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Advanced cancer caregiving as a risk for major depressive episodes and generalized anxiety disorder

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Abstract

Objective: Caregivers of advanced cancer patients provide extensive care associated with high levels of caregiver distress. The degree to which cancer caregiving increases caregivers' risk for a psychiatric disorder is unknown. The current study examines whether advanced cancer caregiving poses distinct risks for initial and recurrent major depressive episodes (MDEs) and generalized anxiety disorder (GAD) relative to the general population.

Methods: Caregivers of advanced cancer patients (N = 540) from Coping with Cancer were compared to general population controls (N = 9282) from the National Comorbidity Survey Replication. The general population comparison sample was propensity-weighted to be demographically similar to the caregiver sample.

Results: Caregivers of advanced cancer patients were more likely than individuals in the general population to have an initial MDE (OR = 7.7; 95% CI, 3.5-17.0; $P < .001$), but no more likely than the general population to have a recurrent MDE (OR = 1.1; 95% CI, 0.6-2.1; $P = .662$). Caregivers were also more likely than the general population to have GAD (OR = 3.0; 95% CI, 1.9-4.8; $P < .001$) and comorbid MDE and GAD (OR = 2.5; 95% CI, 1.1-5.9; $P = .038$).

Conclusions: The increased risk of meeting diagnostic criteria for current MDE and GAD and comorbid MDE and GAD associated with advanced cancer caregiving highlights the degree of emotional burden among cancer caregivers. Clinical services that assess, prevent, and treat depression and anxiety in cancer caregivers are needed to reduce the burden of caregiving and improve the mental health of this growing population.

KEYWORDS
anxiety, cancer, caregiving, depression, oncology

1 | BACKGROUND

Approximately 3 million people serve as informal caregivers to cancer patients in the United States each year.[1] Cancer care is increasingly provided on an outpatient basis with a greater number of caregiving responsibilities falling to informal caregivers.[2,3] Cancer caregivers spend an average of 32.9 hours per week on caregiving tasks and 72% perform complex medical or nursing tasks.[1] Approximately two-thirds (62%) of caregivers are in a "high burden" situation, and the average burden of care is higher for cancer than noncancer caregivers.[1]

Cancer caregivers report high levels of psychological distress that, for many caregivers, does not remit over time.[4] This distress is often greater than that experienced by cancer patients.[5] Up to one-quarter (5%-28%) of cancer caregivers report elevated depressive symptoms

on self-report measures[5,6] and one-fifth to one-third (34.9%) report elevated anxiety.[5,6] This distress may be more severe in the context of advanced cancer.[7] One to two-thirds of caregivers of advanced cancer patients report elevated symptoms of anxiety[8,9] and 15% to 43% report elevated symptoms of depression.[8,9]

While problematic in itself, emotional distress is also associated with worse health-related quality of life,[10] greater perceived caregiving burden,[11,12] greater sleep disturbance,[13] and immune system dysfunction in cancer caregivers.[12] In some studies, higher levels of caregiver distress are associated with greater patient distress,[6,14] suggesting that caregiver distress may negatively impact patient well-being.[15]

Prior research on distress in caregivers of advanced cancer patients has highlighted the emotional burden of cancer caregiving but is limited in multiple ways. First, most studies of depression and

anxiety in cancer caregivers rely on measures of distress severity. Few studies have utilized validated measures of *Diagnostic and Statistical Manual of Mental Disorders-IV* (DSM-IV) diagnoses. In a study of caregivers of patients with head and neck cancer using a structured interview assessing DSM-IV diagnoses, 14.4% met criteria for any depressive disorder with 4.2% meeting criteria for major depressive disorder.[16] In a study of caregivers of advanced cancer patients, 4.5% met criteria for major depressive disorder and 3.5% met criteria for generalized anxiety disorder.[17] These studies suggest that a notable minority of caregivers suffer from distress levels that meet diagnostic criteria. However, research using structured assessments of diagnostic criteria is limited.

Second, few studies have examined the impact of caring for an advanced cancer patient on individuals' risk for developing depression and anxiety. Research suggests that caregivers of advanced cancer patients report higher levels of depressive and anxiety symptoms than healthy controls[18,19] and population norms.[20] In a large study comparing lung cancer caregivers to population controls in Europe, caregivers were more likely to have been diagnosed with depression than noncaregivers.[21] However, rates of depression diagnoses were assessed by asking caregivers if they had been diagnosed with depression; depressive symptoms were not directly assessed.

Third, depression is a highly recurrent disorder, which accounts, in part, for its notable negative impact on individual and public health.[22] Research suggests that the risk profile for initial onset of a major depressive episode (MDE) differs from that of recurrent MDE[22]; stressful life events are a stronger predictor of initial than recurrent MDE.[23,24] Cancer is a highly stressful event that, for many people, constitutes a traumatic stressor.[25,26] Despite this, research on depression in cancer caregivers has not considered the differential impact of caregiving on initial onset versus recurrent depression.

This study examines the impact of caring for an advanced cancer patient on risk for MDE and generalized anxiety disorder (GAD) relative to general population controls. We hypothesized that being a caregiver for an advanced cancer patient would be associated with increased risk for MDE, GAD, and comorbid MDE and GAD relative to population controls. In addition, we hypothesized that caring for an advanced cancer patient would pose an increased risk for an initial diagnosis of MDE but not for a recurrent MDE.

2 | METHODS

2.1 | Study samples

The study sample was composed of an advanced cancer caregiver sample from Coping with Cancer (CwC) and a general population comparison sample from the National Comorbidity Survey Replication. For analysis, the general population comparison sample was propensity-weighted to be demographically similar to the caregiver sample.

The CwC study is a prospective, multi-institutional cohort investigation of advanced cancer patients and their caregivers funded by the National Institute of Mental Health (MH63892) and the National Cancer Institute (CA106370). Participants were recruited between September 2002 and February 2008 at 6 cancer centers: Yale Cancer Center (New Haven, CT), Veterans Affairs Connecticut Healthcare System Comprehensive Cancer Clinics (West Haven, CT), Parkland Hospital (Dallas, TX), Simmons Comprehensive Cancer Center (Dallas, TX), Dana-Farber Cancer Institute (Boston, MA), and New Hampshire Oncology-Hematology (Hooksett, NH). Criteria for patient eligibility included diagnosis of advanced cancer (presence of distant metastases and disease refractory to first-line chemotherapy), estimated life expectancy of 6 months or less, age ≥ 20 years, and presence of an informal caregiver. Participants were identified by reviewing outpatient clinic rosters and initial ascertainment of eligibility occurred via medical record extraction. Research staff subsequently confirmed each patient's diagnosis, treatment, and performance status with the physician. Patients with signs of cognitive impairment (eg, dementia/delirium) based on the evaluations of trained interviewers and clinicians and/or patients who made more than 6 errors on the Short Portable Mental Status Questionnaire (SPMSQ)[27] were excluded. No patient participants resided in a nursing home or other institution. Review boards of all participating institutions approved study procedures; all participants provided written, informed consent. Patients and caregivers received $25 as compensation for participating in the study.

The present study includes data from 540 CwC caregivers with complete diagnostic assessments for lifetime and current MDEs and current GAD. Caregivers were mainly patients' spouses/partners (56%), children (22%), other relatives (17%), or friends (4%).

The National Institute of Mental Health sponsored National Comorbidity Survey Replication (NCS-R; MH60220) is a nationally representative community household survey conducted between February 2001 and December 2002, designed to evaluate the prevalence and correlates of mental disorders in the United States.[28] The NCS-R sample includes 9282 respondents aged 18 years or older. Respondents were selected from a multistage area probability sample of the noninstitutionalized civilian population in the 48 contiguous states. The overall participation rate was 74.6%. Complete NCS-R survey methodology is described elsewhere.[29]

2.2 | Measures

2.2.1 | Caregiver characteristics

Caregivers provided information regarding age, gender, race/ethnicity, education, and marital status.

2.2.2 | Major depressive episodes and generalized anxiety disorder

Both CwC and the NCS-R used DSM-IV compliant tools to assess MDEs and GAD. Trained nonclinician research assistants administered the Structured Clinical Interview for DSM-IV (SCID) modules for current and lifetime MDEs and current GAD to caregivers of patients in the CwC sample.[30] The NCS-R utilized the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0),[31] administered by trained lay interviewers, to assess for 12-month and lifetime episodes of major depression and GAD in the past 12 months. As supported by prior literature suggesting good concordance of the CIDI with standardized clinical assessments,[32] the current study considered MDE and GAD occurring within the last 12 months according to the CIDI 3.0 to be equivalent to a current MDE and GAD as measured by the SCID.

2.3 | Statistical analysis

Chi-square tests and *t* tests were used to compare demographic characteristics, ie, age, gender, race/ethnicity, education, and marital status, between the CwC caregiver group and the NCS-R comparison group. These between-group comparisons were made using 2 sets of weights applied to the NCS-R sample: one set of weights included in the NCS-R data set used to reflect the general US population and another set of weights based on propensity scores, a common method of matching samples to facilitate causal inference for between-group effects,[33] calculated to make the NCS-R sample demographically similar to the CwC caregiver sample. The propensity weights match the NCS-R sample to the CwC caregiver sample in terms of age, gender, race/ethnicity, education, and marital status, and in their use eliminate these factors as potential confounds in the analysis of caregiver-comparison group differences in MDEs, GAD, and comorbid MDE and GAD.

Chi-square tests were used to compare rates of past and current MDEs, current GAD, and current comorbid MDE and GAD between the CwC caregiver sample and the propensity-weighted NCS-R comparison sample. Odds ratios for current MDE associated with prior MDE, caregiving, and the interaction between prior MDE and caregiving (used to compare caregiver risks for a recurrent as opposed to an initial onset MDE) were estimated using multiple logistic regression analysis using the CwC caregiver sample combined with the propensity-weighted NCS-R sample.

Statistical analysis was conducted using SAS statistical software, version 9.2 (Cary, NC). Statistical inferences were based on two-sided tests with *P* < .05 taken to be statistically significant.

3 | RESULTS

Caregivers of advanced cancer patients in the CwC sample were more likely to be older, female, black, more highly educated, and married/cohabitating than comparisons in the NCS-R sample weighed to reflect the general population (Table 1). Caregivers in the CwC sample did not differ from comparisons in the NCS-R sample weighed to be demographically similar to the CwC caregiver sample using propensity score weights (Table 1).

Caregivers of advanced cancer patients and demographically similar comparisons did not significantly differ in rates of prior MDE (OR = 0.9; 95% CI, 0.7-1.1; *P* = .348), but caregivers of advanced cancer patients were significantly more likely to have a current MDE (OR = 1.6; 95% CI, 1.0-2.5; *P* = .037), current GAD (OR = 3.0; 95% CI, 1.9-4.8; *P* < .001), and comorbid current MDE and GAD (OR = 2.5; 95% CI, 1.1-5.9; *P* = .038) than demographically similar comparisons (Table 2).

Based on multiple logistic regression analysis using the propensity-weighted NCS-R sample, prior MDE modified the association between caregiving and current MDE (interaction OR = 0.15; 95% CI, 0.06-0.40; *P* < .001). We examine this interactive effect from 2 perspectives. First, we focus on the relationship between caregiving and current MDE within each of 2 groups of individuals, ie, those without prior MDE (at risk for initial onset MDE) and those with prior MDE (at risk for recurrent MDE). Among individuals without prior MDE, caregivers of advanced cancer patients were more likely to have an initial onset MDE than comparisons (OR = 7.7; 95% CI, 3.5-17.0; *P* < .001) (Table 3). Among individuals with prior MDE, caregivers of advanced cancer patients were no more likely than comparisons to have a

TABLE 1 Demographic comparisons between the Coping with Cancer (CwC) caregiver sample and National Comorbidity Survey Replication samples without (NCS-R) and with propensity weights (NCS-R*)

Characteristic	CwC N = 540		NCS-R N = 9282		CwC vs NCS-R			NCS-R* N = 9282		CwC vs NCS-R*		
	Mean	sd	Mean	sd	t	df	P	Mean	sd	t	df	P
Age in years	53.2	14.2	44.8	17.6	10.87	9820	.000	53.4	17.8	−0.24	9820	.810
	n	%	n	%	χ^2	df	P	n	%	χ^2	df	P
Gender												
Male	151	28.0	4445	47.9	81.35	1	.000	2593	27.9	0.00	1	.989
Female	389	72.0	4837	52.1				6689	72.1			
Race/ethnicity												
Hispanic	65	12.0	1007	10.8	13.65	3	.003	1104	11.9	0.03	3	.999
Black	86	15.9	1073	11.6				1499	16.1			
Other	14	2.6	404	4.4				238	2.6			
White	375	69.4	6798	73.2				6441	69.4			
Education level												
0-11 years	94	17.4	1498	16.1	31.54	3	.000	1617	17.4	0.00	3	1.000
12 years	167	30.9	2993	32.2				2878	31.0			
13-15 years	102	18.9	2568	27.7				1753	18.9			
16+ years	177	32.8	2223	23.9				3034	32.7			
Marital status												
Married/cohabitating	401	74.3	5182	55.8	75.95	2	0.000	6872	74.0	0.05	2	.976
Separated/widowed/divorced	82	15.2	1897	20.4				1441	15.5			
Never married	57	10.6	2202	23.7				969	10.4			

TABLE 2 Comparison of rates of past and current major depressive episodes (MDEs), current generalized anxiety disorder (GAD), and current comorbid MDE and GAD between the Coping with Cancer (CwC) caregiver sample and National Comorbidity Survey Replication sample with propensity weights (NCS-R*)

Diagnosis	CwC N = 540		NCS-R* N = 9282		CwC vs NCS-R*					
	n	%	n	%	OR	(95% CI)		χ^2	df	P
Past MDE										
Yes	85	15.7%	1607	17.3%	0.9	0.7	1.1	0.88	1	0.348
No	455	84.3%	7675	82.7%						
Current MDE										
Yes	22	4.1%	239	2.6%	1.6	1.0	2.5	4.37	1	0.037
No	518	95.9%	9043	97.4%						
Current GAD										
Yes	21	3.9%	125	1.3%	3.0	1.9	4.8	20.54	1	0.000
No	519	96.1%	9157	98.7%						
Current comorbid MDE and GAD										
Yes	6	1.1%	42	0.5%	2.5	1.1	5.9	4.30	1	0.038
No	534	98.9%	9240	99.5%						

recurrent MDE (OR = 1.1; 95% CI, 0.6-2.1; P = .662) (Table 3). Second, we focus on the relationship between prior and current MDE within each of 2 groups, ie, within general population comparisons and within caregivers. The association between prior MDE and current MDE for comparisons (OR = 60.3; 95% CI, 38.0-95.6; P < .001) was significantly higher than that for caregivers of advanced cancer patients (OR = 8.9; 95% CI, 3.7-21.7; P < .001) (Table 3).

Among caregivers, two-fifths of current MDEs were first onset episodes (9/22 = 40.9%). By contrast, in demographically similar individuals from the general population, the vast majority, over 90% (219/239 = 91.6%), of current MDEs were recurrent episodes. Still, caregivers of advanced cancer patients with a previous history of MDE were at greater risk of a current MDE than caregivers of advanced cancer patients without a history of MDE. Within caregivers, 13/85 (15.3%) of those with a previous MDE had a current MDE and 9/455 (2.0%) of those with no previous MDE had a current MDE. In demographically similar comparisons, 219/1607 (13.6%) of those with a previous MDE had a current MDE and 20/7625 (0.3%) of those with no prior history of MDE had a current MDE.

4 | DISCUSSION

Advanced cancer caregivers were more likely to meet diagnostic criteria for current MDE, GAD, and comorbid MDE and GAD than demographically similar population comparisons. However, caregivers were no more likely to have a prior MDE relative to population comparisons. Among individuals without prior MDE, cancer caregiving posed an increased risk for initial onset MDE. Among individuals with prior MDE, cancer caregiving did not pose an additional risk for current MDE.

The increased risk for MDE and GAD associated with cancer caregiving in this study is consistent with existing research demonstrating the burden of cancer caregiving. In contrast to studies using severity ratings of depression and anxiety, the current study assessed rates of psychiatric disorders, a higher threshold for and more severe indicator of distress. The increased risk of meeting diagnostic criteria for current MDE and GAD and comorbid MDE and GAD associated with cancer caregiving highlights the degree to which caregiving damages caregivers' mental health. This association is particularly notable given the relationship between depression and anxiety and impaired physical health and quality of life in cancer caregivers.[11-13] Further, the symptoms of MDE and GAD may make caregiving more difficult, adding to the already burdensome caregiving role[11] and potentially increasing patient distress.[34]

Caregivers in the current study were at increased risk for current MDE relative to the general population. This risk differed by whether caregivers had a history of MDE. Cancer caregiving was associated with an increased risk for current MDE only in caregivers with no prior history of MDE. This finding is consistent with a similar analysis in advanced cancer patients[35] and supports the kindling hypothesis of depression that states that stressful events play less of a role in recurrent than initial onset MDE.[24] However, major depression is a highly recurrent disorder.[22] Caregivers who experience an initial MDE in

TABLE 3 Current major depressive episodes in relation to caregiving and past major depressive episodes

Current MDE associated with	For group	OR	95% CI		χ^2	df	P
Cancer caregiving	without past MDE	7.7	3.5	17.0	25.55	1	0.000
	with past MDE	1.1	0.6	2.1	0.19	1	0.662
Past MDE	noncancer caregiving	60.3	38.0	95.6	303.50	1	0.000
	cancer caregiving	8.9	3.7	21.7	23.53	1	0.000

Abbreviation: MDE, major depressive episode.

the context of cancer caregiving may be at increased risk for life-long depression. Further, caregivers of advanced cancer patients are likely to experience the loss of their loved one and bereavement, additional stressors that may further increase their risk for a mental disorder. Preventing and treating initial MDE in cancer caregivers may have a positive and lasting effect on their mental health. Finally, a history of MDE was associated with an increased risk for current MDE in cancer caregivers. Caregivers with a history of MDE may benefit from psychosocial services to reduce their risk for a recurrent MDE.

Caregivers were also at increased risk for a diagnosis of GAD relative to the general population. Prior research has focused more on caregiver depression than anxiety, despite evidence that a greater number of caregivers report elevated anxiety than depression,[5,9] more cancer caregivers than patients experience elevated anxiety,[5,20] and rates of anxiety in cancer caregivers increase more than rates of depression over final year of the patient's life.[36] Anxiety in advanced cancer caregivers has been associated with a greater number of caregiver physical symptoms[19] and higher levels of physiological stress indicators,[18] suggesting that anxiety may increase caregivers' risk for poor physical health. Caregiver anxiety is also associated with a greater discrepancy between patient and caregiver report of patients' physical symptoms;[8] caregivers' anxiety may interfere with their ability to accurately evaluate patient well-being. Treating caregiver anxiety may have positive implications for caregivers' health and their ability to provide care.

5 | CLINICAL IMPLICATIONS

The increased risk for a psychiatric disorder associated with advanced cancer caregiving highlights the importance of providing mental health care to caregivers. Yet cancer caregivers report high levels of unmet psychosocial needs[5] and low levels of receipt of psychological support.[6] Less than one-third (29%) of cancer caregivers report being asked about their self-care needs.[1] Six months following diagnosis, 50.2% of spousal caregivers report at least one unmet supportive care need and 36.0% report at least 3 unmet needs.[37] These findings and the results of the current study support the implementation of distress screening for cancer caregivers. The American College of Surgeons Commission on Cancer requires that cancer patients are screened for psychosocial distress and provided with appropriate referrals.[38] Informal caregivers may also benefit from distress screening and the provision of psychosocial services. Psychosocial interventions for cancer caregivers have been developed,[39,40] and research on their impact is mixed[40] but promising.[39] Identifying and treating the psychosocial needs of informal cancer caregivers may reduce caregiver distress, improve caregivers' ability to care for the patient, and reduce patient distress. Additional research on the effectiveness of psychosocial interventions for distress in cancer caregivers and strategies for dissemination and implementation of these interventions is needed.

Finally, cancer caregiving was associated with an increased risk for initial MDE but not recurrent MDE, suggesting that the stress of caregiving precipitates the MDE. Resources that mitigate the burden of cancer caregiving may reduce caregivers' risk for initial onset MDE and current GAD. For example, 43% of cancer caregivers report

performing complex medical and nursing tasks with no prior preparation.[1] Providing caregivers with training on the medical care of the patient may lessen the burden of cancer caregiving and, thereby, reduce caregivers' risk for initial onset of a psychiatric disorder.

6 | STRENGTHS AND LIMITATIONS

Strengths of this study include utilization of large samples that allowed for a comparison of caregivers of advanced cancer patients to a nationally representative sample. This comparison provides a benchmark for understanding the degree to which caring for an advanced cancer patient impacts caregivers' mental health. Second, the CwC sample consists of caregivers of patients with a prognosis of 6 months or less to live. Advanced cancer is a unique stressor relative to curable and chronic cancers due to the imminent threat of the death of the patient. Further, advanced cancer patients tend to be sicker and require more care than patients with curable cancers. Third, this study determined rates of psychiatric diagnoses based on structured interviews assessing DSM criteria. Finally, this study examined the impact of caregiving on current MDE in caregivers with and without a history of MDE, providing a more nuanced assessment of the role of cancer caregiving in the context of a highly recurrent psychiatric disease.

Limitations of this study must be considered. Data on the time from the patient's cancer diagnosis to the administration of the SCID is not available. Further, we cannot differentiate between caregivers whose patients were initially diagnosed with advanced cancer from those who were diagnosed with an early stage cancer that progressed to advanced disease. Second, assessments of lifetime MDE may have been subject to recall bias and, in the CwC sample, influenced by the current stress of cancer caregiving. Notably, rates of past MDE were not significantly different across samples, suggesting that cancer caregiving did not bias caregivers' reports of past MDE. Third, the SCID assessment did not include the diagnosis of lifetime GAD. We were therefore unable to assess the relationship between lifetime and current GAD. Fourth, CwC used the SCID to assess psychiatric diagnoses while the NCS-R used the CIDI. While both measures assess DSM diagnostic criteria and were administered by trained lay interviewers, there is some evidence that the CIDI underestimates lifetime prevalence rates relative to the SCID.[32] However, a comparison of rates of diagnosis by the CIDI and SCID found moderate to strong concordance for lifetime prevalence of specific disorders.[32] Further, rates of lifetime MDE in the CwC and NCS-R samples were not significantly different. However, future studies should use the same assessments across samples. Finally, demographic differences across the samples were controlled using propensity weights. Additional confounders not controlled in this analysis such as social support may differentially influence rates of psychiatric disorders across samples.

7 | CONCLUSION

The results of this study highlight the severe psychological burden associated with caring for an advanced cancer patient. Caregiving poses a large risk for meeting diagnostic criteria for an initial MDE, current GAD, and comorbid MDE and GAD relative to the population

although it does not increase risk for a recurrent MDE. Caregivers of advanced cancer patients may benefit from distress screening, support to reduce the burden of caregiving, and provision of evidence-based interventions for distress.

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CONFLICT OF INTEREST

The authors declare no conflicts and no financial interests in this investigation.

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