processes.²⁰ Alzheimer's caregivers who were experiencing emotional or physical strain were found to have a 63% greater mortality than caregivers without strain or noncaregivers.²¹ In contrast, social support has been shown to help reduce the experience of stress among caregivers. For example, prostate cancer caregivers who had high levels of social support had less compromise to their cellular immune response than caregivers with lower levels of social support.²²

In this context, the article by Rohleder et al¹ adds substantially to understanding how the stress response in a group such as cancer caregivers can contribute to dysregulation of bodily systems. The authors have used a well-chosen panel of biomarkers, enabling them to characterize the interplay of important aspects of inflammatory control, for example, the output of neuroendocrine hormones, extent of systemic inflammation, pro- and anti-inflammatory signaling pathways, and tissue sensitivity to glucocorticoids. During the past 30 years, the field of psychoneuroimmunology has characterized extensive connections between the CNS and cells involved in the immune response.²³ Some of these links involve hard-wired connections between neurons of the sympathetic nervous system and lymphocytes within the spleen and other secondary lymphoid organs.²⁴ Neuroendocrine stress hormones such as cortisol also modulate the activities of lymphocytes and serve to downregulate the cellular immune response and control inflammation.

The article by Rohleder et al¹ demonstrates how high levels of chronic stress associated with caring for a glioblastoma patient may be translated into general dysregulation of inflammatory control by the hypothalamic-pituitary-adrenal axis, particularly at a cellular level. One of the strengths of this article is that dynamic patterns of change were examined over time, allowing the authors to capture alterations from before the patient's radiation treatment to 4 months after treatment. They report that caregivers show increased general systemic inflammation, as assessed by C-reactive protein, and that inflammation increases over time. Caregivers demonstrate a variety of specific anomalies in inflammatory control. Although levels of cortisol secretion among caregivers do not differ from those of controls, potential cortisol effects on the body are blunted by receptor changes. These include differences in the ratio of the active to the nonactive

isoform of the glucocorticoid receptor, suggesting poorer ability of this receptor to mediate anti-inflammatory processes; decreases in the anti-inflammatory molecule inhibitory factor- κ B over time; and decreased tissue sensitivity to glucocorticoids over time (although the latter finding was not statistically significant). The fact that these patterns of change are observed over time suggests that inflammatory control continues to deteriorate with time spent caregiving. Although not all results were as hypothesized, (eg, the proinflammatory nuclear factor- κ B proteins increased over time in controls and decreased over time in the caregivers, and there was no difference in levels of cortisol secretion between caregivers and controls), these initial results in a small sample are quite intriguing.

The study by Rohleder et al¹ has important implications for the mental and physical well-being of caregivers of patients with cancer, as it demonstrates increasing inflammation and dysregulation of inflammatory control over time. As inflammatory processes are involved in etiology of a variety of conditions, such as cardiovascular disease, caregivers may be at increased risk for health concerns over time. The time course of this study extended to only to 4 months post-treatment; for many caregivers, their roles go on for years and may become more demanding over time. Thus, research is needed to determine the extent and reversibility of biologic changes in the caregiver that may accompany the ultimate improvement, stabilization, or death of the patient. For example, one previous report noted that 2 years after the death of an Alzheimer's patient, caregivers still demonstrated significant blunting of the immune response.²⁵ These findings also suggest the importance of attention to caregiver distress by medical providers, and the need for research into development of interventions and programs to support caregivers. The US Surgeon General has made suggestions for interventions for caregiver well-being,²⁶ including addressing issues around depression and anxiety; identifying sources of support within the community for the caregivers; focusing on the role of the caregiver's health in their care of the patient; sensitizing the caregivers to their stress and its effect on them; learning more about the illness their loved one is experiencing; and training in a variety of stress management options. As a dyadic interaction, improving the well-being of the caregiver has the potential to improve patient outcomes, and this should also be tested in future well-designed randomized controlled trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Susan K. Lutgendorf

Collection and assembly of data: Susan K. Lutgendorf

Manuscript writing: Susan K. Lutgendorf, Mark L. Laudenslager

Final approval of manuscript: Susan K. Lutgendorf, Mark L. Laudenslager

REFERENCES

- Rohleder N, Marin TJ, Ma R, et al: Biological cost of caring for a cancer patient: Dysregulation of pro- and anti-inflammatory signaling pathways. *J Clin Oncol* 2009 doi:10.1200/JCO.2008.18.7435
- National Alliance for Caregiving, AARP: Caregiving in the U.S., 2004. <http://www.caregiving.org/data/04finalreport.pdf>
- Northouse L: Helping families of patients with cancer. *Oncol Nurs Forum* 32:743-750, 2005
- Emanuel EJ, Fairclough DL, Slutsman J, et al: Assistance from family members, friends, paid caregivers, and volunteers in the care of terminally ill patients. *N Engl J Med* 341:956-963, 1999
- Hodges LJ, Humphris GM, Macfarlane G: A meta-analytic investigation of the relationship between the psychological distress of cancer patients and their carers. *Soc Sci Med* 60:1-12, 2005
- Gaugler JE, Hanna N, Linder JG, et al: Cancer caregiving and subjective stress: A multi-site, multi-dimensional analysis. *Psychooncology* 14:771-785, 2005
- Nijboer C, Tempelaar R, Triemstra M, et al: The role of social and psychologic resource in caregiving of cancer patients. *Cancer* 91:1029-1039, 2001
- Kozachik S, Given C, Given B, et al: Improving depressive symptoms among caregivers of patients with cancer: Results of a randomized clinical trial. *Oncol Nurs Forum* 28:1149-1157, 2001
- Oberst M, Scott D: Post-discharge distress in surgically treated cancer patients and their spouses. *Res Nurs Health* 11:223-233, 1988
- Phipps S, Dunavant M, Lensing S, et al: Psychosocial predictors of distress in parents of children undergoing stem cell or bone marrow transplantation. *J Pediatr Psychol* 30:139-153, 2005
- Kiecolt-Glaser JK, Glaser R, Gravenstein S, et al: Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proc Natl Acad Sci U S A* 93:3043-3047, 1996
- Kiecolt-Glaser JK, Glaser R, Shuttlesworth ED, et al: Chronic stress and immunity in family caregivers of Alzheimer's disease victims. *Psychosom Med* 49:523-535, 1987
- Vitaliano PP, Scanlan JM, Ochs HD, et al: Psychosocial stress moderates the relationship of cancer history with natural killer cell activity. *Ann Behav Med* 20:199-208, 1998
- Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, et al: Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci U S A* 100:9090-9095, 2003
- Lutgendorf S, Garand L, Buckwalter K, et al: Life stress, mood disturbance, and elevated IL-6 in healthy older women. *J Gerontol A Biol Sci Med Sci* 54:M434-9, 1999
- Kiecolt-Glaser JK, Marucha PT, Malarkey WB, et al: Slowing of wound healing by psychological stress. *Lancet* 346:1194-1196, 1995
- Mills PJ, Ziegler MG, Patterson T, et al: Plasma catecholamine and lymphocyte beta 2-adrenergic receptor alterations in elderly Alzheimer caregivers under stress. *Psychosom Med* 59:251-256, 1997
- Vedhara K, Cox NK, Wilcock GK, et al: Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. *Lancet* 353:627-631, 1999
- Vedhara K, McDermott MP, Evans TG, et al: Chronic stress in nonelderly caregivers: Psychological, endocrine and immune implications. *J Psychosom Res* 53:1153-1161, 2002
- Epel ES, Blackburn EH, Lin J, et al: Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci U S A* 101:17312-17315, 2004
- Schulz R, Beach SR: Caregiving as a risk factor for mortality: The Caregiver Health Effects Study. *JAMA* 282:2215-2219, 1999
- Baron R, Cutrona C, Hicklin D, et al: Social support and immune function among spouses of cancer patients. *J Pers Soc Psychol* 59:344-352, 1990
- Ader R, Felton DL, Cohen N (eds): *Psychoneuroimmunology* (ed 3). New York, NY, Academic Press Inc, 2000
- Felten S, Felten D: Innervation of lymphoid tissue, in: Ader R, Felten D, Cohen N (eds): *Psychoneuroimmunology* (ed 2). New York, NY, Academic Press Inc, 1991, pp. 27-71
- Esterling B, Kiecolt-Glaser J, Bodnar J, et al: Chronic stress, social support, and persistent alterations in the natural killer cell response to cytokines in older adults. *Health Psychol* 13:291-298, 1994
- Ulrich B: Caring for the caregivers. *Nephrol Nurs J* 33:129, 2006

Acknowledgment

Supported by National Cancer Institute Grants No. CA88293 and CA104825 (S.K.L.) and CA12967 (M.L.L.).