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## Associations Between Demographic, Clinical, and Symptom Characteristics and Stress in Oncology Patients Receiving Chemotherapy

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### Abstract

**Background** —Patients undergoing cancer treatment experience global stress and cancer-specific stress. Both types of stress are associated with a higher symptom burden.

**Objective** —In this cross-sectional study, we used a comprehensive set of demographic, clinical, and symptom characteristics to evaluate their relative contribution to the severity of global and cancer-specific stress.

**Methods** —Patients (n=941) completed study questionnaires prior to their second or third cycle of chemotherapy.

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**Results** —Consistent with our a priori hypothesis, we found both common and distinct characteristics associated with higher levels of global stress and cancer-specific stress. A significant proportion of our patients had scores on the Impact of Event Scale-Revised suggestive subsyndromal (29.4%) or probable (13.9%) posttraumatic stress disorder. Four of the five stepwise linear regression analyses for the various stress scales explained between 41.6% and 54.5% of the total variance. Compared to various demographic and clinical characteristics, many of the common symptoms associated with cancer and its treatments uniquely explained a higher percentage of the variance in the various stress scales. Symptoms of depression made the largest unique contribution to the percentage of total explained variance across all five scales.

**Conclusion** —Clinicians need to assess for global stress, cancer-specific stress, and depression in patients receiving chemotherapy.

**Implications for Practice** —Patients may benefit from integrative interventions (e.g., mindfulness-based stress reduction, cognitive behavioral therapy, acupuncture) that simultaneously address stress and symptoms commonly associated with cancer and its treatments.

## INTRODUCTION

Stress is a common human experience that activates the hypothalamic-pituitary-adrenal axis so an individual can adapt to the experience. However, unrelieved acute and chronic stress result in poorer health outcomes.<sup>1</sup> A cancer diagnosis and its treatments are regarded as highly stressful events. Chronic stress can adversely impact patients' prognosis and their quality of life.<sup>2, 3</sup>

Throughout the oncology literature,<sup>4, 5</sup> findings regarding oncology patients' experiences of stress are highly variable depending on when stress is evaluated during the course of the cancer trajectory. However, it is recognized that multiple sources of stress (e.g., global stress, cancer-specific stress) can have a negative impact on patients' physical, psychological, and social well-being, as well as their overall quality of life. For example, the initial cancer diagnosis, as well as the stress associated with subsequent treatments (e.g., scheduling appointments, waiting for results of diagnostic tests, fear of unrelieved symptoms and adverse effects) and fears of recurrence, are considered cancer-specific or disease-specific stress. This type of stress may provoke symptoms associated with post-traumatic stress disorder (PTSD).<sup>6</sup>

This cancer-specific stress is distinct from global stress that arises from the ordinary pressures of daily life.<sup>6</sup> For example, global stressors may include: the time needed to care for children or older adults, challenges at work, and difficulties with routine home maintenance activities. These global stressors contribute to decrements in oncology patients' ability to function and in their overall quality of life. Most patients undergoing cancer treatment experience and manage both types of stress.<sup>7, 8</sup>

While both types of unrelieved stress can have a negative impact on all aspects of oncology patients' lives,<sup>9–11</sup> few studies have evaluated for common and unique demographic, clinical, and symptom characteristics associated with elevated levels of global and cancer-specific stress in the same sample of patients. While younger age and unmarried/unpartnered

status were associated with both types of stress,<sup>7, 12</sup> female gender, being White, and having a lower socioeconomic status were associated with higher cancer-related distress.<sup>7</sup> In terms of clinical characteristics, most studies have focused on patients with breast cancer. In a systematic review of 42 studies of breast cancer survivors,<sup>13</sup> a lower functional status, a higher number of comorbidities, receipt of chemotherapy, and disease recurrence were associated with higher levels of psychological distress. In contrast, among newly diagnosed women with breast cancer,<sup>14</sup> while clinical characteristics were not associated with cancer-specific distress, negative illness perceptions were a significant risk factor. Regarding the relationships between stress and symptoms, a growing body of evidence suggests that higher levels of stress are associated with increases in pain,<sup>15</sup> fatigue,<sup>16</sup> sleep disturbance,<sup>17</sup> chemotherapy-induced neurotoxicities,<sup>18</sup> depression,<sup>19</sup> and cognitive impairment<sup>20</sup> in patients with a variety of chronic conditions. Additional research is needed to determine which demographic, clinical, and symptom characteristics are associated with global stress and/or cancer-specific stress in oncology patients.

Therefore, the purpose of this study, in a sample of oncology patients with heterogenous types of cancers (n=941), was to use the same set of demographic, clinical, and symptom characteristics to evaluate their relative contribution to the severity of global (i.e., measures using the Perceived Stress Scale (PSS)<sup>21</sup>) and cancer-specific (i.e., measured using the Impact of Event Scale-Revised (IES-R)<sup>22</sup>) stress. We hypothesized that common and distinct characteristics would be associated with global and cancer-specific stress.

## METHODS

### Patients and Settings

This analysis used data from a descriptive, longitudinal study that evaluated the symptom experience of oncology outpatients who were recruited during their first or second cycle of chemotherapy and assessed six times over two consecutive cycles of chemotherapy. The details of this longitudinal study are described in detail elsewhere.<sup>23</sup> The theoretical framework that guided the larger study was the Theory of Symptom Management.<sup>24</sup> In this theory, patients' demographic and clinical characteristics are included in the person domain. The Theory of Symptom Management suggests that these patient characteristics and symptom experiences are associated with patients' perceptions of global and cancer-specific stress. For this analysis, a prespecified set of demographic, clinical, and symptom characteristics were evaluated as potential risk factors of the severity of global and cancer-specific stress experiences by oncology patients receiving chemotherapy.

Eligible patients were 18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; and were able to read, write, and understand English. Recruitment was done at two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. A total of 2234 patients were approached and 1343 consented to participate (60.1% response rate). Being overwhelmed with their cancer treatment was the primary reason for refusal. For this analysis, 941 patients with complete data were included.

## Study Measures

**Demographic and clinical characteristics**—Patients completed a demographic questionnaire, the Karnofsky Performance Status (KPS) scale,<sup>25</sup> and the Self-Administered Comorbidity Questionnaire (SCQ).<sup>26</sup> The KPS scale is widely used to evaluate functional status in oncology patients and has well established validity and reliability.<sup>27</sup> Patients rated their functional status using the KPS scale that ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms).<sup>25, 27</sup>

The SCQ consists of 13 common medical conditions simplified into language that can be understood without prior medical knowledge.<sup>26</sup> Patients indicated if they had the condition; if they received treatment for it (proxy for disease severity) and if it limit their activities (indication of functional limitations). For each condition, the patient can receive a maximum of 3 points. The total SCQ score ranges from 0 to 39. The SCQ has well-established validity and reliability.<sup>28, 29</sup> Medical records were reviewed for disease and treatment information. Toxicity of the chemotherapy regimen was evaluated using the MAX2 score.<sup>30</sup>

**Stress measures**—The 14-item PSS measures global perceived stress as determined by the degree to which life circumstances are considered stressful over the previous week.<sup>21</sup> Each item was rated on a 0 to 4 Likert scale (i.e., 0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often). The PSS total score ranges from 0 to 56 with higher scores indicating greater stress. For the current study, its Cronbach's alpha was 0.85.

The 22-item IES-R measures cancer-related distress.<sup>22</sup> Patients rated each item in terms of how distressing each potential stressor was over the past week with respect to their cancer and its treatment, using a 0 to 4 Likert scale. Three subscales assess levels of intrusion, avoidance, and hyperarousal. The 7-item intrusion subscale evaluates intrusive recollections about the stressful experience. The 8-item avoidance subscale assesses the avoidance of situations related to the stressful experience. The 8-item hyperarousal subscale evaluates episodes of psychological arousal related to thoughts about the stressful event. Mean scores for each of the subscales is calculated and can range from 0 to 4. A IES-R total score can range from 0 to 88. Scores of  $\geq 24$  indicate clinically meaningful post-traumatic symptomatology and scores of  $\geq 33$  indicate probable PTSD.<sup>31</sup> In the current study, the Cronbach's alpha for the total score was 0.92.

**Symptom measures**—The 20-item Center for Epidemiological Studies-Depression scale (CES-D) was used to assess depressive symptoms.<sup>32</sup> Total scores can range from 0 to 60, with scores of  $\geq 16$  indicating the need for individuals to seek clinical evaluation for major depression. In the current study, its Cronbach's alpha was 0.89.

The 21-item General Sleep Disturbance Scale (GSDS) assesses the quality of sleep over the past week.<sup>33</sup> Each item was rated on a 0 (never) to 7 (everyday) numeric rating scale (NRS). The total GSDS score can range from 0 (no disturbance) to 147 (extreme sleep disturbance). A higher total score indicates greater levels of sleep disturbance. A total score of  $\geq 43$  indicates a clinically meaningful level of sleep disturbance.<sup>34</sup> In the current study, its Cronbach's alpha was 0.83.

The 18-item Lee Fatigue Scale (LFS) assesses physical fatigue and energy. Items are rated on a 0 to 10 NRS with higher ratings indicating greater fatigue and higher levels of energy, respectively.<sup>35</sup> Total fatigue and energy scores were calculated as the mean of the 13 fatigue items and the 5 energy items. Using two separate LFS questionnaires, patients rated the items in terms of how they felt within 30 minutes of awakening (i.e., morning fatigue, morning energy) and prior to going to bed (i.e., evening fatigue, evening energy). Established cut-off scores exist for clinically significant levels of fatigue (i.e., 3.2 for morning fatigue, 5.6 for evening fatigue) and energy (i.e., 6.2 for morning energy, 3.5 for evening energy).<sup>34</sup> In the current study, Cronbach's alphas were 0.96 for morning fatigue, 0.93 for evening fatigue, 0.95 for morning energy and 0.93 for evening energy.

The 16-item Attentional Function Index (AFI) assesses attentional function (i.e., perceived effectiveness with carrying out common activities that require directed attention).<sup>36</sup> Items were rated on a 0 to 10 NRS with a higher total mean score indicating greater capacity to direct attention. Attentional function can be grouped into categories using the total score (i.e., <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function). In the current study, its Cronbach's alpha was 0.93.

Brief Pain Inventory (BPI) evaluated pain occurrence.<sup>37</sup> Patients responded yes if they had pain. If they responded yes, they were asked to indicate the cause(s) of their pain (i.e., only cancer, only non-cancer, or both cancer and non-cancer related pain).

## Study Procedures

Study was approved by the Committee on Human Research at the University of California, San Francisco and by each study site. Eligible patients were approached by a research staff member in the infusion unit during their first or second cycle of chemotherapy to discuss study participation. Written informed consent was obtained from all patients. Data from the enrollment assessment were used in this analysis (i.e., prior to patients' second or third cycle of chemotherapy).

## Data Analysis

Descriptive statistics were generated for the demographic, clinical, and symptom characteristics and for the stress measures. All of the demographic, clinical, and symptom characteristics listed in Table 1 were evaluated in the stepwise linear regressions to determine which characteristics were associated with higher stress scores. Separate regression analyses were done for each of the stress measures (i.e., PSS total score, IES-R total score, IES-R intrusion, IES-R avoidance, IES-R hyperarousal). With 941 patients, one could evaluate a total of 94 potential predictors in each regression analysis (i.e., 941/10). For all the tests, a p-value of <.05 was considered statistically significant. All of the statistical analyses were done using SPSS version 27 (IBM Corporation, Armonk, NY).

## RESULTS

### Demographic, Clinical, and Symptom Characteristics

Patients in this study (n=941) were 56.6 ( $\pm$ 12.2) years of age and well educated. Most patients were female (77.6%), White (72.4%), and married or partnered (64.3%). At enrollment, patients were 1.9 ( $\pm$ 3.7; median 0.42) years from diagnosis, had a mean KPS score of 80.0 ( $\pm$ 12.2), a mean SCQ score of 5.4 ( $\pm$ 3.0), and a mean MAX2 score of 0.17 ( $\pm$ 0.08). The most common comorbidities were high blood pressure (29.5%), back pain (23.9%), and depression (19.0%). Types of cancers included: breast (39%), gastrointestinal (31.3%), gynecological (18.8%), and lung (10.8%) with 1.3 ( $\pm$ 1.2) metastatic sites including lymph nodes (Table 1).

The symptom severity scores are summarized in Table 1. Patients had a mean CES-D score of 12.8 ( $\pm$ 9.6), below the cutoff that suggests the need for further evaluation for major depression. The mean score of 52.9 ( $\pm$ 20.0) for sleep disturbance exceeded the clinically meaningful cutoff. Mean scores for both morning 3.1 ( $\pm$ 2.2) and evening 5.4 ( $\pm$ 2.1) fatigue approached the clinically meaningful cutoff. The mean AFI score of 6.4 ( $\pm$ 1.8) suggests a moderate level of attentional function. The majority of patients (55.6%) reported pain related to cancer and/or its treatment.

### Associations between Various Characteristics and Stress

The mean PSS score of the sample was 18.4 ( $\pm$ 8.1). The mean IES-R total score was 18.6 ( $\pm$ 12.9). The results of the five stepwise regression analyses are shown in Table 2.

**Characteristics Associated with Perceived Global Stress (PSS)**—Five characteristics (i.e., younger age, having child care responsibilities, higher number of metastatic sites, higher level of depressive symptoms, lower attentional function) were associated with a higher level of perceived global stress. The final model explained 54.9% of the total variance.

**Characteristics Associated with Cancer-Specific Stress (IES-R Total)**—Seven characteristics (i.e., being unmarried/unpartnered, higher number of metastatic sites, having gastrointestinal versus breast cancer, and higher levels of depressive symptoms, sleep disturbance, and evening fatigue, and the occurrence of pain) were associated with higher levels of total cancer-specific stress. The final model explained 41.6% of the total variance.

**Characteristics Associated with Avoidance (IES-R Avoidance)**—Six characteristics (i.e., being unmarried/unpartnered, fewer years of education, lower body mass index, lower treatment-related toxicity, and higher levels of depressive symptoms and evening fatigue) were associated with higher levels of avoidance. The final model explained 15.6% of the total variance.

**Characteristics Associated with Intrusion (IES-R Intrusion)**—Six characteristics (i.e., being unmarried/unpartnered, higher number of metastatic sites, higher levels of depressive symptoms and sleep disturbance, lower levels of attentional function and

occurrence pain) were associated with higher levels of avoidance. The final model explained 41.4% of the total variance.

**Characteristics Associated with Hyperarousal (IES-R Hyperarousal)**—Seven characteristics (i.e., younger age, living alone, higher levels of depressive symptoms, evening fatigue and sleep disturbance, lower levels of attentional function, and the occurrence of pain) were associated with higher levels of hyperarousal. The final model explained 49.1% of the total variance.

## DISCUSSION

This study is the first to evaluate for associations between a consistent and comprehensive set of demographic, clinical, and symptom characteristics and multiple dimensions of stress in a large sample of oncology patients with heterogeneous types of cancers. Congruent with our a priori hypothesis, several common and distinct characteristics were associated with measures of global and cancer-specific stress. Moreover, consistent with our a priori hypothesis and prior research,<sup>8</sup> our findings suggest that global and cancer-specific stress are distinct types of stress.

Our patients' mean scores on the PSS ( $18.4 \pm 8.1$ ) and the IES-R ( $18.6 \pm 12.9$ ) are comparable to previous findings among oncology patients undergoing chemotherapy. For example, in a study that examined the relationship between stress and quality of life subsequent to a cancer diagnosis and its treatment among breast cancer patients,<sup>6</sup> the mean PSS score was  $18.1 (\pm 6.9)$  with a range of 0–36. In another study of the associations between global and cancer-specific stress and symptoms among cancer survivors,<sup>38</sup> the mean PSS score was  $17.3 (\pm 8.9)$  and approximately 8.2% of survivors reported an IES-R score of  $>33$ . While the mean IES-R total score of our sample fell below the cutoff for probable PTSD, 29.4% of our patients had scores above the clinically meaningful cutoff score of 24.0 and 13.9% had scores of  $\geq 33.0$ , suggestive of probable PTSD. Taken together, our findings suggest that a significant proportion of our patients (i.e., 43.3%) were experiencing clinically meaningful levels of cancer-specific stress. Clinicians need to be aware that occurrence of PTSD symptoms warrants a referral for additional evaluation and psychological services if needed.

Except for the IES-R avoidance subscale (i.e., 15.6%), the remaining regression analyses explained between 41.6% (i.e., IES-R total score) and 54.5% (i.e., PSS score) of the total variance in the stress measures. As noted in one study,<sup>39</sup> compared to the IES-R intrusion and hyperarousal subscales, the items evaluated on the avoidance subscale do not fit the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for PTSD. While the avoidance subscale focuses on active avoidance strategies, the DSM clusters the symptoms of avoidance and emotional numbing together. Therefore, given the small amount of explained variance for the avoidance subscale, future research needs to include additional characteristics (e.g., coping strategies, personality, mental adjustment to cancer) to determine their relative contribution to the severity of this type of stress.



A higher level of depressive symptoms was the only characteristic that was associated with higher levels of stress across all our measures and made the largest contribution to the percentage of explained variance. Depression explained between 13.3% and 20.1% of the total variance in the stress scales. It should be noted that while the mean CES-D score of the sample was below the clinically meaningful cutoff, 31% of the patients had CES-D scores of  $\geq 16$ . While the other characteristics in the various models were statistically significant, they only explained less than 1% or not more than 3% of the total variance in the various stress scales. This finding is congruent with the growing body of evidence that describes linkages between stress and depression.<sup>40</sup> As noted in one review,<sup>40</sup> prolonged stress can produce maladaptive neuroendocrine changes that can lead to the development of depression. Findings from other studies suggest that given the variety of biological processes that link depressive symptoms with sustained stress responses (e.g., dysregulation of the hypothalamic pituitary axis and the immune system; excessive activation of the sympathetic nervous system and excitatory neurotransmitters; loss of neuroplasticity),<sup>11</sup> multiple feedback loops may occur that render it difficult to discern directionality. Taken together with our finding of a significant percentage of our patients with PTSD symptoms, clinicians need to assess for sources of significant stress, as well as depression during and following chemotherapy administration.

Relative to the associations between various demographic and clinical characteristics, a number of the most common symptoms associated with cancer and its treatments uniquely explained a higher percentage of the total variance in the various stress scales. Overall, our findings concur with previous studies that found positive associations between pain,<sup>15</sup> fatigue,<sup>16</sup> sleep disturbance,<sup>17</sup> cognitive impairment<sup>20</sup> and stress in patients with a variety of chronic conditions. In terms of global stress, our findings are congruent with previous studies that suggested that global stress from environmental factors cumulatively influences decrements in mental health and cognitive function.<sup>41</sup> Additional research is warranted to examine the potential impact of stress reduction strategies to improve mental health and cognition. However, clinicians can recommend a variety of stress reduction techniques (e.g., relaxation, meditation) to oncology patients and assess the effects of these interventions on stress, as well as overall symptom burden.

Our study found that, pain, fatigue, and sleep disturbance were associated with cancer-specific stress. Our findings are consistent with increasing evidence that demonstrates that these three symptoms as well as depressive symptoms often occur as a cluster<sup>42</sup> and are associated with cancer-specific stress. For example, in a study of patients with renal cell carcinoma,<sup>43</sup> symptoms of depression and cancer-specific post-traumatic stress were independently associated with fatigue and sleep disturbance. Moreover, the associations with these two symptoms were even stronger when depression and cancer-related post-traumatic stress co-occurred. In addition, our findings are consistent with studies that reported on the co-occurrence of pain and PTSD symptoms.<sup>44, 45</sup> Considered together, the positive associations between these frequently co-occurring symptoms and global and cancer-specific stress highlight the need for continued research to investigate their common and distinct mechanisms and directionality of the relationships.

In our study, the demographic characteristics associated with higher levels of global stress and cancer-specific stress were consistent with prior research. Similar to previous research that found an association between lower socioeconomic status and higher cancer-related distress,<sup>13</sup> we found an association between lower levels of education and higher levels of cancer-specific stress (i.e., higher IES-R Avoidance scores). These two demographic characteristics may be proxy measures for various social determinants of health that are known to be associated with higher levels of stress and poorer outcomes in oncology patients.<sup>46</sup>

In addition, as noted previously,<sup>12, 47</sup> younger age was associated with higher levels of global and cancer-specific stress. Extending prior findings, our analyses of the IES-R subscales suggest that younger age was associated with higher levels of hyperarousal but not with avoidance or intrusion. Living alone was associated only with higher levels of hyperarousal. Further research is needed to determine whether the associations between younger age and living alone and higher IES-R hyperarousal scores may reflect differences between younger and older adults in illness perceptions, coping, and social support that could lessen typical symptoms of hyperarousal (e.g., anger, reckless behavior, exaggerated startle, hypervigilance).

While prior studies found that not being married/partnered was associated with higher levels of both global and disease specific stress,<sup>12</sup> our findings suggest that this characteristic was associated with only cancer-specific stress (i.e., higher IES-R total, avoidance, and intrusion scores). This finding may be explained by the emotional and practical support (e.g., accompaniment to appointments, treatment decisions, household chores) provided by spouses or partners that may mitigate some of the stress related to a cancer diagnosis and its treatment.

Of note, having child care responsibilities was the only characteristic associated with higher levels of global stress. These responsibilities increase the pressures of daily life (e.g., increased financial burden, role overload, relationship conflict) and contribute to overall life stress.<sup>48</sup> Future research needs to evaluate the efficacy of interventions that support caregiving responsibilities in an effort to reduce stress during cancer treatment.

Limited research exists on the associations between clinical characteristics and stress. While in one study, no associations were found,<sup>14</sup> in other studies, decrements in functional status,<sup>13, 49</sup> increased number of comorbidities,<sup>13, 50</sup> receipt of chemotherapy,<sup>13</sup> and disease recurrence<sup>13</sup> were associated with higher levels of stress. Among the clinical characteristics evaluated in this study, a higher number of metastatic sites including lymph node involvement was the only characteristic associated with both global and cancer-specific stress. This finding is most likely explained by the fact that the presence of metastatic disease is associated with changes in treatment<sup>51</sup> and/or a poorer prognosis.<sup>52</sup> It is not readily apparent why a lower BMI and a lower MAX2 score (i.e., less toxic chemotherapy regimen) were associated with higher avoidance scores. These findings warrant confirmation in future studies.

## Limitations

Several limitations warrant consideration. While the sample size was large and heterogeneous in terms of types of cancer, our findings may not generalize to all oncology patients or to patients with other types of cancer (e.g., leukemia, lymphoma) because the patients were predominantly women who were White, well educated, and earned a relatively high income. Therefore, our findings warrant replication in samples that are more representative of racial and ethnic diversity, other social determinants of health, and other types of cancer. In addition, given that the major reason for refusal to participate was high levels of stress, our findings may be underestimating the impact of stress on patients with cancer. Because of its cross-sectional design, no definitive conclusions can be drawn about the directionality of the associations found between various characteristics and stress.

## Conclusions and Implications for Practice

In conclusion, our findings suggest that global stress and cancer-specific stress are distinct phenomena associated with both common as well as distinct demographic, clinical, and symptom characteristics. Depression was the only characteristic associated with both types of stress and all of the subscales of the cancer-specific stress measure. Given the relationship between higher levels of stress and worse outcomes, early assessments of and interventions for global and disease-specific stress are warranted. In addition, clinicians need to consider referrals for integrative approaches (e.g., mindfulness-based stress reduction, cognitive behavioral therapy, acupuncture) and/or psychological or social work services that may help to mitigate some of the complex relationships among psychological and physical symptoms and stress.

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## REFERENCES

1. Baritaki S, de Bree E, Chatzaki E, Pothoulakis C. Chronic stress, inflammation, and colon cancer: A CRH System-Driven Molecular Crosstalk. *J Clin Med.* 12 2019;8(10).
2. Moreno-Smith M, Lutgendorf SK, Sood AK. Impact of stress on cancer metastasis. *Future Oncol.* 2010;6(12):1863–1881. [PubMed: 21142861]
3. Cordova MJ, Riba MB, Spiegel D. Post-traumatic stress disorder and cancer. *Lancet Psychiatry.* Apr 2017;4(4):330–338. [PubMed: 28109647]
4. Langford DJ, Cooper B, Paul S, et al. Distinct stress profiles among oncology patients undergoing chemotherapy. *J Pain Symptom Manage.* 2020;59(3):646–657. [PubMed: 31711968]
5. Bower JE, Crosswell AD, Slavich GM. Childhood adversity and cumulative life stress: risk factors for cancer-related fatigue. *Clin Psychol Sci.* Jan 2014;2(1).
6. Golden-Kreutz DM, Thornton LM, Wells-Di Gregorio S, et al. Traumatic stress, perceived global stress, and life events: prospectively predicting quality of life in breast cancer patients. *Health Psychol.* 2005;24(3):288–296. [PubMed: 15898865]
7. Langford DJ, Cooper B, Paul S, et al. Evaluation of coping as a mediator of the relationship between stressful life events and cancer-related distress. *Health Psychol* 2017;36(12):1147–1160. [PubMed: 28825498]

8. Arnaboldi P, Riva S, Crico C, Pravettoni G. A systematic literature review exploring the prevalence of post-traumatic stress disorder and the role played by stress and traumatic stress in breast cancer diagnosis and trajectory. *Breast Cancer*. 2017;9:473–485. [PubMed: 28740430]
9. Shin KJ, Lee YJ, Yang YR, et al. Molecular mechanisms underlying psychological stress and cCancer. *Curr Pharm Des*. 2016;22(16):2389–2402. [PubMed: 26916018]
10. Kruk J, Aboul-Enein BH, Bernstein J, Gronostaj M. Psychological stress and cellular aging in cancer: A meta-analysis. *Oxid Med Cell Longev*. 2019;2019:1270397. [PubMed: 31814865]
11. Antoni MH, Dhabhar FS. The impact of psychosocial stress and stress management on immune responses in patients with cancer. *Cancer*. 2019;125(9):1417–1431. [PubMed: 30768779]
12. Miceli J, Geller D, Tsung A, et al. Illness perceptions and perceived stress in patients with advanced gastrointestinal cancer. *Psychooncology*. 2019;28(7):1513–1519. [PubMed: 31090125]
13. Syrowatka A, Motulsky A, Kurteva S, et al. Predictors of distress in female breast cancer survivors: A systematic review. *Breast Cancer Res Treat*. 2017;165(2):229–245. [PubMed: 28553684]
14. Gibbons A, Groarke A, Sweeney K. Predicting general and cancer-related distress in women with newly diagnosed breast cancer. *BMC Cancer*. 2016;16(1):935. [PubMed: 27914469]
15. Sager ZS, Wachen JS, Naik AD, Moye J. Post-traumatic stress disorder symptoms from multiple stressors predict chronic pain in cancer survivors. *J Palliat Med*. 2020;23(9):1191–1197. [PubMed: 32228350]
16. Weber D, O'Brien K. Cancer and cancer-related fatigue and the interrelationships with depression, stress, and inflammation. *J Evid Based Complementary Altern Med*. 2017;22(3):502–512. [PubMed: 30208733]
17. Dolsen MR, Crosswell AD, Prather AA. Links between stress, sleep, and inflammation: Are there sex differences? *Curr Psychiatry Rep*. 2019;21(2):8. [PubMed: 30729328]
18. Miaskowski C, Paul SM, Mastick J, et al. Associations between perceived stress and chemotherapy-induced peripheral neuropathy and ototoxicity in adult cancer survivors. *J Pain Symptom Manage*. 2018;56(1):88–97. [PubMed: 29524582]
19. Thakur M, Sharma R, Mishra AK, Singh KR. Prevalence and psychobiological correlates of depression among breast cancer patients. *Indian J Surg Oncol*. 2021;12(2):251–257. [PubMed: 34295067]
20. Henneghan A Modifiable factors and cognitive dysfunction in breast cancer survivors: a mixed-method systematic review. *Support Care Cancer*. 2016;24(1):481–497. [PubMed: 26416490]
21. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. 1983;24(4):385–396. [PubMed: 6668417]
22. Weiss DS, Marmar CR. *The Impact of Event Scale - Revised*. New York: Guilford Press; 1997.
23. Miaskowski C, Cooper BA, Aouizerat B, et al. The symptom phenotype of oncology outpatients remains relatively stable from prior to through 1 week following chemotherapy. *Eur J Cancer Care*. 2017;26(3).
24. Humphreys J, Janson S, Donesky D, et al. A middle range theory of symptom management. In: Smith MJ, Liehr PR, eds. *Middle Range Theory in Nursing*. 3rd ed. New York: Springer Publishing Company; 2014:141–164.
25. Karnofsky D *Performance scale*. New York: Plenum Press; 1977.
26. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Rheum*. 2003;49(2):156–163. [PubMed: 12687505]
27. Karnofsky D, Abelmann WH, Craver LV, Burchenal JH. The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer*. 1948;1:634–656.
28. Brunner F, Bachmann LM, Weber U, et al. Complex regional pain syndrome 1--the Swiss cohort study. *BMC Musculoskelet Disord*. Jun 23 2008;9:92. [PubMed: 18573212]
29. Cieza A, Geyh S, Chatterji S, Kostanjsek N, Ustun BT, Stucki G. Identification of candidate categories of the International Classification of Functioning Disability and Health (ICF) for a Generic ICF Core Set based on regression modelling. *BMC Med Res Methodol*. 2006;6:36. [PubMed: 16872536]

30. Extermann M, Bonetti M, Sledge GW, O'Dwyer PJ, Bonomi P, Benson AB 3rd. MAX2--a convenient index to estimate the average per patient risk for chemotherapy toxicity; validation in ECOG trials. *Eur J Cancer*. 2004;40(8):1193–1198. [PubMed: 15110883]
31. Creamer M, Bell R, Failla S. Psychometric properties of the Impact of Event Scale - Revised. *Behav Res Ther*. 2003;41(12):1489–1496. [PubMed: 14705607]
32. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*. 1977;1(3):385–401.
33. Lee KA. Self-reported sleep disturbances in employed women. *Sleep*. 1992;15(6):493–498. [PubMed: 1475563]
34. Fletcher BS, Paul SM, Dodd MJ, et al. Prevalence, severity, and impact of symptoms on female family caregivers of patients at the initiation of radiation therapy for prostate cancer. *J Clin Oncol*. 2008;26(4):599–605. [PubMed: 18235118]
35. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. *Psychiatry Res*. 1991;36(3):291–298. [PubMed: 2062970]
36. Cimprich B, Visovatti M, Ronis DL. The Attentional Function Index--a self-report cognitive measure. *Psychooncology*. 2011;20(2):194–202. [PubMed: 20213858]
37. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain*. 1983;17(2):197–210. [PubMed: 6646795]
38. Mazor M, Paul SM, Chesney MA, et al. Perceived stress is associated with a higher symptom burden in cancer survivors. *Cancer*. 2019;125(24):4509–4515. [PubMed: 31503333]
39. Beck JG, Grant DM, Read JP, et al. The impact of event scale-revised: psychometric properties in a sample of motor vehicle accident survivors. *J Anxiety Disord*. 2008;22(2):187–198. [PubMed: 17369016]
40. Tafet GE, Nemeroff CB. The links between stress and depression: Psychoneuroendocrinological, genetic, and environmental interactions. *J Neuropsychiatry Clin Neurosci*. 2016;28(2):77–88. [PubMed: 26548654]
41. Reid-Arndt SA, Cox CR. Stress, coping and cognitive deficits in women after surgery for breast cancer. *J Clin Psychol Med Settings*. 2012;19(2):127–137. [PubMed: 22231422]
42. Pud D, Ben Ami S, Cooper BA, et al. The symptom experience of oncology outpatients has a different impact on quality-of-life outcomes. *J Pain Symptom Manage*. 2008;35(2):162–170. [PubMed: 18082357]
43. Thekdi SM, Milbury K, Spelman A, et al. Posttraumatic stress and depressive symptoms in renal cell carcinoma: association with quality of life and utility of single-item distress screening. *Psychooncology*. 2015;24(11):1477–1484. [PubMed: 25690556]
44. Bosco MA, Gallinati JL, Clark ME. Conceptualizing and treating comorbid chronic pain and PTSD. *Pain Res Treat*. 2013;2013:174728. [PubMed: 23819047]
45. Fishbain DA, Pulikal A, Lewis JE, Gao J. Chronic pain types differ in their reported prevalence of post-traumatic stress disorder (PTSD) and there is consistent evidence that chronic pain is associated with PTSD: An evidence-based structured systematic Review. *Pain Med*. 2017;18(4):711–735. [PubMed: 27188666]
46. McCall MK, Connolly M, Nugent B, Conley YP, Bender CM, Rosenzweig MQ. Symptom experience, management, and outcomes according to race and social determinants including genomics, epigenomics, and metabolomics (SEMOARS + GEM): An explanatory model for breast cancer treatment disparity. *J Cancer Educ*. 2020;35(3):428–440. [PubMed: 31392599]
47. Avis NE, Levine BJ, Case LD, Naftalis EZ, Van Zee KJ. Trajectories of depressive symptoms following breast cancer diagnosis. *Cancer Epidemiol Biomarkers Prev*. 2015;24(11):1789–1795. [PubMed: 26377192]
48. Nomaguchi K, Milkie MA. Parenthood and well-being: A decade in review. *J Marriage Fam*. 2020;82(1):198–223. [PubMed: 32606480]
49. Wong ML, Paul SM, Cooper BA, et al. Predictors of the multidimensional symptom experience of lung cancer patients receiving chemotherapy. *Support Care Cancer*. 2017;25(6):1931–1939. [PubMed: 28160076]

50. Miaskowski C, Paul SM, Snowberg K, et al. Stress and symptom burden in oncology patients during the COVID-19 pandemic. *J Pain Symptom Manage.* 2020;60(5):e25–e34. [PubMed: 32889039]
51. Yin Z, Tang H, Li L, et al. Impact of sites versus number of metastases on survival of patients with organ metastasis from newly diagnosed cervical cancer. *Cancer Manag Res.* 2019;11:7759–7766. [PubMed: 31496818]
52. Wang R, Zhu Y, Liu X, Liao X, He J, Niu L. The Clinicopathological features and survival outcomes of patients with different metastatic sites in stage IV breast cancer. *BMC Cancer.* 2019;19(1):1091. [PubMed: 31718602]

**Table 1 -**

Demographic and Clinical Characteristics and Symptom Severity and Stress Scores of the Sample (n=941)

Characteristic	Mean (SD)
Age (years)	56.6 (12.2)
Education (years)	16.4 (3.0)
Body mass index (kg/m <sup>2</sup> )	26.1 (5.6)
Karnofsky Performance Status score	80.0 (12.2)
Number of comorbidities	2.3 (1.4)
SCQ score	5.4 (3.0)
Time since cancer diagnosis (years)	1.9 (3.7)
Time since cancer diagnosis (median, years)	0.42
Number of prior cancer treatments	1.6 (1.5)
Number of metastatic sites including lymph node involvement	1.3 (1.2)
Number of metastatic sites excluding lymph node involvement	0.81 (1.1)
MAX2 score	0.17 (0.08)
	% (n)
Gender	
Female	77.6 (730)
Male	22.4 (211)
Ethnicity	
White	72.4 (681)
Non-white	27.6 (260)
Married or partnered (% yes)	64.3 (605)
Lives alone (% yes)	22.2 (209)
Child care responsibilities (% yes)	23.2 (218)
Care of adult responsibilities (% yes)	7.1 (63)
Currently employed (% yes)	36.6 (344)
Income	
<\$30,000	16.4 (154)
\$30,000 to <\$70,000	21.1 (199)
\$70,000 to <\$100,000	16.7 (157)
\$100,000	45.8 (431)

Characteristic	Mean (SD)
Specific comorbidities (% yes)	
Heart disease	5.1 (48)
High blood pressure	29.5 (278)
Lung disease	10.8 (102)
Diabetes	8.2 (77)
Ulcer or stomach disease	4.5 (42)
Kidney disease	1.7 (16)
Liver disease	6.4 (60)
Anemia or blood disease	11.8 (111)
Depression	19.0 (179)
Osteoarthritis	11.2 (105)
Back pain	23.9 (225)
Rheumatoid arthritis	2.6 (24)
Exercise on a regular basis (% yes)	
	71.4 (672)
Smoking current or history of (% yes)	
	34.5 (325)
Cancer diagnosis	
Breast	39.0 (367)
Gastrointestinal	31.3 (295)
Gynecological	18.8 (177)
Lung	10.8 (102)
Type of prior cancer treatment	
No prior treatment	24.0 (222)
Only surgery, CTX, or RT	41.9 (388)
Surgery & CTX, or Surgery & RT, or CTX & RT	21.4 (198)
Surgery & CTX & RT	12.7 (118)
CTX cycle length	
14-day cycle	44.2 (416)
21-day cycle	49.0 (461)
28-day cycle	6.8 (64)
Emetogenicity of CTX	
Minimal/Low	19.2 (181)
Moderate	60.8 (572)
High	20.0 (188)
Antiemetic regimens	
None	7.0 (64)
Steroid alone or serotonin receptor antagonist alone	20.6 (189)
Serotonin receptor antagonist and steroid	48.9 (449)
NK-1 receptor antagonist and two other antiemetics	23.6 (217)



Characteristic	Mean (SD)
Symptom severity scores <sup>a</sup>	
Center for Epidemiological Studies-Depression Scale ( 16.0)	12.8 (9.6)
General Sleep Disturbance Scale ( 43.0)	52.9 (20.0)
Lee Fatigue Scale – Morning Fatigue ( 3.2)	3.1 (2.2)
Lee Fatigue Scale – Evening Fatigue ( 5.6)	5.4 (2.1)
Attentional Function Index (< 5 = low, 5–7.5 = moderate, > 7.5 = high)	6.4 (1.8)
Occurrence of pain related to cancer and/or its treatment (% yes)	55.6
Stress scale scores	
Perceived Stress Scale	18.4 (8.1)
Impact of Event Scale – Revised – Intrusion	0.90 (0.70)
Impact of Event Scale – Revised – Avoidance	0.93 (0.68)
Impact of Event Scale – Revised – Hyperarousal	0.66 (0.66)
Impact of Event Scale – Revised – Total score ( 24.0)	18.6 (12.9)

Abbreviations: CTX, chemotherapy; kg, kilograms; m<sup>2</sup>, meters squared; NK-1, Neurokinin-1; RT, radiation therapy; SCQ, Self-administered Comorbidity Questionnaire; SD, standard deviation.

<sup>a</sup>Numbers in parentheses indicate clinically meaningful cutpoints for the symptom and stress measures.

**Table 2 –**

Effects of Select Demographic, Clinical, and Symptom Characteristics on Stress Scores (n=941)

PERCEIVED STRESS SCALE – TOTAL SCORE					
Characteristic	R <sup>2</sup>	r	β	R <sup>2</sup> -change (sr <sup>2</sup> )	p-value
Overall	.549	---	---	---	<.001
Age	---	-.214	-.075	.005	.002
Child care responsibilities	---	.121	.056	.003	.018
Number of metastatic sites	---	.011	.047	.002	.033
Depressive symptoms	---	.709	.558	.194	<.001
Attentional function	---	-.575	-.226	.032	<.001
IMPACT OF EVENT SCALE - REVISED – TOTAL SCORE					
Characteristic	R <sup>2</sup>	r	β	R <sup>2</sup> -change (sr <sup>2</sup> )	p-value
Overall	.416	---	---	---	<.001
Married/partnered	---	-.052	.089	.007	.001
Number of metastatic sites	---	.021	.042	.002	.104
GI versus breast cancer	---	.040	.080	.005	.005
Depressive symptoms	---	.618	.565	.201	<.001
Sleep disturbance	---	.439	.160	.016	<.001
Evening fatigue	---	.191	-.078	.005	.006
Occurrence of pain (no versus yes)	---	-.221	-.057	.003	.030
IMPACT OF EVENT SCALE - REVISED – AVOIDANCE SUBSCALE SCORE					
Characteristic	R <sup>2</sup>	r	β	R <sup>2</sup> -change (sr <sup>2</sup> )	p-value
Overall	.156	---	---	---	<.001
Married/partnered	---	-.002	.080	.006	.009
Level of education	---	-.115	-.088	.007	.004
Body mass index	---	-.044	-.067	.004	.028
MAX2 score	---	-.036	-.069	.005	.023
Depressive symptoms	---	.356	.404	.133	<.001
Evening fatigue	---	.046	-.088	.007	.007
IMPACT OF EVENT SCALE - REVISED – INTRUSION SUBSCALE SCORE					
Characteristic	R <sup>2</sup>	r	β	R <sup>2</sup> -change (sr <sup>2</sup> )	p-value
Overall	.414	---	---	---	<.001
Married/partnered	---	-.046	.090	.008	<.001
Number of metastatic sites	---	.044	.078	.006	.002
Depressive symptoms	---	.612	.585	.181	<.001
Sleep disturbance	---	.443	.168	.018	<.001
Attentional function	---	-.337	.109	.007	.001
Occurrence of pain (no versus yes)	---	-.243	-.076	.005	.004
IMPACT OF EVENT SCALE - REVISED – HYPERAROUSAL SUBSCALE SCORE					

Characteristic	R <sup>2</sup>	R	β	R <sup>2</sup> -change (sr <sup>2</sup> )	p-value
Overall	.491	---	---	---	<.001
Age	---	-.189	-.057	.003	.019
Lives alone	---	.004	-.065	.004	.006
Depressive symptoms	---	.665	.501	.133	<.001
Sleep disturbance	---	.510	.183	.020	<.001
Attentional function	---	-.494	-.104	.006	.001
Evening fatigue	---	.249	-.069	.004	.009
Occurrence of pain (no versus yes)	---	-.075	-.269	.005	.002

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