

Symptom trajectories in posttreatment cancer survivors.

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Abstract:

Background: Cancer survivorship following cancer treatment is uncertain as physical and psychological sequelae related to the disease or its treatment may persist. However, little is known about the experience of symptoms after treatment.

Objectives: The purposes of this study were to (1) examine postchemotherapy (post-CTX) symptom trajectories in cancer survivors and (2) determine whether demographic characteristics predicted symptom trajectories.

Methods: One hundred patients who recently completed CTX for lung cancer, colorectal cancer, or lymphoma rated symptoms on an electronic patient care monitor system prior to ambulatory care visits. Latent growth curve analyses were conducted to examine the trajectories of pain, fatigue, sleep disturbance, distress, and depression for 16 months after initial CTX.

Results: Symptoms were present at the first follow-up visit following CTX ($P < .0001$) and persisted over 16 months. The depression trajectory was predicted by sex: males showed a convex curvilinear growth trajectory, whereas females showed a concave trajectory ($P < .05$). Higher distress was predicted by

younger age ($P < .05$).

Conclusions: Psychological and physical symptoms persisted over the 16-month period following CTX for the entire sample. Sex differences in coping could partially explain the different trajectories of growth for depression, but further studies are warranted. Younger patients may be more vulnerable for distress during this posttreatment phase.

Implications for Practice: The posttreatment surveillance plan for cancer survivors should include a comprehensive assessment of psychological and physical symptoms. Persistence of symptoms can be expected in some patients, and supportive interventions should be tailored according to symptom reports.

Keywords: cancer | cancer survivors | post treatment cancer patients | cancer treatment | post chemotherapy symptoms | lung cancer | colorectal cancer | lymphoma

Article:

More than 10 million cancer survivors live in the United States. Cancer survival rates have tripled over the past 30 years, primarily due to earlier detection and advances in cancer treatment.¹ Cancer survivorship is a dynamic experience that ebbs and flows through various phases and transitions. One of the most challenging and worrisome transitions is the one from active cancer treatment to follow-up. Even though cancer treatment is either temporarily or permanently completed, patients may continue to experience physical and psychosocial sequelae associated with cancer and its treatment.² According to the National Coalition for Cancer Survivorship and the National Cancer Institute's Office of Cancer Survivorship, a cancer survivor is any individual who has been diagnosed with cancer.³ This trajectory extends from the time of diagnosis throughout the balance of one's life. For this study, posttreatment survivors were considered those individuals who have completed primary cancer treatment, regardless of stage of disease.

Pain, fatigue, and sleep disturbance are common adverse effects in posttreatment survivors.^{2,4,5} Symptoms can be related to the disease itself, cancer treatment, or a nonmalignant cause. A handful of studies have evaluated the physical symptoms of cancer survivors. Patients with a history of breast cancer⁶ and Hodgkin disease⁷ reported fatigue for months after the completion of therapy. Disease-free patients with rectal cancer experienced residual pain and constipation.⁸ Sixty-two percent of lung cancer survivors had postthoracotomy pain 6 months after surgery,⁹ and insomnia was reported by 30% of cancer survivors up to 11 years after diagnosis.¹⁰ These cross-sectional studies measured symptoms at varying time points and did not examine the

intensity or trajectories of symptoms along the survivorship trajectory. Only 1 cross-sectional study was found that reported fatigue intensity among a physically active cohort of survivors in active treatment and posttreatment.¹¹ Mean levels of fatigue were reported at 3.0 (scale range from 1= not at all to 5= extremely).

Psychological effects including depressed mood and distress are additional concerns during the treatment transition. Fear of recurrence, financial distress, changes in family dynamics, and uncertainty about the future all contribute to the emotional distress of the survivor.² Depressed mood and distress may also contribute to more intense fatigue and sleep disturbances.^{2,5} In fact, psychological morbidity was shown to persist in some posttreatment cancer survivors. For example, survivors of colorectal cancer and Hodgkin disease were found to be at increased risk for psychological distress.^{12,13} Other studies found that individual characteristics such as younger age, preexisting depressed mood, distress, other comorbidities, and a lack of social support predicted the presence psychological morbidity in patients with breast cancer¹⁴⁻²¹ and prostate cancer.²²⁻²⁴

Only 2 longitudinal studies examined symptoms in posttreatment survivors. Higher stage of disease, more comorbidities, and lung cancer were significant predictors of pain and fatigue in elderly cancer survivors in the year after their cancer diagnosis.²⁵ Another study found 5 distinct patterns of depressed mood in women with breast cancer who were evaluated after treatment and at 3 and 6 months. In addition, an increased number of children at home predicted more depressed mood.²⁶

Although pain, fatigue, sleep disturbance, depression, and distress are reported symptoms in posttreatment survivors, little research is available regarding the intensity and posttreatment trajectories of these symptoms over time. Understanding how symptoms change in the immediate posttreatment period, whether they worsen or improve over time, the rate or type of change that occurs, and which patients are at higher risk for persistent symptoms can assist clinicians in prevention and management strategies during the posttreatment follow-up period.

Furthermore, this study examined symptoms among cancer survivors with 3 cancer diagnoses (ie, lung cancer, colorectal cancer, lymphoma) that have not been investigated routinely. The 3 types of cancer in this study comprise 31% of all malignancies²⁷ in all stages of disease. The incidence and survival rates for these 3 malignancies are increasing, even in late-stage disease. The increase in 5-year survival for all stages of lung cancer is modest, 13% to 16% in the last 30

years, but survival is increasing in earlier stages of the disease. The 5-year survival rate of non-Hodgkin lymphoma and colorectal cancer is 65%, making colorectal cancer survivors the third largest cancer survivorship population. Finally, as previously reported, the transition period from primary cancer treatment to cancer surveillance is an especially vulnerable transition period for cancer survivors and warrants further investigation.²⁷

Therefore, the aims of this study were (1) to examine the postchemotherapy (post-CTX) symptom experience (ie, pain, fatigue, sleep disturbance, depressed mood, distress) for the first 16 months after treatment in patients who were newly diagnosed with lymphoma, colorectal cancer, or lung cancer and (2) to determine whether demographic (ie, age, sex, race and ethnicity, marital status, education, religion) and clinical characteristics (ie, co-morbid conditions, type of cancer, stage of disease, type of therapy) predicted trajectories of symptom change. This study used latent growth curve analyses (LGCAs) to answer the following research questions:

(1) What was the baseline mean (intercept) and trajectory (mean, intercept, slope, or quadratic curve) for each symptom for the entire sample?

(2) What was the average trajectory of change and degree of interindividual variation for the posttreatment symptoms?

(3) To what extent were demographic and clinical characteristics associated with posttreatment trajectories (intercept, slope, or quadratic term)?

Theoretical Framework

The Symptoms Experience Model 28 served as the theoretical framework for this study. The model takes into account the global cancer symptom experience. Antecedents of the model include demographic characteristics that can affect the symptom experience such as age, sex, and race/ethnicity. Other antecedents include disease characteristics such as the type of cancer, the cancer treatment, and related medical factors including comorbid conditions. Together, the antecedents influence or moderate input into the symptom experience. The symptom experience, individually defined by the patient, includes characteristics such as frequency, intensity, distress, and meaning. The symptoms in this study included pain, fatigue, depressed mood, distress, and sleep disturbances. Although not included in this study, the consequences of the Symptoms

Experience Model include overall adjustment to the illness, quality of life, functional status, disease progression, and survival.

Patients and Methods

Sample

The sample included 100 patients with lung cancer (n = 41), colorectal cancer (n = 28), or lymphoma (n = 31) who received CTX at the Hematology Oncology Centers of the Northern Rockies outpatient clinic from June 2004 through March 2007. These malignancies were chosen because of similar age and sex distributions and because few studies have examined symptoms specific to these malignancies. Although the sample used in this study was limited to 1 outpatient oncology clinic, it included the entire population of clinic patients who recently had completed CTX for the 3 diagnoses. Patients self-reported symptom data in the waiting room prior to an ambulatory visit on a handheld electronic patient care monitor (PCM).

The initial sample consisted of 532 patients who represented 4287 points in time, screened for the following inclusion criteria: (1) patients who had completed an initial course of CTX for newly diagnosed lymphoma, colorectal cancer, or lung cancer and (2) patients who had at least 4 measures after the completion of CTX in the PCM database. Patients excluded from the study were those whose surveillance visits were not associated with initial CTX and whose CTX course and cycle records were not available.

Data Collection Tool

The data set was part of the AIM (Assessment Information Management) Higher clinical initiative to improve the assessment, documentation, and management of cancer symptoms in adult outpatients.²⁹ The initiative includes a unique data collection system in which patients rate symptom experiences via a handheld electronic tablet called the PCM. Table 1 includes an overview of the data-entry procedures. The PCM has undergone rigorous psychometric testing. Internal consistency was examined for 6 subscales and for the total quality-of-life scale of the PCM. Cronbach [alpha] ranged from .80 to .89.³⁰ Hematology Oncology Centers of the Northern Rockies was an initial [alpha] site for this initiative and began data collection in June 2004. The program is now a part of Supportive Oncology Services.

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Patients entered demographic and disease-related variables into the PCM at the initial outpatient visit. Nine of these variables were used in this study: age, sex, type of cancer, stage of disease, comorbidities, marital status, education level, race, and religion. Comorbidities were verified through chart review. A total of 38 physical and psychological symptoms were entered into the original PCM that underwent 2 revisions, which resulted in 86 items. Patients self-reported symptoms in the PCM during each outpatient visit but no more than once every 2 weeks. Each symptom was rated on a scale from 0 to 10, with 0 = not a problem, 1 to 3 = mild problem, 4 to 6 = moderate problem, 7 to 9 = severe problem, and 10 = as bad as possible. The numeric ratings appeared on the screen in conjunction with verbal anchor cues. Pain, fatigue, and sleep disturbance were measured using a single item. Depressed mood (7 items) and distress (4 items) were measured using 2 separate subscales. The subscales were converted to normalized T scores based on a comparative reference group of heterogeneous ambulatory oncology patients (n = 449) from the West Clinic in Memphis, Tennessee.³¹

Data Download and Cleaning

Following approval from the Inter-institutional Review Board of Billings, Montana, the data were downloaded to the principal investigator's locked personal computer into SPSS for Windows. The download included 532 patients with lung cancer, colorectal cancer, or lymphoma representing 4287 points in time. Patients in the database were matched to paper and other electronic records at the Hematology Oncology Centers of the Northern Rockies clinic. These records were screened by hand for inclusion criteria. Reasons for ineligibility were wrong diagnosis (n = 27), treated for relapsed disease (n = 53), no CTX (n = 222), unavailable CTX cycle data (n = 37), and less than 3 follow-up visits post-CTX (n = 91). For eligible patients, 3 additional time points were inserted into the database and indicated (1) CTX cycle number, (2) the day of each CTX cycle, and (3) follow-up visits after initial CTX. An Access (Microsoft) database was created to manage variables not included in the PCM such as types of CTX, medications, and stage of disease.³² Additional data were extracted from the paper record including verification of comorbidities, stage of disease, and type of therapy (ie, CTX, radiation therapy, combined therapy).

Because of the variability in surveillance times for each patient, data were reviewed for temporal distances between visits. Consideration was made for various follow-up schedules and the potential for late visits. The goal was to retain data for as many posttreatment visits as possible for the 16-month follow-up period. The final follow-up periods were included as time points in

the analysis: 2 to 6 weeks, 6 to 14 weeks, 14 to 28 weeks, 28 to 42 weeks, 42 to 56 weeks, and 56 to 70 weeks. If 2 visits were conducted within the follow-up period, the earliest visit was discarded, and the later visit was retained due to programming restraints in MPlus.³³

Statistical Analysis

Descriptive statistics and LGCAs were conducted using SPSS 12.0 for Windows 34 and MPlus 5.0,³³ respectively, to answer the research questions in this study. The means, SDs, and variance for each symptom were examined during each surveillance interval. Latent growth curve analyses were used to examine posttreatment symptoms and to determine if demographic or disease-related characteristics predicted distinct symptom trajectories. The first surveillance visit following treatment represented the intercept of the growth curve for each patient. The rate of change for each symptom over the surveillance periods was measured by the linear (slope) or quadratic parameter depending on the shape of the growth trajectory.

Initially, the 5 continuous individual symptom variables (ie, pain, fatigue, sleep, depressed mood, distress) were modeled unconditionally, that is, without the influence of predictor variables. The intercepts were fixed to zero and represented time 1 (ie, 2 to 6 weeks after the last CTX treatment). Linear and quadratic models were compared for best fit according to recommendations in the literature.³⁵⁻³⁹ A nonsignificant $[\chi]^2$ value, a comparative fit index greater than 0.90, and a Tucker Lewis Index greater than 0.95 were used as the fit statistics with the greatest weight. A Tucker Lewis Index of greater than 1 was a potential sign that the model was overfit. Other fit measures included root-mean-square error of approximation of less than 0.06 for a good fit and 0.06 to 0.08 for a fair fit and a standard root-mean-square residual of less than 0.08.

Each of demographic and clinical characteristics was individually loaded into the symptom models to test for covariation. Specifically, these conditional models examined potential predictors of the posttreatment symptom trajectories. Age, comorbidities, and stage of disease were entered as continuous variables. All other variables (ie, sex, type of cancer, marital status, educational level, race and ethnicity, religion) were categorical, which resulted in collapsing some variables. Those collapsed and recoded included type of cancer coded as lung cancer or not, married/partnered or not, white or nonwhite and Hispanic, and high school diploma or less versus more than high school. The significance level for the unconditional and conditional models was set at $P < .05$.

Results

Patient and Clinical Characteristics

The demographic and clinical characteristics of the sample are included in Table 2. Slightly more males than females (56% vs 44%) were included in the sample, with a mean age of 62.9 (SD, 12.63) years (range, 24-84 years). More than half were married or partnered (67%), and the majority was white (91%). A high-school degree or less existed in 57% of the sample. More than one-third of the patients had lung cancer (41%), and 42% of the patients had stage IV cancer. The mean number of comorbidities for the sample was 2.24 (range, 0-6); 73% of the sample had at least 1 comorbidity. The most common comorbidities were hypertension (31%), gastric problems such as gastrointestinal esophageal reflux disorder (21%), cardiac problems (18%), and chronic obstructive pulmonary disease (14%). Whereas 70% of the patients had received CTX alone, 18% received concurrent CTX and radiation therapy, and 12% had received radiation therapy during this follow-up. CHOP (cyclophosphamide, doxorubicin, oncovin, prednisone) with or without rituximab was the most common CTX used for patients with lymphoma. For colorectal cancer, FOLFOX (5-FU, oxaliplatin, and leucovorin) and less commonly FOLFIRI (5-fluorouracil, irinotecan, leucovorin) were given for colorectal cancer. Lung cancer had the greatest variability of CTX regimens administered and included cisplatin/etoposide, carboplatin/paclitaxel, carboplatin/docetaxel, and cisplatin/carboplatin. Avastin was also used in conjunction with some of the lung cancer regimens.

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Symptom Intensity Post-CTX

Table 3 includes a summary of the percentage of patients with each symptom along with the means and SDs of symptom severity scores over the follow-up times. Depressed mood scores stayed close to the normalized mean of 50 (SD, 10) for the entire sample. However, variance (range, 58.71-84.56) was statistically significant, which suggests that some patients were depressed. Distress scores were also not significantly different from the mean of 50. However, the distress scores exhibited greater variance (range, 92.53-109.03) than depressed mood scores. The highest level of fatigue was reported at time 1, the first follow-up visit after CTX. Whereas fatigue and pain scores fluctuated throughout the follow-up times, the overall trend decreased over time (2.25 to 1.70 for fatigue and 3.87 to 2.67 for pain). Interestingly, pain had the highest

mean score of any symptom at time 1. The mean scores for sleep disturbance were less than 2 for all follow-up times and had less variability over time than the other symptoms.

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Fit Statistics for the Growth Curve Models

Growth curve modeling for each symptom was conducted in MPlus 5.0,33 and linear and quadratic models were compared for best fit. Fit statistics were examined to determine whether data fit a linear or quadratic pattern. Model fit was unstable over 6 points in time for depressed mood, fatigue, and sleep disturbance. These models were rerun using the first 4 and 5 time points. Depressed mood showed a good quadratic fit over 4 time points. Both fatigue and sleep disturbance resulted in a linear fit over 4 follow-up time points. Models for distress and pain were stable over 6 points in time. Whereas distress demonstrated a quadratic growth trajectory, pain showed a linear growth.

Unconditional Symptom Models

Table 4 lists the estimates, SEs, and levels of significance for the unconditional models, that is, the data modeled without predictor variables. Intercepts were significant ($P < .0001$) for all symptoms indicating a significant presence of symptoms at the intercept (time 1 follow-up). Significant variances at the intercepts ($P < .01$) occurred for all symptoms except for sleep disturbance, which suggests a high degree of interindividual variability in symptoms at the intercept or a wide range of intensity scores.

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None of the symptom slope or quadratic terms were significantly different from zero. This finding indicates a lack of change in symptom severity scores during the posttreatment trajectory. Interpretation of this finding suggests that symptom intensity persisted throughout the posttreatment follow up visits for the entire sample. The variance was significant for the quadratic estimates for depressed mood ($P < .01$) and distress ($P = .02$) and for the slope of fatigue ($P < .01$), which indicates interindividual variability around the posttreatment trajectories. Therefore, a wide range of symptom intensity was experienced by the sample. The variability in depressed mood scores is illustrated in Figure 1 as an example of individually varying trajectories. Figure 1A illustrates the variability of the depressed mood trajectories of 10 patients. Because of the normalized T scoring, there is a floor effect for depressed mood at 42.92,

indicating all zeros in the responses for depressed mood. Figure 1B illustrates the variability in the depressed mood scores for the entire sample.

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Conditional Symptom Models: Predictors of Symptom Trajectories

Depressed Mood

Conditional models were constructed on each symptom to determine whether covariates predicted the posttreatment growth curve symptom trajectories (Table 5). The quadratic growth curve for depressed mood was predicted by sex ($P < .05$). As shown in Figure 2, the shape of the trajectory for men was convex curvilinear, indicating an increase in depressed mood initially and then a decrease by time 4 (42 weeks). Women had an opposite concave curvilinear trajectory with depressed mood scores decreasing initially and then increasing by the end of time 4. Variance in depressed mood scores at time 1 (intercept) was predicted by race ($P < .05$). White patients had a mean depressed mood score of 47.68 (SD, 7.52) compared with nonwhite and Hispanic patients ($n = 9$), whose mean depressed mood score at time 1 was 54.54 (SD, 10.91) (Table 6).

Table 5-6 and Figure 2 have been omitted from this formatted document.

Distress

Age was a significant predictor of distress at time 1 ($P < .01$). For each 1-year increase in age, distress scores decreased by 0.58. The mean distress score at time 1 for patients younger than 65 years was 48.74 (SD, 9.72), whereas the mean score for those older than 65 years was 44.61 (SD, 9.16).

Pain

Significant predictors of pain intensity at the intercept were cancer diagnosis and stage of disease ($P < .001$ and $P < .05$, respectively). Patients with lung cancer had a mean pain score of 4.88 (SD, 2.03) at the intercept compared with a mean pain score of 2.94 (SD, 2.11) in patients with colorectal cancer and lymphoma. Pain was also highest in those with stage III (mean, 4.16; SD, 2.11) and stage IV (mean, 4.13; SD, 2.36) disease compared with patients with stage I (2.67; SD, 1.15) and stage II (mean, 2.7; SD, 2.16) disease. Race/ethnicity also predicted pain intensity at the intercept ($P < .05$). Nonwhite and Hispanic patients had a mean pain score of 5.11 (SD, 2.47) compared with white patients (mean, 3.68; SD, 2.21). Upon further examination, no

demographic or clinical differences were found between nonwhite and Hispanic patients and white patients in regard to type of cancer or stage of disease.

Fatigue

Fatigue was not predicted by any of the demographic characteristics evaluated in this study.

Sleep Disturbance

Race ($P < .05$) and religion ($P < .01$) were significant predictors of fatigue severity at the intercept. White patients had a mean score of 1.25 (SD, 2.0), and nonwhite and Hispanic patients had a mean score of 2.22 (SD, 2.82). The patients who claimed no religion or a non-Catholic or non-Protestant faith had a mean sleep disturbance score of 3.15 (SD, 3.31) compared with Catholic and Protestant patients, who had a mean score of 0.96 (SD, 1.77).

Discussion

This study examined symptom trajectories of pain, fatigue, sleep disturbance, depressed mood, and distress in posttreatment cancer survivors and investigated whether demographic and disease-related variables predicted the distinct posttreatment symptom growth curve trajectories. Unlike previous research, this longitudinal study used a clinical symptom monitoring tool (PCM) and used LGCA to examine symptoms after CTX treatment beyond the first year of posttreatment survival.

None of the linear or quadratic terms were significant for the entire sample, indicating that the trajectories were not significantly different than zero. These near-flat line trajectories suggest that overall symptom severity scores remained the same over the 16-month posttreatment period. However, all of the symptoms, except sleep, demonstrated significant variance in the intercepts and/or growth trajectories, which suggests a large amount of interindividual variability in these symptom trajectories. This finding is similar to those reported by Miaskowski and colleagues⁴⁰ for fatigue in patients who underwent radiation therapy for prostate cancer.

The quadratic shapes for depressed mood were significantly predicted by sex. Whereas men had an increase in depressed mood at midyear after treatment (convex curve), women exhibited a

decrease in depressed mood at midyear (concave curve) (Figure 2). Further exploration of this phenomenon revealed no significant differences in diagnosis between men and women, but significantly more men had stage IV disease. It is possible that the different trajectories are due to different stages of disease or differences in coping and psychological adjustment between men and women in respect to uncertainty about the future, fear, role adjustment, finances, and other survivorship issues.

The published literature sheds some light on sex differences in depression in oncology patients, but findings are inconsistent.⁴¹ Some studies reported no sex differences in the prevalence^{42,43} or severity^{41,44} of depression, whereas others found an increase in the prevalence of depression in women when compared with men.^{43,45} Two studies reported more depression in elderly women.^{46,47} A handful of other studies also examined long-term depression and psychological adjustment in cancer survivors, but none reported information on sex differences.^{26,48,49} Further investigation regarding sex differences in oncology patients' depression trajectories is warranted. Depressed mood was also predicted by race/ethnicity. However, the small number of nonwhite and Hispanic patients limits discussion and comparison with other studies of diverse populations.

Distress was predicted by a younger age at the first follow-up visit. The transition from treatment to posttreatment survivor was noted as a time of significant distress in the Institute of Medicine report, "From Cancer Patient to Cancer Survivor: Lost in Transition."² In addition, previous findings suggest that younger age is a risk factor for distress and psychological adjustment following a cancer diagnosis.^{14,18,22,50} However, these studies consisted of patients with breast cancer, study designs were cross-sectional, and only 1 study examined patients after treatment.¹⁸

Although pain decreased slightly over time for the entire sample, this downward trend was not statistically significant. Given et al²⁵ found that pain and fatigue decreased over time in the first year after diagnosis. Samples and methodologies of the studies are different in that Given et al²⁵ included elderly oncology patients with various cancer diagnoses and reported pain prevalence, whereas this study reported pain intensity in 3 specific diagnoses without age limitation.

The mean pain score of 3.87 at the first follow-up visit posttreatment was the highest intensity of any symptom. It is unknown whether this pain was disease related, treatment related, or related to a nonmalignant cause. However, 42% of patients had stage IV disease, and pain was predicted

by a higher stage of disease and by lung cancer in this study. Whereas advanced disease may be an explanation for the increased pain intensity, a study by Senturk et al 9 found that 62% of lung cancer survivors 6 months after surgery experienced postthoracotomy pain, and residual pain and constipation were found to be a long-term effect in patients with rectal cancer.⁸ In addition, many CTX agents used to treat the 3 malignancies in this study are neurotoxic.⁵¹⁻⁵⁵ One study noted an occurrence rate of 38% for sensory neuropathy in a group of patients treated for lung cancer.⁵⁶ It is unknown whether patients interpreted neuropathy as pain in their PCM symptom reports, but more studies are needed to determine the types of pain that patients experience after treatment. Patients in this study received a variety of neurotoxic agents including cisplatin, oxaliplatin, vincristine, paclitaxel, and docetaxel.

Pain intensity was predicted by younger age at the intercept in this study. One published study examined the age-related experience of pain, nausea, and vomiting in patients with cancer and found that elderly patients reported less severe symptoms, although the correlations between age and symptoms were moderate to weak (pain, $r = -0.22$; nausea and vomiting, $r = -0.43$).⁵⁷ It is possible that a response shift occurs in the elderly as they learn to live with cancer and its associated sequelae,⁵⁸ although more research is needed in this area.

A higher pain intensity score was significantly predicted by nonwhite race and Hispanic ethnicity at the first follow-up visit. This finding is consistent with previous reports that minority patients report more pain than white patients.^{59,60} For example, Beck and Falkson⁶⁰ found that blacks had a higher prevalence of pain (56.1% compared with 29.4%), and 81% of blacks experienced moderate to severe pain compared with 65% of whites. However, generalizability is limited because of the small number of nonwhite and Hispanic patients in the study.

Sleep disturbance was the only symptom to show a slight increase over the 16 months of this study, but the trajectory of sleep disturbance was not significantly different than zero. It is important to note that pain, depressed mood, and sleep disturbance were predicted by race/ethnicity in this study. Other studies have noted that these symptoms often coexist.^{44,61-63} Interestingly, race/ethnicity did not predict fatigue, another symptom often found within that cluster, but overall fatigue intensity was higher for nonwhite and Hispanic patients. However, this analysis did not cluster patients, an important difference in study designs. Because the slopes of the 3 symptoms in this study were not significantly different from zero (flat line trajectory), nonwhite and Hispanic patients had more intense symptoms throughout the follow-up periods.

Although this study has presented some significant findings, several limitations are noted. First, although the time points were used to identify follow-up visits, the analysis could incorporate only 1 visit per follow-up time, which led to the loss of some data. More frequent assessments may result in different symptom trajectories. Second, although the heterogeneity of the sample increased generalizability, the different stages of disease and the wide array of CTX regimens and symptom management medications used may have influenced the results, and these variables were not included in the analysis. In particular, the CTX agents may have contributed to different pain, fatigue, and sleep disturbance trajectories. Third, a lack of racial and ethnic diversity was a limitation in this study. Whereas 91% of the patients were white, this distribution is representative of the Montana population. Therefore, study findings regarding race and ethnicity should be interpreted cautiously.

Finally, the depressed mood and distress scales use normalized T scores that can be difficult to interpret. Because they are normalized according to a cancer population, it may appear that the sample was not distressed or depressed. However, on closer look, the significant variance indicated that there was a wide range of growth trajectories for individual patients, with some being distressed or depressed. Approximately 7% to 9% of the sample had a score of 1.5 SD above the depressed mood and distress means, respectively.

Future opportunities for research are plentiful. First, the sex differences in depressed mood trajectories warrant further investigation. Studies that examine specific aspects of psychological adjustment such as financial stress, work-related issues, and coping styles should be conducted. Second, the majority of growth trajectory parameters (slope and quadratic) were not significantly different from zero, indicating a flat curve. This finding suggests that for many patients, symptoms persist after CTX. Future studies should focus on which patients have an improvement in symptoms and which patients continue to experience physical and psychological symptoms as some patients may not recover. Overall, more research is needed with clinical database repositories. These data can provide valuable information regarding patient experiences in the clinical setting, but databases may need revision to be conducive to both patient needs and research objectives.

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