

Predictors of Depression in Patients Diagnosed with Cancer and Their Caregivers

by

Reyna E. Jones

Bachelor of Philosophy, University of Pittsburgh, 2020

Submitted to the Graduate Faculty of the
University Honors College in partial fulfillment
of the requirements for the degree of
Bachelor of Philosophy

University of Pittsburgh

2020

UNIVERSITY OF PITTSBURGH

UNIVERSITY HONORS COLLEGE

This thesis was presented

by

Reyna E. Jones

It was defended on

April 21, 2020

and approved by

Thomas Kamarck, PhD, Department of Psychology, University of Pittsburgh

Youngmee Kim, PhD, Department of Psychology, University of Miami

Kathryn Roecklein, PhD, Department of Psychology, University of Pittsburgh

Thesis Advisor: Jennifer Steel, PhD, Department of Surgery, University of Pittsburgh

Copyright © by Reyna E. Jones

2020

Predictors of Depression in Patients Diagnosed with Cancer and Their Caregivers

Reyna E. Jones, BPhil

University of Pittsburgh, 2020

Background: Patients diagnosed with cancer and their caregivers have an increased risk for depression compared to the general population. The aims of the present study were to determine the rate of depressive symptoms in the clinical range, identify predictors of depression, and to determine if depression was a predictor of immune system parameters in both patients and caregivers.

Methods: A secondary analysis of baseline data from two clinical trials was used for the purposes of this study. Patients and caregivers completed a battery of questionnaires. Patients were assessed on sociodemographic factors, fatigue, perceived stress, and pain levels. Caregivers reported measures on sociodemographic factors, quality of life, and sleep quality. Descriptive statistics and logistic regression were performed to test the hypotheses.

Results: Of the 259 patient and caregiver dyads that were included in the analyses, the mean age of patients was 64.7 (SD = 10.5), and the majority were Caucasian (92.9%) and female (56.6%). The mean age of caregivers was 58.5 (SD = 12.5), and the majority were Caucasian (93.2), female (73.7%), and the spouse of the cancer patient (63.5%). The rate of depressive symptoms in the clinical range in patients was 37.4% and 36.7% in caregivers. In 35 dyads (15.6%) both the patient and caregiver reported depressive symptoms in the clinical range. We found that high levels of fatigue ($\beta = -0.116$; OR = 0.890; 95% CI, 0.848-0.935; $p = <0.001$) and perceived stress ($\beta = 0.198$; OR = 1.219; 95% CI, 1.127-1.318; $p = <0.001$) were predictive of depressive symptoms in patients.

Poor quality of life ($\beta = 0.067$; OR = 1.069; 95% CI, 1.040-1.099; $p = <0.001$) was a significant predictor of depressive symptoms in cancer caregivers. We found that depressive symptoms did not predict immune system parameters in either patients or caregivers after adjusting for sociodemographic factors and psychosocial and behavioral covariates.

Conclusions: This one of a limited number of studies to examine the predictors of depression for patients and caregivers in the context of the dyad. Due to the high rates of depression observed, psychosocial interventions designed to target the predictors, for patients and caregivers, is recommended.

Table of Contents

1.0 Introduction.....	6
1.1 Predictors of Depression in Patients & Their Caregivers and Link with Immunity	7
2.0 Method	11
2.1 Participants	11
2.2 Instruments	12
2.2.1 Demographic Factors (Patients and Caregivers)	12
2.2.2 Depressive Symptoms (Patients and Caregivers).....	12
2.2.3 Fatigue (Patients)	12
2.2.4 Pain (Patients)	13
2.2.5 Sleep Quality (Caregivers)	13
2.2.6 Perceived Stress (Patients)	13
2.2.7 Caregiver Quality of Life (Caregivers)	13
2.3 Immunity	14
2.3.1 Cytokines (Patients and Caregivers)	14
2.4 Procedure	14
2.5 Data Analytics.....	15
3.0 Results	16
3.1 Sociodemographic Characteristics and Depressive Symptoms in Patients and Caregivers	16
3.2 Predictors of Depression in Patients Diagnosed with Cancer	16
3.3 Predictors of Depression in Caregivers of Those Diagnosed with Cancer	17

3.4 Depression and Immunity.....	17
4.0 Discussion.....	19
Appendix A Tables.....	23
Bibliography	25

List of Tables

Appendix Table 1 Sociodemographic Characteristics and Prevalence of Depression in Patients and Caregivers.....	23
Appendix Table 2 Predictors of Depression in Patients	24
Appendix Table 2 Predictors of Depression in Caregivers	24

1.0 Introduction

One of the most common mental health conditions in the United States is depression. According to the NIH, in 2017 there were approximately 17.3 million adults that experienced at least one episode of major depressive disorder, representing 7.1 percent of adults in the U.S.¹ Depression has a significant, negative impact on quality of life such that depression severity is proportional to quality of life deterioration.² Furthermore, mental health conditions such as depression are associated with an increased risk of mortality.³ A meta-analysis of 293 studies determined that the overall relative risk of mortality in depressed individuals in comparison to individuals without depression was 1.52.⁴

Higher rates of depression are common among individuals with chronic physical health conditions like cancer. Decades of research have demonstrated the psychological impact of cancer. The rates of depression in cancer patients can be highly variable and depend in part on the cancer type and stage but are frequently higher in cancer patients than the general population.^{5, 6} In a study which consisted of 10,153 patients diagnosed with various cancer types, researchers reported that the prevalence of depression was nearly 13 percent overall.⁷ However, other studies have reported the prevalence of depression and depressive disorders in cancer patients as high as 60 percent.⁶

Like in the general population, numerous studies have documented that depression has a negative impact on a cancer patient's quality of life.^{8, 9} Furthermore, co-morbid depression in cancer patients has been associated with worsened pain, poor sleep, and fatigue.¹⁰⁻¹² Depression in cancer patients is also linked to an increased risk of mortality.^{13, 14} However, in patients diagnosed with cancer, depression has not only an impact on mental and physical health but also an economic burden on the patient and health care system. Mausbach et al. found that yearly health care charges

for cancer patients suffering from depression were 113% higher than cancer patients without depression.¹⁵ Furthermore, depressed patients diagnosed with cancer typically pay more for increased usage of health care services such as ambulatory care, emergency department usage, overnight hospitalizations, and hospital fees.^{15, 16}

While a cancer diagnosis has a significant impact on the patient's physical and emotional health, it also greatly affects the lives of loved ones providing care. Caregivers experiencing emotional strain are at an increased risk for mortality.¹⁷ Individuals who fulfill a caregiving role are also at an increased risk for mental health disorders.¹⁸ In a meta-analytic review of nearly 22,150 participants, the overall prevalence of depression in cancer caregivers was reported to be approximately 42 percent.¹⁹ However, depression rates in cancer caregivers often vary and have been reported as high as 82.2 percent in familial caregivers.²⁰ Cancer caregivers suffering from depression have a lower quality of life.²¹ As depression has an impact on physical health, impaired quality of life, and increased mortality, it is critical to determine predictors that increase the risk of depression in both cancer patients and caregivers so that interventions can be given to improve mental and long-term health outcomes in these populations.

1.1 Predictors of Depression in Patients & Their Caregivers and Link with Immunity

Sociodemographic factors have been linked to depression in both cancer patients and their caregivers. Overall, being female and having lower educational attainment is predictive of depression.^{19, 22, 23} However, males diagnosed with cancer who are either unemployed or unable to work due to a disability have previously demonstrated more depressive symptoms than women.²² Gagiee et al. found that there are no age-related differences in depression levels in the context of

cancer patients experiencing pain.²⁴ Yet, among caregivers, researchers have suggested that depression could be higher among younger (<57 years of age) caregivers as well as caregivers over the age of 65.^{25, 26} Additionally, other factors such as unemployment, caregiving duration, being the spouse of the individual needing care, as well as financial issues, have been associated with depression in cancer caregivers.¹⁹

Depression rates also vary among cancer types and cancer stages.⁶ In particular, individuals with advanced cancer have exhibited higher levels of depression.²⁷ Furthermore, cancer-related symptoms are also reported to impact emotional health. Spiegel indicated that depressive disorders were prevalent among 33 percent of patients reporting higher levels of pain compared to a frequency of 13 percent among cancer patients with lower pain levels.²⁸ Fatigue, considered the most common symptom of cancer, has also been demonstrated to be significantly associated with depression.^{12, 29} Like pain and fatigue, perceived stress is thought to be a possible risk factor for depression.³⁰ Furthermore, according to the National Cancer Institute, patients diagnosed with cancer who use proper coping mechanisms to manage their stress have lower levels of depression.³¹ Social support is thought to possibly mediate coping style and is also negatively related to depression such that it may buffer high depression levels in cancer patients.³²⁻³⁴

In contrast, predictors of depression in cancer caregivers are both caregiver and patient-related. A patient predictor reported to have an effect on caregiver depression is mental health. Fleming et al. demonstrated that patient depression levels are correlated to caregiver depression levels.³⁵ Poor sleep quality and sleep disturbances have been associated with depression in caregivers, particularly familial caregivers of patients with advanced cancer.^{36, 37} Finally, poor social support and caregiver stress also predict depression in caregivers of cancer patients^{38, 39}

Developing a better understanding of depression in cancer patients and caregivers is critical as depression not only has an impact on mental health but immune functioning and survival. A prevailing theory related to depression involves the hypothalamic–pituitary–adrenal (HPA) axis which is often dysregulated in cancer patients suffering from depression.⁴⁰ Depression is thought to activate the HPA axis, generating a pro-inflammatory cytokine response.⁴¹ In patients diagnosed with cancer, depression was previously found to be positively associated with IL-1, IL-6, IL-8, and TNF- α and negatively associated with IL-10.⁴² Among cancer patients, cytokines play a role in cancer tumor growth and metastatic spread.⁴³⁻⁴⁷ A better understanding of the link between depression and cytokines could better inform our understanding of the increased risk for physical morbidities and mortality in cancer patients and their caregivers.

Rates of depression in cancer patients and their caregivers are highly variable across various cancer types and are less frequently studied in the context of patients and caregivers facing cancers affecting the hepatobiliary or pancreatic system. Thus, we will contribute to the literature by reporting the rate of depressive symptoms among patients with this rare cancer type and their family caregivers, as well as among dyads in which both individuals have depressive symptoms in the clinical range. Understanding the predictors of depression in cancer patients and caregivers within this population is also particularly important as both patient and caregiver experience can vary among cancer types and impact depression and health differently. Additionally, in many studies, predictors of depression are examined independently of each other. However, these predictors are often associated with each other. Thus, in this study, we will perform a multivariate analysis to examine all predictors simultaneously. In the patient analyses we included fatigue, perceived stress, and pain as non-sociodemographic predictors of interest. In caregivers, we included quality of life and sleep quality as additional predictors. These predictors were chosen as

they have known associations with depression and are components commonly impacted within these specific populations.^{12, 21, 28-30, 37} Practically, these variables were chosen as they were included in both clinical trials that were used as part of this proposed study. While many studies have examined the link between depression and biomarkers of inflammation, few have included sociodemographic and psychosocial covariates that have been previously reported to be related to immunity. The cytokines included in the present study were chosen secondary to their link with psychosocial factors and association with disease progression in the context of cancer. ⁴¹⁻⁴⁷

2.0 Method

2.1 Participants

Patients and caregivers were recruited at a large cancer center. Participants were enrolled in one of two randomized controlled trials testing a stepped collaborative care intervention between April 2007 to October 2011 (K07CA118576, R21CA127046, and P30CA047904) and December 2016 to January 2020 (R01CA196953). Inclusion criteria of the patients included: biopsy or radiographically proven diagnosis of cancer affecting the hepatobiliary or pancreatic system; (2) age 21 years or older; (3) fluency in English; and (4) no evidence of thought disorder, hallucinations, or delusions. The inclusion and exclusion criteria for the caregivers were: (1) the individual was caring for someone with a diagnosis of cancer, (2) age 21 years or older; (3) fluency in English; and (4) no evidence of thought disorder, hallucinations, or delusions. The baseline assessment of psychosocial factors and immune system parameters was performed during the first year after diagnosis with a mean = 9.53 (SD = 23.23) months after diagnosis.

2.2 Instruments

2.2.1 Demographic Factors (Patients and Caregivers)

The patients and caregivers completed a questionnaire designed specifically for the attainment of sociodemographic information. Sociodemographic data collected included gender, age, race, educational level, employment status, and income.

2.2.2 Depressive Symptoms (Patients and Caregivers)

The Center for Epidemiologic Studies-Depression (CES-D) is a 20-item, self-report questionnaire designed to assess depressive symptoms through questions relating to, for example, restlessness, enjoyment in life, and focus.⁴⁸ Patients and caregivers responded on a 4-point scale. High levels of depressive symptoms in the clinical range are indicated by a score of 16 or greater. The CES-D has established validity evidence and reliability.⁴⁸

2.2.3 Fatigue (Patients)

Fatigue in cancer patients was measured using the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale which is a 13-item assessment that asks patients to rate their fatigue performing daily activities over the past week. Fatigue levels are measure on a four-point Likert scale (4 = not at all fatigued to 0 = very much fatigued). A low composite score reflects increased levels of fatigue. The instrument has high internal validity and test-retest reliability.⁴⁹

2.2.4 Pain (Patients)

Pain was measured using the Brief Pain Inventory (BPI) which is a 16-item questionnaire designed for cancer patients. Specifically, average pain was determined by asking patients to numerically rate their average pain levels on a scale of zero to ten. The BPI has good construct and concurrent validity.⁵⁰

2.2.5 Sleep Quality (Caregivers)

The Pittsburgh Sleep Quality Index (PSQI) is a questionnaire that assesses one's sleep in the past month.⁵¹ The instrument can be broken into component scores such as subjective sleep quality. The questionnaire has reported reliability and validity.⁵¹

2.2.6 Perceived Stress (Patients)

The Perceived Stress Scale (PSS) is a 14 item self-report questionnaire that focuses on the degree to which one finds life unpredictable, uncontrollable, and overloading.⁵² Patients were asked to rate each item in regard to the past month on a 5-point Likert-type. The instrument has test-retest reliability and substantial validity evidence.⁵²

2.2.7 Caregiver Quality of Life (Caregivers)

The Caregiver Quality of Life Index- Cancer (CQOLC) scale is a 35-item instrument that assesses quality of life in cancer caregivers. Caregivers responded on a 5-point scale. A higher

total score was indicative of poor quality of life. The instrument is considered to be both reliable and valid.⁵³

2.3 Immunity

2.3.1 Cytokines (Patients and Caregivers)

Serum levels of cytokines IL-1 α , IL-1 β , IL-2, IL-6, and TNF α were measured for both patients and caregivers. To obtain the serum levels, blood was drawn typically between 8 am and noon. Red top vacutainer tubes without anticoagulant were used to collect blood samples. After at least 30 minutes to allow for clot formation, the blood was processed in a University of Pittsburgh laboratory. The serum was processed and stored within four hours and frozen at -80° C. It was thawed once and then tested using Luminex. The standard curve range of Millipore multi-plex kit, HCYTOMAG-60K for each cytokine was 10,000 to 0.064 pg/ml. Milliplex Analyst 5.1 software was used to determine standard curve concentrations and the Minimum Detectable Concentration (MinDC). Quality control samples of established concentrations were analyzed with the samples. The quality controls were within the acceptable range for all analytes on all analyzed samples.

2.4 Procedure

Both studies were approved by the University of Pittsburgh's Institutional Review Board prior to participant enrollment. Following the recommendation of the medical team, the patient

and caregiver spoke with a member of the research team about the associated risks and benefits of each study. Prior to completing any study questionnaires, written and informed consent was obtained for each participant.

2.5 Data Analytics

Data was analyzed using SPSS version 25 (IBM Corp, Armonk, NY). Descriptive statistics were used in order to determine the prevalence of higher levels of depressive symptoms in patients, caregivers, and patient-caregiver dyads. Logistic regression was then utilized to examine which constructs were predictive of depression in cancer patients and their caregivers, accounting for sociodemographic factors such as gender, race, age, education, and employment status. Finally, we also performed logistic regression to test the link between depression and IL-1 α , IL-1 β , IL-2, IL-6, and TNF α after adjusting for gender, race, age, years of education, employment status, and other psychosocial and behavioral factors associated with immunity among cancer patients and caregivers.

3.0 Results

3.1 Sociodemographic Characteristics and Depressive Symptoms in Patients and Caregivers

A total of 259 patient and caregiver dyads were included in the analyses. The mean age of patients was 64.7 (SD = 10.5), and the majority were Caucasian (92.9%) and female (56.6%). The mean age of caregivers was 58.5 (SD = 12.5), and the majority were Caucasian (93.2), female (73.7%), and the spouse of the cancer patient (63.5%). The rate of depressive symptoms in the clinical range among patients was 37.4% and 36.7% in caregivers. In 35 dyads (15.6%), both the patient and caregiver reported depressive symptoms in the clinical range. See Appendix Table 1.

Appendix Table 1

3.2 Predictors of Depression in Patients Diagnosed with Cancer

Binary logistic regression was used to test the predictors of depression in patients diagnosed with cancer. Predictors in the model included gender, race, age, years of education, employment status, fatigue, perceived stress, and pain. We found that high levels of fatigue ($\beta = -0.116$; OR = 0.890; 95% CI, 0.848-0.935; $p < 0.001$) and perceived stress ($\beta = 0.198$; OR = 1.219;

95% CI, 1.127-1.318; $p = <0.001$) were predictive of depressive symptoms in patients. See Appendix Table 2.

Appendix Table 2

3.3 Predictors of Depression in Caregivers of Those Diagnosed with Cancer

Binary logistic regression was used to test the predictors of depression in caregivers. Predictors in the model included gender, race, age, years of education, employment status, caregiver quality of life, and sleep quality. We found that poor quality of life, measured as a higher score on the CQOLC instrument ($\beta = 0.067$; OR = 1.069; 95% CI, 1.040-1.099; $p = <0.001$) was a significant predictor of depression in cancer caregivers. See Appendix Table 3.

Appendix Table 3

3.4 Depression and Immunity

Binary logistic regression was used to determine if patient depressive symptoms were predictive of the cytokines IL-1 α , IL-1 β , IL-2, IL-6, and TNF α in separate, multivariate analyses. Gender, race, age, years of education, and employment as well as other known predictors of

cytokines such as fatigue, perceived stress, and pain were adjusted for in each analysis. After adjusting for these factors, we found that depression did not significantly predict IL-1 α ($\beta = -0.902$; OR = 0.406; 95% CI, 0.158-1.043; $p = 0.061$), IL-1 β ($\beta = -0.264$; OR = 0.768; 95% CI, 0.315-1.869; $p = 0.560$), IL-2 ($\beta = -0.287$; OR = 0.751; 95% CI, 0.281-2.007; $p = 0.568$), IL-6 ($\beta = 0.726$; OR = 2.067; 95% CI, 0.673-6.354; $p = 0.205$), or TNF α ($\beta = 0.410$; OR = 1.506; 95% CI, 0.564-4.021; $p = 0.413$).

Binary logistic regression was used to test predictors of cytokines in caregivers including IL-1 α , IL-1 β , IL-2, IL-6, and TNF α . Gender, race, age, years of education, employment, caregiver quality of life, and sleep quality were adjusted for in each analysis. We found that depression did not significantly predict caregivers' IL-1 α ($\beta = 0.982$; OR = 2.669; 95% CI, 0.737-9.658; $p = 0.135$), IL-1 β ($\beta = 0.529$; OR = 1.697; 95% CI, 0.443-6.510; $p = 0.440$), IL-2 ($\beta = 0.550$; OR = 1.733; 95% CI, 0.335-8.965; $p = 0.512$), IL-6 ($\beta = 0.137$; OR = 1.147; 95% CI, 0.379-3.473; $p = 0.809$), or TNF α ($\beta = 1.426$; OR = 4.163; 95% CI, 0.428-40.489; $p = 0.219$).

4.0 Discussion

Depressive symptoms in the clinical range were observed in patients diagnosed with cancer and their family caregivers. We found that fatigue and higher perceived stress in patients, as well as poor quality of life in cancer caregivers, were most predictive of increased depressive symptoms. Several studies establish the relationship between fatigue and depression in cancer patients.^{12, 54} For example, in a study analyzing the relationship between fatigue and depression, scientists reported a significant, positive relationship within patients in remission for hematological malignancies.⁵⁴ Previous literature also suggests the positive relationship between perceived stress and depression in cancer patients.³⁰ In the context of cancer caregivers, quality of life (in part, reflective of burden, disruption to one's life, and financial concern) has previously been shown to be linked with depression such that there is a negative relationship between quality of life and depression.^{19, 55, 56} Our study is different from other studies which analyze predictors of depression such that we do not study predictors of depression independent of each other or merely adjust for sociodemographic factors.

Interestingly, neither depressive symptoms in patients diagnosed with cancer or caregivers were predictive of immunity. Several studies have suggested a link between depression and pro-inflammatory cytokines in cancer patients and caregivers. However, depression is often studied independently of other factors associated with immunity, or in some cases, is studied adjusting for sociodemographic factors only.⁴² Himmerich et al. suggest, "Even though cytokines are often discussed as biomarkers for depression, they have also been shown to be altered in other psychiatric disorders. Moreover, many environmental, social, psychological, biological, and medical factors are also associated with cytokine changes."⁵⁷ These factors should be included in

any analyses testing the link between depression and biomarkers of inflammation. In this study, we not only accounted for sociodemographic factors but additional predictors of immunity such as pain, fatigue, perceived stress, and quality of life. Our findings suggest that other predictors of immunity may influence or underlie the previously established link between depression and cytokines such that depression is not an independent risk factor for immunity alternations.

One limitation of this study is the lack of a demographically diverse population of patients and caregivers. The majority of patients and caregivers were middle age, Caucasian females. Notably, nearly two-thirds of caregivers were female. Ideally, over time, more men could be recruited into the studies to enable a better understanding of the role of caregiving in this population. However, despite this limitation, previous literature does suggest that women make up approximately two-thirds of caregivers, consistent with the rate of female caregivers in these studies.⁵⁸ Furthermore, the studies would ideally be conducted with a racially diverse group of patients and caregivers. In addition, assessing various predictors of depression and cytokines in various cancer diagnoses and stages is important in establishing the validity of these predictors and our findings outside the context of cancers affecting the hepatobiliary and pancreatic system.

Another limitation of this study was a lack of the same psychosocial predictors included in both the patient and caregiver analyses. The aims of the original clinical trials were not to examine the predictors of depression and immune system parameters. Therefore including the same predictors for both patients and caregivers was not previously planned for the purposes of this study. Future studies interested in the predictors of patients and caregiver dyads may consider including the same predictors across patients and caregivers.

In this study, we also used dichotomous outcome variables (e.g. depression and cytokines) as opposed to continuous variables in the analysis. One limitation of this approach is that

individuals close to the cutpoint on either side would be considered as being dissimilar when they are actually more similar with regard to symptoms. However, by using dichotomous variables, we obtain more clinically meaningful outcomes that have been shown in prior research to be linked to disease progression and mortality.^{4, 13, 14, 43-47} Although power is also a consideration as the use of continuous variables often results in greater power, even with the use of dichotomous outcomes, the power was sufficient to test the hypotheses and therefore is our rationale for using dichotomous rather than continuous variables. Finally, while we propose that fatigue and perceived stress in patients, as well as poor quality of life in caregivers, are predictors of depression in this cross-sectional study, there is a possibility that these factors do not cause depression but rather are the result of depression. Thus, longitudinal data collection and analysis in the future is important to obtain a better understanding of the directionality of this relationship.

Despite several limitations, there are multiple strengths to this study. First determining predictors of depression among patients and caregivers facing hepatobiliary cancer is particularly important as psychological health is less commonly studied in this context. Furthermore, as the experience of a cancer diagnosis and caregiving for a loved one with cancer can vary among cancer types, it is important to address predictors of depression in cancers affecting the hepatobiliary and pancreatic system. The specific finding that perceived stress and fatigue are predictors of depression among patients is particularly useful in a clinical setting. Depression has an adverse impact on both the patient, family, and the health care system. Thus, developing interventions to target fatigue and stress could be useful in managing or decreasing the risk of depression in cancer patients.⁵⁹ In terms of caregiving, finding that poor quality of life is associated with depression informs clinicians of the importance of monitoring caregiver psychological health and quality of life. Interventions could also be put in place to help caregivers improve their well-being during a

typically stressful period in their lives. Finally, our study also informs future research that analyzes the link between depression and immunity. We have demonstrated the importance of studying the relationship between depression and cytokines in terms of both sociodemographic factors and other known predictors of immunity.

Appendix A Tables

Appendix Table 1 Sociodemographic Characteristics and Prevalence of Depression in Patients and Caregivers

Characteristics	Patients	Caregivers
Age (mean, SD)	64.7 (10.5)	58.5 (12.5)
Female (n, %)	146 (56.6)	191 (73.7)
Race (n, %)		
Caucasian	235 (92.9)	234 (93.2)
Black	14 (5.5)	14 (5.6)
Asian	4 (1.6)	1 (0.4)
American Indian	-	2 (0.8)
Years of Education (mean, SD)	13.2 (2.6)	14.4 (6.8)
Employment Status (n, %)		
Full/Part-Time	80 (32.4)	137 (54.6)
Unemployed/Disabled	57 (23.1)	25 (10.0)
Homemaker/Student	35 (14.2)	28 (11.2)
Retired & Not Employed	75 (30.4)	61 (24.3)
Income (n, %)		
< \$30,000	63 (30.9)	52 (24.3)
> \$30,000	141 (69.1)	162 (75.7)
Familial Caregivers (n, %)	-	211 (84.1)
Relationship to Patient (n, &)		
Spouse	-	158 (63.5)
Intimate Partner	-	16 (6.4)
Adult Child	-	36 (14.5)
Siblings	-	8 (3.2)
Other	-	31 (12.4)
Depression (n, %)	95 (37.4)	84 (36.7)

Appendix Table 2 Predictors of Depression in Patients

Factor	Beta	Standard Error	Odds Ratio	p-value	95% Confidence	
Gender (ref: female)	-0.193	0.474	0.824	0.684	0.326	2.087
Race (ref: Caucasian)	-1.600	0.864	0.202	0.064	0.037	1.098
Age (years)	0.061	0.029	1.062	0.035	1.004	1.124
Education (years)	0.093	0.094	1.097	0.325	0.912	1.319
Employment (ref: Full/Part-Time)				0.275		
Unemployed/Disabled	0.594	0.676	1.812	0.379	0.482	6.815
Homemaker/Student	1.424	0.735	4.154	0.053	0.984	17.528
Retired & Not Employed	0.152	0.625	1.164	0.808	0.342	3.961
FACIT Fatigue Scale	-0.116	0.025	0.890	<0.001	0.848	0.935
Perceived Stress	0.198	0.040	1.219	<0.001	1.127	1.318
Pain ₁	0.052	0.088	1.053	0.557	0.886	1.251

₁ Average pain in last week (0-10)

Appendix Table 3 Predictors of Depression in Caregivers

Factor	Beta	Standard Error	Odds Ratio	p-value	95% Confidence	
Gender (ref: female)	-0.718	0.536	0.488	0.181	0.171	1.396
Race (ref: Caucasian)	-1.23	0.891	0.292	0.167	0.051	1.674
Age (years)	-0.039	0.021	0.962	0.060	0.924	1.002
Education (years)	-0.166	0.093	0.847	0.076	0.705	1.017
Employment (ref: Full/Part-Time)				0.386		
Unemployed/Disabled	0.477	0.700	1.611	0.495	0.409	6.353
Homemaker/Student	1.019	0.697	2.771	0.144	0.707	10.864
Retired & Not Employed	0.772	0.634	2.164	0.224	0.624	7.502
Caregiver Quality of Life Index-Cancer	0.067	0.014	1.069	<0.001	1.04	1.099
Sleep Quality (ref: Very Good)				0.307		
Fairly Good	0.383	0.678	1.467	0.572	0.388	5.539
Fairly Bad	1.171	0.735	3.226	0.111	0.764	13.612
Very Bad	0.700	1.081	2.014	0.517	0.242	16.766

Bibliography

1. National Institute of Mental Health. "Major Depression." 2019.
2. Berlim MT and Fleck MPA. Quality of Life and Major Depression. In: M. S. Ritsner and A. G. Awad, eds. *Quality of Life Impairment in Schizophrenia, Mood and Anxiety Disorders: New Perspectives on Research and Treatment* Dordrecht: Springer Netherlands; 2007: 241-252.
3. Walker ER, McGee RE and Druss BG. Mortality in Mental Disorders and Global Disease Burden Implications. *JAMA Psychiatry*. 2015;72:334.
4. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J and Penninx BW. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *Am J Psychiatry*. 2014;171:453-62.
5. Massie MJ. Prevalence of depression in patients with cancer. *J Natl Cancer Inst Monogr*. 2004;57-71.
6. Caruso R, Nanni MG, Riba M, Sabato S, Mitchell AJ, Croce E and Grassi L. Depressive spectrum disorders in cancer: prevalence, risk factors and screening for depression: a critical review. *Acta Oncologica*. 2017;56:146-155.
7. Linden W, Vodermaier A, MacKenzie R and Greig D. Anxiety and depression after cancer diagnosis: Prevalence rates by cancer type, gender, and age. *Journal of Affective Disorders*. 2012;141:343-351.
8. Wilson KG, Chochinov HM, Skirko MG, Allard P, Chary S, Gagnon PR, Macmillan K, De Luca M, O'Shea F, Kuhl D, Fainsinger RL and Clinch JJ. Depression and anxiety disorders in palliative cancer care. *J Pain Symptom Manage*. 2007;33:118-29.
9. Frick E, Tyroller M and Panzer M. Anxiety, depression and quality of life of cancer patients undergoing radiation therapy: a cross-sectional study in a community hospital outpatient centre. *Eur J Cancer Care (Engl)*. 2007;16:130-6.
10. Gerbershagen HJ, Ozgur E, Straub K, Dagtekin O, Gerbershagen K, Petzke F, Heidenreich A, Lehmann KA and Sabatowski R. Prevalence, severity, and chronicity of pain and general health-related quality of life in patients with localized prostate cancer. *Eur J Pain*. 2008;12:339-50.
11. Irwin MR. Depression and insomnia in cancer: prevalence, risk factors, and effects on cancer outcomes. *Curr Psychiatry Rep*. 2013;15:404-404.
12. Brown LF and Kroenke K. Cancer-related fatigue and its associations with depression and anxiety: a systematic review. *Psychosomatics*. 2009;50:440-447.
13. Sullivan DR, Forsberg CW, Ganzini L, Au DH, Gould MK, Provenzale D and Slatore CG. Longitudinal Changes in Depression Symptoms and Survival Among Patients With Lung Cancer: A National Cohort Assessment. *J Clin Oncol*. 2016;34:3984-3991.
14. Zhu J, Fang F, Sjölander A, Fall K, Adami HO and Valdimarsdóttir U. First-onset mental disorders after cancer diagnosis and cancer-specific mortality: a nationwide cohort study. *Ann Oncol*. 2017;28:1964-1969.
15. Mausbach BT, Yeung P, Bos T and Irwin SA. Health care costs of depression in patients diagnosed with cancer. *Psycho-oncology*. 2018;27:1735-1741.

16. Mausbach BT and Irwin SA. Depression and healthcare service utilization in patients with cancer. *Psycho-oncology*. 2017;26:1133-1139.
17. Schulz R and Beach SR. Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *Jama*. 1999;282:2215-9.
18. Association AP. Mental Health of Caregivers. 2020.
19. Geng H-M, Chuang D-M, Yang F, Yang Y, Liu W-M, Liu L-H and Tian H-M. Prevalence and determinants of depression in caregivers of cancer patients: A systematic review and meta-analysis. *Medicine*. 2018;97:e11863-e11863.
20. Park B, Kim SY, Shin J-Y, Sanson-Fisher RW, Shin DW, Cho J and Park JH. Suicidal ideation and suicide attempts in anxious or depressed family caregivers of patients with cancer: a nationwide survey in Korea. *PloS one*. 2013;8:e60230-e60230.
21. Heidari Gorji MA, Bouzar Z, Haghshenas M, Kasaeyan AA, Sadeghi MR and Ardebil MD. Quality of life and depression in caregivers of patients with breast cancer. *BMC Res Notes*. 2012;5:310-310.
22. Cheng HH, Kamarck TW, Gianaros PJ, Roeklein KA, Vanegas Y, Tsung A, Geller DA, Marsh JW, Ahmed NS and Steel JL. Socioeconomic disparities of depressive symptoms and cytokines in hepatocellular carcinoma. *Psycho-oncology*. 2019;28:1624-1632.
23. Friberg AS, Rask Moustsen I, Benzon Larsen S, Hartung T, Wreford Andersen E, Halgren Olsen M, Tjønneland A, Kjaer SK, Johansen C, Brasso K and Oksbjerg Dalton S. Educational level and the risk of depression after prostate cancer. *Acta Oncologica*. 2019;58:722-729.
24. Gagliese L, Gauthier LR and Rodin G. Cancer pain and depression: a systematic review of age-related patterns. *Pain Res Manag*. 2007;12:205-211.
25. Butler SS, Turner W, Kaye LW, Ruffin L and Downey R. Depression and caregiver burden among rural elder caregivers. *J Gerontol Soc Work*. 2005;46:47-63.
26. Covinsky KE, Newcomer R, Fox P, Wood J, Sands L, Dane K and Yaffe K. Patient and caregiver characteristics associated with depression in caregivers of patients with dementia. *J Gen Intern Med*. 2003;18:1006-14.
27. Boyd CA, Benarroch-Gampel J, Sheffield KM, Han Y, Kuo Y-F and Riall TS. The effect of depression on stage at diagnosis, treatment, and survival in pancreatic adenocarcinoma. *Surgery*. 2012;152:403-413.
28. Spiegel D, Sands S and Koopman C. Pain and depression in patients with cancer. *Cancer*. 1994;74:2570-8.
29. Cella D, Lai JS, Chang CH, Peterman A and Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer*. 2002;94:528-38.
30. Li Y, Yang Y, Zhang R, Yao K and Liu Z. The Mediating Role of Mental Adjustment in the Relationship between Perceived Stress and Depressive Symptoms in Hematological Cancer Patients: A Cross-Sectional Study. *PLoS One*. 2015;10:e0142913.
31. Institute NC. Psychological Stress and Cancer. 2012.
32. Tan M. Social support and coping in Turkish patients with cancer. *Cancer nursing*. 2007;30:498-504.
33. Naseri N and Taleghani F. Social Support and Depression in Iranian Cancer Patients: the Role of Demographic Variables. *J Caring Sci*. 2018;7:143-147.
34. Godding PR, McAnulty RD, Wittrock DA, Britt DM and Khansur T. Predictors of depression among male cancer patients. *J Nerv Ment Dis*. 1995;183:95-8.

35. Fleming DA, Sheppard VB, Mangan PA, Taylor KL, Tallarico M, Adams I and Ingham J. Caregiving at the end of life: Perceptions of health care quality and quality of life among patients and caregivers. *J Pain Symptom Manage.* 2006;31:407-20.
36. Lee KC, Yiin JJ, Lin PC and Lu SH. Sleep disturbances and related factors among family caregivers of patients with advanced cancer. *Psycho-oncology.* 2015;24:1632-8.
37. Lee KC, Hsieh YL, Lin PC and Lin YP. Sleep Pattern and Predictors of Sleep Disturbance Among Family Caregivers of Terminal Ill Patients With Cancer in Taiwan: A Longitudinal Study. *Am J Hosp Palliat Care.* 2018;35:1109-1117.
38. Karabekiroğlu A, Demir EY, Aker S, Kocamanoğlu B and Karabulut GS. Predictors of depression and anxiety among caregivers of hospitalised advanced cancer patients. *Singapore Med J.* 2018;59:572-577.
39. Kim Y, Carver CS, Rocha-Lima C and Shaffer KM. Depressive symptoms among caregivers of colorectal cancer patients during the first year since diagnosis: a longitudinal investigation. *Psycho-oncology.* 2013;22:362-7.
40. Saxton JM, Scott EJ, Daley AJ, Woodroffe MN, Mutrie N, Crank H, Powers HJ and Coleman RE. Effects of an exercise and hypocaloric healthy eating intervention on indices of psychological health status, hypothalamic-pituitary-adrenal axis regulation and immune function after early-stage breast cancer: a randomised controlled trial. *Breast Cancer Research.* 2014;16:R39.
41. Miller AH, Maletic V and Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry.* 2009;65:732-41.
42. Oliveira Miranda D, Soares de Lima TA, Ribeiro Azevedo L, Feres O, Ribeiro da Rocha JJ and Pereira-da-Silva G. Proinflammatory cytokines correlate with depression and anxiety in colorectal cancer patients. *Biomed Res Int.* 2014;2014:739650.
43. Han D, Pottin-Clemenceau C, Imro MA, Scudeletti M, Doucet C, Puppo F, Brouty-Boye D, Vedrenne J, Sahraoui Y, Brailly H, Poggi A, Jasmin C, Azzarone B and Indiveri F. IL2 triggers a tumor progression process in a melanoma cell line MELP derived from a patient whose metastasis increased in size during IL2/INFalpha biotherapy. *Oncogene.* 1996;12:1015-23.
44. Ito R, Kitadai Y, Kyo E, Yokozaki H, Yasui W, Yamashita U, Nikai H and Tahara E. Interleukin 1 α Acts as an Autocrine Growth Stimulator for Human Gastric Carcinoma Cells. *Cancer Research.* 1993;53:4102.
45. Voorzanger N, Touitou R, Garcia E, Delecluse HJ, Rousset F, Joab I, Favrot MC and Blay JY. Interleukin (IL)-10 and IL-6 are produced in vivo by non-Hodgkin's lymphoma cells and act as cooperative growth factors. *Cancer Res.* 1996;56:5499-505.
46. Gangopadhyay A, Bajenova O, Kelly TM and Thomas P. Carcinoembryonic antigen induces cytokine expression in Kupffer cells: implications for hepatic metastasis from colorectal cancer. *Cancer Res.* 1996;56:4805-10.
47. Sehgal PB and Tamm I. Interleukin-6 enhances motility of breast cancer cells. *Cancer Invest.* 1990;8:661-3.
48. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement.* 1977;1:385-401.
49. Chandran V, Bhella S, Schentag C and Gladman DD. Functional assessment of chronic illness therapy-fatigue scale is valid in patients with psoriatic arthritis. *Ann Rheum Dis.* 2007;66:936-9.

50. Kumar SP. Utilization of brief pain inventory as an assessment tool for pain in patients with cancer: a focused review. *Indian J Palliat Care*. 2011;17:108-115.
51. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR and Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research*. 1989;28:193-213.
52. Cohen S, Kamarck T and Mermelstein R. A global measure of perceived stress. *Journal of health and social behavior*. 1983;24:385-96.
53. Weitzner MA, Jacobsen PB, Wagner H, Jr., Friedland J and Cox C. The Caregiver Quality of Life Index-Cancer (CQOLC) scale: development and validation of an instrument to measure quality of life of the family caregiver of patients with cancer. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 1999;8:55-63.
54. Dimeo F, Schmittl A, Fietz T, Schwartz S, Kohler P, Boning D and Thiel E. Physical performance, depression, immune status and fatigue in patients with hematological malignancies after treatment. *Ann Oncol*. 2004;15:1237-42.
55. Heidari Gorji MA, Bouzar Z, Haghshenas M, Kasaeeyan AA, Sadeghi MR and Ardebil MD. Quality of life and depression in caregivers of patients with breast cancer. *BMC Res Notes*. 2012;5:310.
56. Shin JY, Lim JW, Shin DW, Kim SY, Yang HK, Cho J, Jeong A, Jo D, Yim CY, Park K and Park JH. Underestimated caregiver burden by cancer patients and its association with quality of life, depression and anxiety among caregivers. *Eur J Cancer Care (Engl)*. 2018;27:e12814.
57. Himmerich H, Patsalos O, Lichtblau N, Ibrahim MAA and Dalton B. Cytokine Research in Depression: Principles, Challenges, and Open Questions. *Frontiers in Psychiatry*. 2019;10.
58. Institute on Aging. "Read how IOA views aging in America."
59. Steel JL, Geller DA, Kim KH, Butterfield LH, Spring M, Grady J, Sun W, Marsh W, Antoni M, Dew MA, Helgeson V, Schulz R and Tsung A. Web-based collaborative care intervention to manage cancer-related symptoms in the palliative care setting. *Cancer*. 2016;122:1270-1282.