

Repetitive Negative Thinking, Depressive Symptoms, and Cortisol in Cancer Caregivers and Noncaregivers

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OBJECTIVES: To examine the effect of informal cancer caregiving and repetitive negative thinking (RNT) on depressive symptoms and salivary cortisol levels.

SAMPLE & SETTING: The sample was recruited from a hospital bone marrow unit and caregiver support organizations. It included 60 informal cancer caregivers (52% partners) of individuals with cancer who provided care for a median of 27.5 hours per week for 12 months, and 46 noncaregiver participants.

METHODS & VARIABLES: In this cross-sectional study, participants completed questionnaires assessing RNT and depressive symptoms and provided saliva samples to measure cortisol levels.

RESULTS: Cancer caregiving and RNT, but not the interaction, were associated with more depressive symptoms. RNT, but not cancer caregiving, was associated with salivary cortisol. A disordinal interaction effect suggests that cancer caregiving was associated with lower cortisol levels, and RNT in noncaregivers was associated with higher cortisol levels.

IMPLICATIONS FOR NURSING: Given that RNT is related to depressive symptoms and cortisol, connecting cancer caregivers who experience RNT to resources and the development and evaluation of brief nurse-led interventions to reduce RNT in informal cancer caregivers seems warranted.

KEYWORDS cancer caregivers; repetitive negative thinking; depressive symptoms; salivary cortisol

ONF, 46(6), E202–E210.

DOI 10.1188/19.ONF.E202-E210

According to the National Alliance for Caregiving (2016), more than 2.8 million family members and friends provided care for individuals with cancer in the United States in 2015. With this prevalence, cancer is one of the most common health issues requiring informal caregiving (Aoun, 2004). In addition, cancer can require years of caregiving, and, in many cases, caregiving can become equivalent to a full-time job ($\bar{X} = 31.8$ hours per week, $SD = 34.46$ hours) (Kim & Schulz, 2008).

Cancer caregivers experience more psychological stress (Jansen et al., 2018) and stress-related mental health conditions, such as depression, than noncaregivers (Bevans et al., 2016; Goren, Gilloteau, Lees, & DaCosta Dibonaventura, 2014). Cancer caregivers exhibit high rates of depression and depressive symptoms, ranging from 10%–53% (Girgis, Lambert, Johnson, Waller, & Currow, 2013).

Although patterns may vary based on stress or mental health condition, heightened stress among caregivers is also reflected at the physiologic level, such as elevated cortisol levels (Allen et al., 2017). Elevated levels of cortisol are important because cortisol is related to depression (Burke, Davis, Otte, & Mohr, 2005) and is a risk factor for cardiovascular disease (CVD) (Hamer, Endrighi, Venuraju, Lahiri, & Steptoe, 2012; Hamer, O'Donnell, Lahiri, & Steptoe, 2010). However, as Park, Ross, Klagholz, and Bevans (2018) argued in their review, the use of biomarkers in cancer caregiver research is underdeveloped. This is problematic because the integration of biomarkers into informal caregiver research provides a more comprehensive assessment of an individual's health (Corwin & Ferranti, 2016). Data examining the effects of caregiver stress on psychological and physiological functioning may contribute to interventions that address heightened rates of

poor mental and physical health outcomes in this population.

Although caregiving for patients with chronic health issues is stressful, the psychological stress associated with cancer caregiving is even higher than caregiving for individuals with other health issues (e.g., dementia, diabetes, frailty/older age) (Bevans et al., 2016; Kim & Schulz, 2008). Therefore, identifying modifiable factors associated with health outcomes of cancer caregiver stress is crucial for caregivers. However, as Fitzell and Pakenham (2010) posited, although the negative impact of informal cancer caregiving is clear, research has focused much less on modifiable factors.

One such modifiable factor is how a caregiver responds to stress associated with the caregiving. Repetitive negative thinking describes a maladaptive thought process focused on stress or the emotional responses to stress (e.g., sadness, worry) that is repetitive, intrusive, and unproductive (Ehring et al., 2011) and includes multiple specific forms of negative thinking, such as rumination (Nolen-Hoeksema & Morrow, 1991) and worry (Meyer, Miller, Metzger, & Borkovec, 1990). Brosschot, Gerin, and Thayer (2006) proposed in the perseverative cognition hypothesis that repetitive negative thinking maintains sympathetic activation and cardiovascular arousal after a stressor. Specifically, repetitive negative thinking moderates the effect of a stressor by keeping the mental representations of a stressor active and expanding the duration of stress-related emotional and physiological responses. By prolonging and worsening stress-related emotional responses, repetitive negative thinking can lead to the development of stress-related mental health concerns, such as depressive symptoms, in the general population (Ehring et al., 2011; McEvoy & Brans, 2013), dementia caregivers (Segerstrom, Schipper, & Greenberg, 2008), and cancer caregivers (Mitchell & Pössel, 2017). In addition, as predicted in the perseverative cognition hypothesis, research links repetitive negative thinking to stress-related physiologic responses, like increased cortisol levels (Ottaviani et al., 2016; Zoccola & Dickerson, 2012), and some authors even propose it to be a vulnerability of CVD (Busch, Pössel, & Valentine, 2017). Repetitive negative thinking is one potentially modifiable cognitive factor that is theoretically linked to increased cortisol levels and physical health problems.

In the current study, the authors examined the effect of cancer caregiving and repetitive negative thinking on depressive symptoms and salivary cortisol

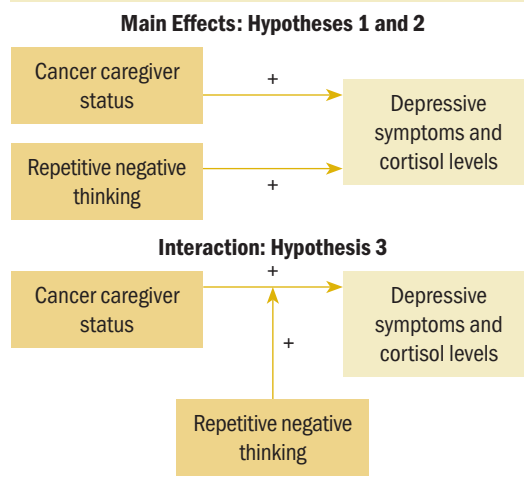
in 60 cancer caregivers and 46 noncaregivers. Based on the previously described theories about repetitive negative thinking (Brosschot et al., 2006; Ehring et al., 2011; Meyer et al., 1990; Nolen-Hoeksema & Morrow, 1991) and other research, the authors proposed that caregivers would experience more depressive symptoms (Girgis et al., 2013; Goren et al., 2014) and higher levels of cortisol (Allen et al., 2017) than non-caregivers (see Figure 1). In addition, the authors hypothesized that repetitive negative thinking is associated with more depressive symptoms (Ehring et al., 2011; McEvoy & Brans, 2013; Mitchell & Pössel, 2017; Segerstrom et al., 2008) and higher levels of cortisol (Ottaviani et al., 2016; Zoccola & Dickerson, 2012). Finally, consistent with the conceptualization of repetitive negative thinking as moderator in the association between stress and mental and physical outcomes (Brosschot et al., 2006; Ehring et al., 2011; Meyer et al., 1990; Nolen-Hoeksema & Morrow, 1991), the authors proposed that repetitive negative thinking increases the negative effect of caregiving on depressive symptoms and cortisol. Namely, the authors expected that repetitive negative thinking would be associated with more depressive symptoms and higher levels of salivary cortisol in cancer caregivers.

Methods

Participants

This pilot study examined the relationship between informal cancer caregiving and repetitive negative thinking with depressive symptoms and cortisol levels. Given that this was a pilot study, no a priori power analyses were conducted. The informal

FIGURE 1. Study Hypotheses



caregiver group consisted of 60 caregivers of individuals with cancer. Recruitment efforts included in-person requests at the bone marrow unit of the University of Louisville Hospital in Kentucky (n = 34, 57%), email invitations to a local cancer support organization (n = 14, 23%) and members of a caregiver support group at the University of Louisville James Graham Brown Cancer Center (n = 9, 15%), and Listserv announcements to the University of Louisville community (n = 3, 5%). The 46 noncaregiver control group participants were recruited using Listserv announcements to the University of Louisville community. The demographics of both groups are presented in Table 1. The mean age of the informal caregivers was 51.17 years (SD = 15.22, range = 19–77 years), and the mean age of the noncaregivers was 36.61 years (SD = 12.8, range = 22–66 years). No significant differences between the informal caregiver group and the noncaregiver control group were found for race/ethnicity ($\chi^2[3] = 4.21, p = 0.24$) and income ($\chi^2[7] = 11.84, p = 0.106$). However, caregivers were significantly older ($t[104] =$

5.22, $p < 0.001$) and more likely female ($\chi^2[1] = 10.18, p = 0.001$).

Procedure

A cross-sectional design was used to examine associations between repetitive negative thinking with depressive symptoms and repetitive negative thinking with salivary cortisol levels in cancer caregivers and noncaregivers. The study was approved by the University of Louisville Institutional Review Board, and informed consent was obtained from all participants; surveys were completed using an online program or on paper. Data from cancer caregivers were collected at the University of Louisville Hospital and during meetings of cancer caregiver support groups. The noncaregiver control group completed the study visit on the university campus. In-person study visits were conducted by research assistants associated with the University of Louisville.

Measures

Demographics: Self-reports of gender, weight, height, age, socioeconomic status, race/ethnicity, health (e.g., allergies, date of last period, gum bleeding, smoking), and other issues (e.g., shift work), as well as time of food, fluid, and other substance (e.g., caffeine, hormones) intakes during the day that may affect cortisol in saliva, were collected.

Repetitive negative thinking: The 15-item Perseverative Thinking Questionnaire (PTQ) measures the degree to which individuals engage in repetitive negative thinking (Ehring et al., 2011). Participants responded to items (e.g., “The same thoughts keep going through my mind again and again”) using a five-point Likert-type scale ranging from 0 (never) to 4 (almost always). Items were summed to calculate a total score. Higher scores reflect greater levels of repetitive negative thinking. Previous research has found evidence of convergent validity for the PTQ with measures of rumination ($r = 0.82$) and worry ($r = 0.7$) and predictive validity with measures of depressive ($r = 0.54$) and anxiety ($r = 0.64$) symptoms (Ehring et al., 2011). In addition, reliability coefficients in prior samples have been good, with internal consistency ranging from a Cronbach alpha of 0.94–0.95 (Ehring et al., 2011); these values are comparable to internal consistency shown in the current sample ($\alpha = 0.95$).

Depressive symptoms: The 20-item Center for Epidemiologic Studies Depression Scale (CES-D) measures depressive symptoms during the past week (Radloff, 1977). Participants responded to items (e.g., “I felt lonely”) using a four-point Likert-type scale

TABLE 1. Sample Characteristics by Group

Characteristic	Cancer Caregivers (N = 60)	Noncaregivers (N = 46)
	n	n
Gender		
Female	43	44
Male	17	2
Race		
White	53	45
Black	4	-
Multiracial	2	1
Asian	1	-
Relationship status		
Married	38	23
Single	10	15
Divorced or separated	7	3
Living together	3	2
Widowed	2	1
Unspecified	-	2
Annual income (\$)		
Less than 35,000	20	8
35,001–50,000	11	6
50,001–100,000	16	23
More than 100,000	11	7
Unspecified	2	2

TABLE 2. Descriptive Statistics and Correlations for Cancer Caregivers (N = 60) and Noncaregivers (N = 43)

Variable	RNT	DS	Cortisol	\bar{X}	SD
RNT	–	0.74***	–0.34*	22	10.19
DS	0.65***	–	–0.12	18.6	10.82
Cortisol	0.35**	0.22	–	0.082	0.052
\bar{X}	22.35	14.6	0.109	–	–
SD	12.45	10.72	0.069	–	–

* $p < 0.1$; ** $p < 0.05$; *** $p < 0.001$

CES-D—Center for Epidemiologic Studies Depression Scale; DS—depressive symptoms; PTQ—Perseverative Thinking Questionnaire; RNT—repetitive negative thinking

Note. Data for the cancer caregivers group are presented above the diagonal, and data for the noncaregiver group are presented below the diagonal.

Note. RNT is presented as PTQ scores, DS as CES-D scores, and cortisol as cortisol level (mcg/dl).

Note. CES-D scores range from 0 to 60, with higher scores representing more frequent DS. PTQ scores range from 0 to 60, with higher scores representing more frequent RNT.

ranging from 0 (rarely) to 3 (most of the time). The items were summed to calculate a total score. Higher scores reflect greater levels of depressive symptoms. The Cronbach alpha of the CES-D in a previous caregiver study was 0.9 (Carter & Chang, 2000), which is consistent with the internal consistency in the current study ($\alpha = 0.91$).

Cortisol: Saliva samples were collected from 4 pm to 6 pm. The passive drooling method was used for collecting a single whole saliva sample during a period of five minutes while the participants responded to the survey questions. Saliva was collected in Salivette® sampling devices and kept frozen until analyzed. Salivary cortisol was measured using the salivary cortisol electrochemiluminescence immunoassay (ELISA) kit. The assay is based on a competitive ELISA method. The minimal detectable concentration of the method is 0.007 mcg/dl. The intra- and inter-assay coefficient of variations are 3%–7% and 3%–11%, respectively.

Data Analysis

To be able to calculate proposed interaction effects, the authors z-transformed the PTQ scores and then calculated the group (noncaregiver participants = 0 versus cancer caregiver = 1) by z-transformed PTQ scores interaction scores. Using these scores as predictors, the authors calculated one linear regression model with depressive symptoms and one with cortisol as outcome variables. None of the previously listed demographic variables that were found in the literature as potentially affecting cortisol levels (e.g., allergies, caffeine, date of last period, gum bleeding, hormones, shift work, smoking) were correlated in the current sample. Because age

and gender were significantly different between cancer caregivers and noncaregiver control participants, the authors included those variables as covariates in both regressions. Control variables were entered in step 1 of the regressions. To test the hypothesis that repetitive negative thinking is associated with more depressive symptoms and higher levels of cortisol, the main effects of group and z-transformed PTQ scores were entered as predictors in step 2. In step 3, the group by z-transformed PTQ scores interaction was entered to test for the hypothesis that repetitive negative thinking moderates the association between stress and depressive symptoms and cortisol level. To further examine significant group by repetitive negative thinking interaction effects, the authors constructed model-implied graphs.

Results

The descriptive statistics and correlations for the cancer caregiver group and the noncaregiver control participants are presented in Table 2, and the regression results are reported in Table 3. As predicted, the main effects of group ($p = 0.003$) and repetitive negative thinking ($p < 0.001$) predicted depressive symptoms. To be more precise, cancer caregivers experience more depressive symptoms than noncaregivers, and more repetitive negative thinking is associated with more depressive symptoms. However, contrary to the moderation hypothesis, the group by repetitive negative thinking interaction was not significant ($p = 0.14$).

As predicted, the main effect of repetitive negative thinking ($p = 0.017$) and the group by repetitive negative thinking interaction ($p = 0.011$) predicted salivary cortisol level. Contrary to the hypothesis, the main

effect of group was not significant ($p = 0.606$). The model-implied graph revealed a disordinal interaction, which means the main effects should not be interpreted (Lubin, 1961). The group by repetitive negative thinking interaction effect demonstrated that noncaregivers high in repetitive negative thinking have a higher salivary cortisol level than noncaregivers low in repetitive negative thinking and caregivers with low and high repetitive negative thinking. Although noncaregivers high in repetitive negative thinking have a higher salivary cortisol level, the other three groups seem to have similarly low levels of cortisol. This finding confirmed that a moderation existed, but the direction of the association was unexpected.

Discussion

Consistent with the conceptualization of repetitive negative thinking as moderator in the association

between stress and mental and physical outcomes (Brosschot et al., 2006; Ehring et al., 2011; Meyer et al., 1990; Nolen-Hoeksema & Morrow, 1991), the authors proposed that repetitive negative thinking strengthens the associations of caregiving with depressive symptoms and cortisol. In other words, the authors expected that repetitive negative thinking would be associated with more depressive symptoms and higher levels of salivary cortisol in cancer caregivers. The results revealed that cancer caregiving and repetitive negative thinking are associated with more depressive symptoms. However, the authors did not find the proposed interaction effect on depressive symptoms. Regarding salivary cortisol, the authors found a main effect of repetitive negative thinking and group by repetitive negative thinking interaction. Because the interaction effect is disordinal, the main effect of repetitive negative thinking interaction on

TABLE 3. Linear Regressions With Group, RNT, and Their Interaction as Predictors of DS and Cortisol

Dependent Variable	Step 1 ^a		Step 2 ^b		Step 3 ^c	
	R ²	β	R ²	β	R ²	β
DS						
Age	-	-0.115	-	-0.159*	-	-0.152*
Gender	-	0.042	-	0.019	-	0.025
Group	-	-	-	0.261***	-	0.256***
RNT	-	-	-	0.665****	-	0.566****
Group x RNT	-	-	-	-	-	0.144
R ² change	0.014	-	0.502****	-	0.011	-
Total R ²	0.014	-	0.516	-	0.527	-
Cortisol						
Age	-	0.212*	-	-0.158	-	-0.174*
Gender	-	0.083	-	-0.048	-	-0.058
Group	-	-	-	-0.081	-	-0.077
RNT	-	-	-	0.154	-	0.336**
Group x RNT	-	-	-	-	-	-0.356**
R ² change	0.057	-	0.026	-	0.093**	-
Total R ²	0.057	-	0.083	-	0.176	-

* $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$; **** $p < 0.001$

^a Control variables were entered.

^b To test the hypothesis that RNT is associated with more DS and higher levels of cortisol, the main effects of group and z-transformed PTQ scores were entered as predictors.

^c The group by z-transformed PTQ scores interaction was entered to test for the hypothesis that RNT moderates the association between stress and DS and cortisol level.

CES-D—Center for Epidemiologic Studies Depression Scale; DS—depressive symptoms; PTQ—Perseverative Thinking Questionnaire; RNT—repetitive negative thinking

Note. Group is cancer caregivers versus noncaregivers. RNT is presented as z-transformed PTQ scores, DS as CES-D scores, and cortisol as cortisol level (mcg/dl).

Note. CES-D scores range from 0–60, with higher scores representing more frequent DS. PTQ scores range from 0–60, with higher scores representing more frequent RNT.

salivary cortisol should not be interpreted (Lubin, 1961). More importantly, the direction of the interaction with noncaregivers high in repetitive negative thinking having higher salivary cortisol levels compared to noncaregivers low in repetitive negative thinking and caregivers with low and high repetitive negative thinking was unexpected.

One possible explanation for this lack of a group by repetitive negative thinking interaction effect on depressive symptoms could be that repetitive negative thinking does not moderate but instead mediates the relationship between stress and depressive symptoms. This would be consistent with the idea that repetitive negative thinking can only focus on stress or the responses to stress after the stress occurs and is activated by it, both crucial conditions for mediation (Preacher & Hayes, 2008). This is also consistent with the high correlations between repetitive negative thinking and depressive symptoms in both of the samples ($r = 0.65$) and previous research identifying repetitive negative thinking as mediator between caregiver stress and depressive symptoms (Mitchell & Pössel, 2017). Because the mediator must be measured temporally after the independent variable (i.e., stress) and before the dependent variable (i.e., depressive symptoms) (Maric, Wiers, & Prins, 2012), testing for mediation is only meaningful in a three-wave longitudinal study. Therefore, a comparison of repetitive negative thinking as moderator versus as mediator in the relation between cancer caregiving and depressive symptoms should be the aim of such a longitudinal study.

The second unexpected finding in the current study was that cancer caregivers demonstrate low salivary cortisol levels independent of their repetitive negative thinking. However, in noncaregivers, repetitive negative thinking is associated with increasing cortisol levels. Although the authors did not predict this pattern, some previous studies found lower cortisol levels in cancer caregivers compared to noncaregivers (Bevans et al., 2016; Thomas et al., 2012). In addition, Bevans et al. (2016) found a decrease of cortisol levels in cancer caregivers and an increase in noncaregivers over time. Bevans et al. (2016) interpreted their findings as an indicator that the chronic stress of cancer caregiving causes “wear and tear” on the hypothalamic-pituitary-adrenal axis, of which cortisol is a part. This interpretation of the current findings would also make sense, considering the length of time the cancer caregivers in this study provided care (median = 12 months, range = 1 week to 264 months) for a significant amount of time per week (median = 27.5 hours per week, range =

KNOWLEDGE TRANSLATION

- Cancer caregiving and more repetitive negative thinking are independently associated with more depressive symptoms.
 - Independent of repetitive negative thinking, cancer caregiving is associated with lower salivary cortisol levels.
 - Connecting caregivers with resources and professionals to encourage the reduction of repetitive negative thinking may help reduce mental health issues in cancer caregivers.
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1–168 hours per week). Therefore, in cancer caregivers, repetitive negative thinking is not related to salivary cortisol because of the severe chronic nature of their stress. In other words, it is possible that cancer caregiving is so stressful that there is no additional room to allow for differences in the physiological response. To examine this possible explanation, a longitudinal study should recruit cancer caregivers at the time of the diagnosis. If the authors’ prediction is correct, one would expect that repetitive negative thinking and cortisol are associated at the time of the diagnosis and for some time after that, but that the association becomes weaker over time as caregiving establishes chronicity. An alternative explanation may be related to the association between symptoms of post-traumatic stress disorder (PTSD) and lower cortisol levels, because cancer caregiving is associated with an increased level of PTSD symptoms (Thomas et al., 2012). In addition, rumination and worry, two specific forms of repetitive negative thinking, predict symptoms of PTSD (Seligowski, Lee, Bardeen, & Orcutt, 2015). Therefore, it is possible that cancer caregiving and repetitive negative thinking are both associated with decreased cortisol levels through their effect on PTSD symptoms. To examine this (mediation) hypothesis, a longitudinal study should also measure PTSD symptoms.

Despite the unexpected findings, the current study provides evidence for the clinical relevance that repetitive negative thinking has for cancer caregivers. Particularly, the findings provide some support that repetitive, intrusive, and unproductive thinking focused on caregiver stress or the responses to this stress is a maladaptive coping process that is associated with poor mental health of cancer caregivers. Therefore, the findings suggest that repetitive negative thinking may be worthy of targeting in psychoeducational interventions for cancer caregivers that have been demonstrated to reduce repetitive negative thinking in the general population (Heeren & Philippot, 2011).

Limitations

When discussing potential implications of this study, some limitations should be considered. The discussion of future studies already highlighted one limitation of the study: The cross-sectional design prevented the authors from examining mediation effects. Therefore, authors of future studies may want to follow the previously mentioned suggestions and use a three-wave longitudinal design. Another limitation of the current study is that participants in both samples largely identified as female (more than 70%) and White (more than 85%). Because some studies suggest mental and physical differences regarding distress depending on gender and race/ethnicity (Girgis et al., 2013; Martin et al., 2012), future studies should include more men and racially/ethnically diverse samples to be more generalizable or to examine the potential moderating effects of both sociodemographic variables.

The outcomes of the current study are limited to depressive symptoms and salivary cortisol. Depression is relevant because of its prevalence in as many as 53% of cancer caregivers (Girgis et al., 2013), and cortisol is a widely used biomarker of the stress response (Allen et al., 2017) because of its association with physical disease such as CVD (Hamer et al., 2010, 2012). However, cancer caregiving and repetitive negative thinking are associated with other mental health issues, including PTSD (Seligowski et al., 2015), and inflammatory markers, such as interleukin-6 and C-reactive protein (Segerstrom et al., 2008; Zoccola, Figueroa, Rabideau, Woody, & Benencia, 2014). Therefore, the sole inclusion of depressive symptoms and salivary cortisol may be seen as limitations of the current study, and authors of future studies may want to consider further examining mental health outcomes and biomarkers.

Implications for Nursing

The current findings have clinical implications for nursing. Nurses are often a primary source of interactions with cancer caregivers. Therefore, nurses are the healthcare providers most likely to witness repetitive negative thinking in cancer caregivers. Because of this, nurses are potentially in an optimal position to connect cancer caregivers not only with support mechanisms (e.g., educational materials, support groups), but also with behavioral health professionals (e.g., psychologists, social workers) to facilitate a reduction of repetitive negative thinking in cancer caregivers. In addition, psychoeducational programs for cancer caregivers implemented by nurses have shown positive effects on cancer caregivers' burden and even on quality of life of individuals with cancer (Belgacem et al.,

2013). Given that nurses likely interact with most caregivers for relatively short time frames (e.g., healthcare visits for the patient), studies examining the effectiveness of brief nursing-led interventions on reducing repetitive negative thinking are needed.

Conclusion

Based on these findings, cancer caregiving and repetitive negative thinking are associated with depressive symptoms and salivary cortisol, which is a risk factor for CVD. More specifically, cancer caregiving and repetitive negative thinking were independently related to more depressive symptoms. Contrary to expectations, results regarding cortisol suggest that noncaregivers with higher levels of repetitive negative thinking had higher salivary cortisol levels, and the cortisol levels were similar in noncaregivers with low levels of repetitive negative thinking and caregivers with high and low levels of repetitive negative thinking. To build on this study, the authors suggest following a group of racially/ethnically diverse cancer caregivers from the time of diagnosis and measuring symptoms of PTSD and multiple biomarkers of health in addition to repetitive negative thinking, depressive symptoms, and cortisol at three times. If such a study confirms the current findings, the development and evaluation of a brief nurse-led intervention for cancer caregivers would be warranted.

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No financial relationships to disclose.

Pössel and Mitchell contributed to the conceptualization and design. Mitchell, Harbison, and Fernandez-Botran completed the data collection. Pössel and Fernandez-Botran provided the analysis. Pössel, Mitchell, and Harbison contributed to the manuscript preparation.

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