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Perceived Stress Is Associated With A Higher Symptom Burden In Cancer Survivors

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Abstract

Background: While multiple co-occurring symptoms are a significant problem for cancer survivors, little is known about phenotypic characteristics associated with a higher symptom burden. Study purposes were to evaluate the occurrence, severity, and distress associated with 32 symptoms and examine phenotypic and stress characteristics associated with a higher symptom burden.

Methods: Cancer survivors (n=623) completed a demographic questionnaire, as well as, measures of functional status, comorbidity, and global (Perceived Stress Scale (PSS)) and cancer-related (Impact of Events Scale-Revised (IES-R)) stress. Memorial Symptom Assessment Scale (MSAS) was used to evaluate symptom burden. Multiple linear regression analysis was used to determine the phenotypic characteristics associated with a higher symptom burden.

Results: Mean number of symptoms was 9.1 (±5.2). Most common, severe, and distressing symptoms were lack of energy, problems with sexual interest/activity, and hair loss, respectively. Poorer functional status, a higher level of comorbidity, and a history of smoking, as well as higher PSS and IES-R scores were associated with a higher symptom burden. The overall model explained 45.6% of the variance in symptom burden.

Conclusions: While cancer survivors report a high number of co-occurring symptoms of moderate severity and distress, no disease or treatment characteristics were associated with a higher symptom burden. Clinicians need to assess for general and disease specific stressors and provide referrals for stress management interventions. Future studies need to examine the longitudinal relationships among symptom burden, functional status, and level of comorbidity, as well as the mechanisms that underlie the associations between stress and symptom burden.

Precis:

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Cancer survivors report a high number of co-occurring symptoms of moderate to severe intensity. Both general and disease-specific stressors are associated with a higher symptom burden.

Keywords

cancer survivor; symptoms; symptom burden; stress; functional status; comorbidity

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INTRODUCTION

Given that the number of cancer survivors in the United States is expected to reach 22.1 million by 2030,[1] increased emphasis is being placed on an evaluation of persistent adverse effects associated with its treatment.[2] Persistent fatigue, anxiety, depression, pain, sleep disturbance, and cognitive deficits are extremely common;[3] often co-occur;[4] and result in significant decrements in survivors' functional status and quality of life (QOL).[5] Given the growing number of cancer survivors, as well as recent reports of the negative impact of persistent symptoms,[6] a detailed evaluation of their symptom experience is warranted.

While emerging evidence suggests that multiple co-occurring symptoms are a significant problem, only three studies have evaluated multiple dimensions of symptom experience (i.e., occurrence, severity, and/or distress) in survivors with a variety of cancer diagnoses.[7–9] Among the three that evaluated symptom occurrence and severity,[7–9] fatigue,[9] pain,[8] and sleep disturbance[7] had the highest severity ratings. However, findings from two of these studies cannot be generalized to post treatment cancer survivors[7,9] because they included individuals who were receiving chemotherapy (CTX) and/or radiation therapy.

While more detailed information is needed on cancer survivors' symptom experience, the identification of phenotypic characteristics associated with a higher symptom burden warrants consideration. The identification of survivors who are at increased risk for a higher symptom burden will facilitate more timely symptom management interventions.[10] In a recent systematic review, that evaluated demographic and clinical characteristics associated with higher distress in breast cancer survivors,[11] younger age, being non-white, being unmarried, and having a lower socioeconomic status were the consistent demographic characteristics identified. In terms of clinical characteristics, having a higher number of comorbidities and functional limitations, as well as receipt of CTX, less time since completion of treatment, and disease recurrence were associated with higher levels of distress. Because the 42 studies included in this review evaluated only one symptom (i.e., psychological distress) and only breast cancer survivors, it is not clear if the associations identified generalize across survivors with heterogeneous cancer diagnoses and the extent to which they are associated with a higher symptom burden.

A growing body of evidence suggests that stress is a common experience among cancer survivors[12] and is associated with a higher symptom burden. While adaptive in the acute setting,[13] chronic stress can lead to persistent and more severe anxiety,[14]depression,[14] and pain.[15,16] Recent evidence suggests that increased levels of perceived stress were associated with the occurrence of CTX-induced peripheral neuropathy, hearing loss, and tinnitus.[16]

These preliminary findings suggest that the relationships between global and cancer-related stress and symptom burden in cancer survivors warrant additional evaluation.

While clinical experience suggests that some cancer survivors experience a high symptom burden, evidence to support this impression is extremely limited. Therefore, the purposes of this study, in a relatively large sample of cancer survivors (n=623), were to evaluate the occurrence, severity, and distress associated with 32 common symptoms and examine which phenotypic and stress characteristics were associated with a higher symptom burden (i.e., number of co-occurring symptoms).

METHODS

Survivors and Settings

The methods for the parent study, funded by the National Cancer Institute, are described in detail elsewhere.[17] Survivors who had completed their primary cancer treatment were recruited from throughout the San Francisco Bay area. Of the 1450 survivors who were screened, 754 were enrolled, and 623 completed the self-report questionnaires at home prior to their study visit.

Study Procedures

Survivors communicated their willingness to participate in our study by phone, email, or completion of an online screening questionnaire. Research nurses phoned these survivors, determined eligibility, and obtained phone consent. Survivors were sent and asked to complete the study questionnaires prior to their study visit. During the study visit, the research nurse obtained written informed consent and reviewed the study questionnaires for completeness.

Subjective Measures

Demographic and Clinical Characteristics - Survivors completed a demographic questionnaire, the Karnofsky Performance Status (KPS) scale,[18,19] and the 13-item Self-Administered Comorbidity Questionnaire (SCQ).[20] Survivors were interviewed to obtain information on their cancer diagnosis, previous and current cancer treatments, and concurrent medications. Medical records were reviewed for disease and treatment information.

The 14-item Perceived Stress Scale (PSS) provides a global evaluation of perceived stress due to life circumstances appraised as stressful over the course of the past week.[21] Total scores can range from 0 to 56 with higher scores indicating greater stress.[22] In our study, its Cronbach’s alpha was 0.91.

The 22-item Impact of Events Scale-Revised (IES-R) was used to measure stress associated with cancer and its treatment.[23,24] The total IES-R score can range from 0 to 88. For the total score, a score between 24 and 29 suggests a partial post traumatic stress disorder (PTSD) and a score of ≥ 37 indicates a high presence of post-traumatic symptomatology.[25–27] In our study, the Cronbach’s alpha for the IES-R total score was 0.92.

The valid and reliable Memorial Symptoms Assessment Scale (MSAS) was adapted to assess multiple dimensions of survivors' symptom experience and symptom burden.[28,29] For the 32 MSAS symptoms, survivors indicated whether or not they had experienced each symptom in the past week (i.e., symptom occurrence). If they had experienced the symptom, they were asked to rate its severity and distress. Symptom severity was rated on a 0 (none) to 10 (intolerable) numeric rating scale (NRS). Symptom distress was rated on a 0 (not at all distressing) to 10 (most distressing) NRS. In order to have a broader range of scores, the ratings of symptom severity and distress were changed from Likert scales to valid and reliable NRS.[30]

Data Analysis

Data were analyzed using the Statistical Package for the Social Sciences.[31] Descriptive statistics and frequency distributions were calculated for the phenotypic and stress characteristics. Occurrence rates were generated for each symptom and mean severity and distress scores were calculated for survivors who reported the symptom. To determine symptom burden, the total number of symptoms each survivor reported was calculated. Individual symptom severity and distress scores were categorized as mild (1 to 3), moderate (4 to 6), or severe (≥7) using cutpoints reported in the literature.[32]

Multiple linear regression analysis was used to evaluate for phenotypic and stress characteristics associated with a higher symptom burden. In the univariate analysis, associations between a number of phenotypic and stress characteristics[33] and the total number of co-occurring symptoms were evaluated. Only those characteristics with a p-value of <0.05 in the univariate analysis were evaluated in the multiple regression model.

RESULTS

Demographic and Clinical Characteristics

As shown in Table 1, survivors (n=623) were 60.1 (±11.2) years of age; 84.7% were female, 61.6% were married/partnered, 28.7% lived alone, and 20.6% had an annual household income of <$30,000. The majority was White (78.8%) and well educated (16.4 ±2.7 years). At enrollment, survivors were 4.7 (±4.8) years from their cancer diagnosis, had a mean KPS score of 85.7 (±10.6), and a mean SCQ score of 3.8 (±3.3). The most common comorbid conditions were: back pain (31.3%), osteoarthritis (26.0%), high blood pressure (24.4%), and depression (21.8%). Cancer diagnosis included: breast (55.7%), ovarian (8.7%), colon (8.0%), lung (3.0%), or other (24.6%). The majority of survivors underwent prior surgery (92.6%), radiation therapy (62.7%), and/or CTX (100%).

Symptom Occurrence, Severity, and Distress

The mean number of MSAS symptoms (out of 32) was 9.1 (±5.2; range 0 to 29; Table 1). Occurrence, severity, and distress scores for the 32 MSAS symptoms are summarized in Supplementary Table 1.). The most common symptom was lack of energy. The most severe symptom was problems with sexual interest/activity. The most distressing symptom was hair loss. The majority of symptoms were rated as moderately severe and distressing.

Rankings of Symptoms

The most common, severe, and distressing symptoms (Supplemental Table 2) were lack of energy, problems with sexual interest/activity, and hair loss, respectively. Only three symptoms ranked in the top ten across the three dimensions (i.e., pain, difficulty sleeping, numbness/tingling in hands/feet). All of the top ten severe and distressing symptoms were rated as moderately severe and distressing.

Characteristics Associated With Higher Symptom Burden

As shown in Table 2, of the eight characteristics that were significant in the univariate analysis, five (i.e., lower KPS score, higher SCQ score, higher PSS score, higher IES-R score, and a positive history of smoking) were significantly associated with a higher symptom burden. The final predictive model explained 45.6% of the variance in symptom burden.

DISCUSSION

This study is the first to describe multiple dimensions of co-occurring symptoms, as well as phenotypic and stress characteristics associated with a higher symptom burden in survivors who completed primary treatment for a variety of cancer diagnoses. While our survivors were an average of five years from their diagnosis, they reported very high symptom burden. On average, our survivors reported the co-occurrence of 9 out of 32 MSAS symptoms. Of note, among all the characteristics evaluated, higher levels of both global and cancer-related stress made the largest unique contributions to explaining the total variance in symptom burden.

In this study, approximately 70% of the survivors reported lack of energy (i.e., fatigue), pain, and difficulty sleeping. While these occurrence rates were similar to ratings from older (mean age 70 years)[34] and minority[8] breast cancer survivors (i.e., 75%−78% for fatigue, 72%−85% for pain, 62%−65% for difficulty sleeping), they are higher than previous reports that evaluated heterogeneous samples of disease free cancer survivors (e.g., 60% for fatigue,[35] 40% for pain,[36] 25%−59% for sleep disturbance[37]). Our higher occurrence rates may be partially explained by the fact that these survivors had received an average of three previous treatments and all of them had received neurotoxic CTX which are known to influence the occurrence of persistent symptoms.[17]

Consistent with a previous study,[2] approximately 15% of our survivors reported that their fatigue, pain, and sleep disturbance were severe and very distressing. Given these consistent findings, clinicians need to assess for these three symptoms on a routine basis and initiate appropriate interventions.

Of note, the total number of physical and psychological symptoms were relatively similar across all three dimensions evaluated. For example, three physical symptoms (i.e., pain, numbness and tingling in the hands and feet, sweats) were among the top ten most common, severe and/or distressing symptoms. Equally important, worrying, problems with sexual interest/activity and body image changes were among the top ten psychological symptoms (Supplemental Table 2). While our findings suggest that both physical and psychological symptoms warrant assessment, given that no studies were available for comparative purposes, these results warrant confirmation in an independent sample of cancer survivors.

Throughout the survivorship period, higher levels of stress may be related to the negative effects of persistent symptoms,[38] fears of disease recurrence,[39] and financial toxicity.[40] In this study, both global (i.e., PSS) and disease-specific (i.e., IES-R) stress were evaluated. The PSS evaluates non-specific stress or a feeling that one's life is unpredictable and overwhelming to a point that exceeds an individual's coping ability. This type of stress represents an individual's current levels of life stressor and may fluctuate over time. In our study, global stress uniquely explained 6.9% of the variance of symptom burden. As noted in our previous paper,[16] the mean PSS score reported by our survivors (i.e., 17.3 (±8.9) were similar to those reported by breast (11.6 (±7.9))[41] and prostate cancer survivors (17.9 (±8.1)).[42] Moreover, our findings are consistent with a longitudinal study of breast cancer survivors that found that higher levels of general stress were associated with greater physical symptom bother up to 16 months after the cancer diagnosis.[43]

The experience of a diagnosis of cancer and related treatments can lead to symptoms of post traumatic stress in 7.3% to 35.2% of cancer patients.[44] In our study, cancer-specific stress (i.e., total score on the IES-R) uniquely explained 3.2% of the variance in symptom burden. Similarly, among survivors of leukemia, higher levels of cancer-specific stress were associated with higher levels of depressive symptoms, sleep problems, and fatigue interference.[45] Of note, 8.2% of survivors in our study reported a IES-R total score of >33, the suggested clinically meaningful cut-off score for 'probable caseness' of a PTSD.[25] Among these 51 survivors, the number of co-occurring symptoms was 16.1 (±6.1) (as compared to 9.1 (±5.2) for the entire sample). In other words, survivors who reported very high levels of cancer-related stress experience almost twice the number of co-occurring symptoms. Clinicians need to assess for both general and disease specific stressors and provide referrals for stress management interventions.

A growing body of evidence suggests that a lower functional status and/or a higher level of comorbidity are associated with a higher symptom burden.[33,46–48] However, the relative contribution of a lower functional status and higher comorbidity to survivors' symptom burden was much smaller than the effects of stress (i.e., 3.0% and 0.9%, respectively). Given the cross-sectional nature of our study, additional research is warranted to evaluate the longitudinal relationships between changes in symptom burden, levels of comorbidity, and functional status among cancer survivors.

Several study limitations warrant consideration. Given the cross-sectional nature of the study, it is unknown whether the various symptoms and overall symptom burden were related to the cancer itself and associated treatments, to the normal aging process, and/or to co-occurring chronic conditions. However, both age and level of comorbidity were accounted for in the regression analysis. While no gender difference in symptom burden was found in the univariate analysis, given that the majority of the survivors were female, future studies need to evaluate for differences in symptom burden between male and female cancer survivors. Finally, in this study, symptom burden was defined as the total number of co-occurring symptoms reported on the MSAS. Given that no consensus exists on the definition of symptom burden,[2,3] this one was chosen because it is relatively easy to implement in clinical practice.

In summary, in this study, cancer survivors, an average of 5 years after treatment, reported a mean of nine co-occurring symptoms of moderate severity and distress. Higher levels of global and cancer-specific stress, lower functional status scores, and a higher level of comorbidity, accounted for most of the explained variance associated with a higher symptom burden. Of note, no disease or treatment characteristics were associated with a higher symptom burden. Moreover, findings from this study suggest that despite improvements in symptom management interventions, symptom burden remains high in cancer survivors. Research is warranted to evaluate the efficacy of symptom management interventions for these persistent, severe, and distressing symptoms. In addition, more comprehensive evaluations of the relationships between stress and the mechanisms that underlie these persistent and co-occurring symptoms may guide the development of more targeted symptom management interventions as well as stress management interventions.[49,50]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Phenotypic characteristics of cancer survivors

Demographic characteristics	**Mean (SD)**
Age (years)	60.1 (11.2)
Education (years)	16.4 (2.7)
	% (n)
Female	84.7 (527)
Married/partnered (% yes)	61.6 (374)
Lives alone (% yes)	28.7 (176)
Employed (% yes)	44.4 (276)
Ethnicity	
White	78.8 (491)
Non-white	21.2 (132)
Total annual household income	
<$30,000	20.6 (119)
$30,000 to $69,000	20.4 (118)
$70,000 to $99,999	17.8 (103)
≥ $100,000	41.2 (238)
Child care responsibilities (% yes)	15.1 (93)
Adult care responsibilities (% yes)	3.8 (22)
Clinical characteristics	Mean (SD)
Karnofsky Performance Status score	85.7 (10.6)
Body mass index (kg/m^2)	26.0 (5.4)
Total number of MSAS symptoms (out of 32)	9.1 (5.2)
Number of comorbidities	2.6 (1.9)
Self-Administered Comorbidity Questionnaire score (0 to 39)	3.8 (3.3)
Perceived Stress Scale score	17.3 (8.9)
Impact of Events Scale-Revised total score	12.9 (12.5)
Years since cancer diagnosis	4.7 (4.8)
Years since cancer diagnosis (median)	3.04
Number of prior cancer treatments	3.2 (1.0)
Prior surgery (% yes)	92.6 (575)
Prior chemotherapy (% yes)	100.0 (623)
Previous neurotoxic chemotherapy regimen	
Only platinum	24.3 (151)
Only taxane	48.2 (300)
Both platinum and taxane	27.5 (171)
Prior radiation therapy (% yes)	62.7 (387)
Prior hormonal therapy (% yes)	39.8 (246)
Current surgery (% yes)	0.2 (1)

Demographic characteristics	**Mean (SD)**
Current chemotherapy (% yes)	0.0 (0)
Current radiation therapy (% yes)	1.8 (11)
Current hormonal therapy (% yes)	32.3 (201)
Current targeted therapy (% yes)	6.3 (39)
Number of metastatic sites (out of 7)	0.7 (0.8)
Number of metastatic sites without lymph node involvement (out of 6)	0.2 (0.6)
	% (n)
Smoker (ever)	36.3 (224)
Exercise on a regular basis (% yes)	86.3 (535)
Occurrence of comorbid conditions (% and number of survivors who reported each comorbid condition from the Self-Administered Comorbidity Questionnaire)	
Osteoarthritis	26.0 (162)
Back pain	31.3 (195)
Depression	21.8 (136)
High blood pressure	24.4 (152)
Heart disease	6.4 (40)
Diabetes	5.3 (33)
Lung disease	5.3 (33)
Anemia or blood disease	5.5 (34)
Ulcer or stomach disease	3.5 (22)
Kidney disease	1.6 (10)
Rheumatoid arthritis	2.6 (16)
Liver disease	2.2 (14)
Cancer diagnosis Breast	55.7 (347)
Colon	8.0 (50)
Lung	3.0 (19)
Ovarian	8.7 (54)
Other*	24.6 (153)

Abbreviations: kg = kilogram; m^2 = meters squared; MSAS = Memorial Symptom Assessment Scale; SD = standard deviation

*Other cancer diagnoses include: bladder, head and neck, Hodgkin's and Non-Hodgkin's lymphoma, multiple myeloma, pancreatic, prostate, sarcoma, stomach, testicular, uterine, vaginal

Table 2.

Multiple linear regression model of predictors of higher symptom burden (i.e., number of co-occurring symptoms on MSAS scale)

Characteristic	**R^2**	**r**	**ß**	**R^2 change[*] (sr^2)**	**p-value**
Age		−.167	−.017	.001	.618
Ethnicity – Non-White		.124	.037	<.001	.255
Body mass index		.093	−.001	<.001	.980
History of smoking		.092	.084	.007	.009
Comorbidity (SCQ score)		.317	.113	.009	.002
Functional status (KPS score)		−.453	−.203	.030	<.001
Perceived stress (PSS score)		.571	.336	.069	<.001
Cancer-related stress (IES-R total)		.529	.229	.032	<.001
Percent of variance explained	45.6%				

[*] R^2 change = percentage of total variance uniquely explained by each characteristic included in the model.

Abbreviations: IES-R = Impact of Event Scale-Revised; KPS score = Karnofsky performance status score; MSAS = Memorial Symptom Assessment Scale; PSS = Perceived Stress Scale; SCQ = Self-Administered Comorbidity Questionnaire