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REDUCING SYMPTOM LIMITATIONS: A COGNITIVE BEHAVIORAL INTERVENTION RANDOMIZED TRIAL

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SUMMARY

Until now, little research has been conducted examining the reactive dimension, or the degree to which a symptom limits an individual's life, in a multiplicity of symptoms. This research examines how problem-solving therapy organizes an intervention to decrease symptom limitations. The purpose was threefold: to determine if a cognitive behavioral intervention decreases the impact of symptom limitations among individuals newly diagnosed with cancer, who are receiving chemotherapy; to determine, after adjusting for covariates, how symptom limitations change over time; and to describe which symptoms are most limiting. This randomized control trial was conducted in two comprehensive and four community cancer centers. Two hundred thirty-seven individuals, aged 31–87, newly diagnosed with solid tumor cancers, participated. The experimental group (118 individuals) received a 10-contact, 18-week cognitive behavioral intervention focused on cancer- and chemotherapy-related symptoms. The control group (119 individuals) received conventional care. Interviews occurred at baseline, 10, 20, and 32 weeks. Data analysis used a two-level hierarchical linear model. Participants receiving the cognitive behavioral intervention had lower scores of symptom limitation than did participants in the control group. At the onset of the study, younger patients reported more symptom limitations than their older counterparts; however, this was reversed by the end of the study. The cognitive behavioral intervention was key to decreasing symptom limitations. Findings also suggest that nursing interventions may be particularly helpful to younger individuals in managing cancer-related symptom limitations.

INTRODUCTION

Being diagnosed with cancer is a life event that occurs for one out of four Americans (American Cancer Society, 2004). Individuals with cancer often suffer from many symptoms that impair their quality of life. Increasing attention is being focused on studying symptom management, as indicated by heightened public and governmental attention, including by the National Institute of Health (Patrick *et al.*, 2003).

Research has demonstrated that cognitive behavioral interventions produce positive health behavior changes in individuals with cancer (Dobson, 2001; Given *et al.*, 2003). Recently, numerous trials of cognitive behavioral interventions have been directed towards the

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management of symptoms resulting from cancer or chemotherapy (Devine and Westlake, 1995; Meyer and Mark, 1995; Sheard and Maguire, 1999). To date, the vast majority of cognitive behavioral interventions for cancer have focused primarily on single symptoms, such as pain, fatigue, or insomnia (Oliver *et al.*, 2001; Pickett *et al.*, 2002; Quesnel *et al.*, 2003; West *et al.*, 2003). Studies focusing on single symptoms, however, fail to produce a full understanding of the cancer symptom experience. Individuals with cancer suffer from multiple symptoms, the complications of which result in poor health outcomes (Cleeland, 2000). This multiplicity of symptomatic issues requires a multifaceted response in order to achieve meaningful improvement in quality of life. This research examines how problem-solving therapy, one of several cognitive behavioral intervention approaches, organizes an intervention to decrease symptom limitations.

Symptom limitations

Two dimensions to the symptom experience have been noted: the *sensory dimension*, or a symptom's direct severity, and the *reactive dimension*, or the degree to which a symptom limits or interferes in an individual's life (Cleeland, 1989). Research has found that, in individuals with cancer, a linear relationship does not exist between symptom severity and the limitations caused by cancer symptoms (Serlin *et al.*, 1995; Jensen *et al.*, 2001). This lack of correlation between the sensory and reactive dimensions has also been reported in studies examining changes in pain over time among individuals with cancer (Hwang *et al.*, 2002). Thus, assessment of not only symptom severity, but also symptom limitations, is essential in understanding the symptom experience for individuals with cancer.

Understanding how symptoms limit daily functioning in individuals with cancer may enable health care practitioners both to help individuals manage the symptoms, and to tailor strategies that will enable individuals to minimize their symptom-related limitations. For example, two individuals might similarly rate their insomnia severity as five on a 10-point scale; however, the limitations imposed on the individuals may vary drastically. In order to facilitate improvements in individuals' abilities to manage the limitations imposed by their symptoms, the outcome measure of this research focuses on the reactive dimension of symptom limitations experienced by those newly diagnosed with cancer and receiving chemotherapy.

Theoretical framework: cognitive behavioral interventions

In this study, the problem-solving approach of cognitive behavioral intervention was used to impact symptom limitations. Problem solving is one of several cognitive behavioral intervention approaches used to frame stressful events and drive positive behavioral changes (Nezu *et al.*, 1999). Four major steps in any problem-solving strategy are as follows: problem definition and formulation; generation of alternative solutions; decision making; and solution implementation and verification (D'Zurilla and Nezu, 2001, p. 215).

The experimental group received a nursing intervention providing evidence-based resources for problem-solving strategies, including: self-care management (Lev *et al.*, 2001); providing information and decision-making skills (Gattellari and Ward, 2003); counseling and support (Classen *et al.*, 2001); and communication with providers (Detmar *et al.*, 2003; Gattellari *et al.*, 2001). The conventional care provided to the control group in this study tended to focus primarily on direct treatment of the cancer, and did not place significant emphasis on providing support for self-managed behavioral, cognitive, or emotional responses to symptoms.

In this study, the various demographic characteristics and biomedical characteristics of the individuals with cancer were measured, as they were expected to influence the effectiveness of the problem-solving intervention. Findings regarding the effects that demographic characteristics of age and gender have on symptoms are contradictory; some studies have found

older age and being female to be associated with higher symptom prevalence (Walsh *et al.*, 2000), while others have not (Kurtz *et al.*, 2002). Biomedical characteristics of the individual—such as comorbid conditions, and stage and site of the cancer—have clearly been shown to affect symptoms (Yancik *et al.*, 2001a; Zabora *et al.*, 2001).

Depressive symptoms have been associated with the sensory dimension of a symptom or symptom severity (Kurtz *et al.*, 2002). Although the association of depression on symptom limitation has yet to be explored, one can assume that depression may also impact a participant's report of the reactive dimension of a symptom or symptom severity.

The purposes of this research were to test, through a randomized trial, if a tailored problem-solving cognitive behavioral intervention would decrease symptom limitations among individuals newly diagnosed with cancer, and receiving chemotherapy, when compared with conventional care; to identify, after adjusting for covariates, how symptom limitations change over time; and finally, to describe which symptoms are most limiting.

METHODS

Sample selection

The sample consisted of individuals newly diagnosed with solid tumor cancers, who were within the first two cycles of chemotherapy at one of four community and two comprehensive cancer centers. Those qualifying were at least 21 years of age, English speaking, and able to participate in telephone interviews. All those under the active care of a psychologist or psychiatrist, or having any diagnosed emotional or psychological disorders, were excluded. Participants also agreed to a 10-contact (5 in person and 5 via telephone), 18-week intervention, and four telephone interviews, occurring at baseline and at weeks 10, 20, and 32.

Nurse recruiters from six cancer centers identified 609 individuals who met the aforementioned criteria. Not every qualifying person participated in the research study. Of the 346 who did not participate, the three most common reasons for not participating were 'not interested' ($n = 155$, 45%), 'too overwhelmed by the disease or the treatment' ($n = 55$, 16%), or 'too busy' ($n = 48$, 14%). The remaining 263 patients (43%) agreed to participate and signed consent forms. In the end, 26 patients did not complete the initial interview for various reasons, and therefore did not participate in the study. The final sample consisted of 237 patients who completed the baseline interview and were randomly assigned either to the 10-contact, 18-week experimental group or to the control group. Participants were stratified by site of cancer, as it was expected that different symptom limitations would be experienced by individuals with different sites of cancer, and then randomized to either the intervention or control with the assistance of a computer program.

Analysis examining baseline equivalencies revealed no significant differences between groups among age, gender, site, or stage of cancer. Additionally, baseline differences were examined by (1) comprehensive versus community cancer center; (2) treatment protocols by sites of cancer; and (3) evaluations of supportive care offered at cancer centers. No differences were found.

After the baseline interview, further interviews occurred midway through the intervention (week 10), and at the end of the intervention (week 20). To assess sustained effects of the intervention on symptom limitation, an additional participant interview was conducted at week 32. There were no statistically significant differences in attrition between the experimental and control groups according to symptom limitation, age, gender, CES-D scores, chronic health conditions, stage, or site of cancer. However, a trend was detected within the experimental group, wherein more participants dropped out between weeks 20 and 32 than for the same

period in the control group. This trend had no discernable pattern. (See Table 1 for descriptive statistics of participants by experimental and control groups of all waves.)

Intervention

The intervention targeted 15 symptoms: pain, fatigue, nausea, vomiting, insomnia, difficulty breathing, diarrhea, motor co-ordination problems, anorexia, fever, cough, dry mouth, constipation, mouth sores, and inability to concentrate. The participant and the nurse intervener collaboratively developed a plan of care when symptom severity reached or exceeded 5 on a scale of 0 (no symptom severity) to 10 (the worst each symptom could be).

Up to four symptoms, mutually selected by the nurse and participant, were addressed at each visit. Of the 10 contacts, five were in person and five occurred over the telephone. Using a computer documentation protocol, symptoms were matched with specific problem-solving strategies: self-care management, information and decision-making, counseling and support, and communication with providers. Evaluation of the success of the problem-solving strategies occurred at subsequent contacts, where participants rated problems as resolved, improving, unchanged, or deteriorating.

Fidelity to the intervention was checked by nurse interveners requesting participants to report whether or not they attempted the problem-solving strategies. Strategies were modified if rated ineffective or unsuccessful by the participant. Where strategies were not attempted, participants were questioned about barriers to implementation. Additionally, the nurses' adherence to the computer-guided protocol was monitored by review of the computer data, taping intervention contacts, and reviewing tapes of completeness and quality of intervention.

Measures of the effectiveness of the overall intervention strategy were obtained during the data collection interviews. Interviewers repeated the survey of symptom limitations at the 10, 20, and 32 week interviews. These data, gathered independently of the intervention process, measured the result of the iterative cognitive interventions, proposed by the intervention nurse and accepted by participants, for addressing symptom limitations at each point in time.

MEASURES

Symptom limitations were measured using the Physical Symptom Experience Tool (Given *et al.*, 1993), which has been extensively tested and shown to be valid among cancer populations. Participants who acknowledged experiencing a symptom were asked: 'On a scale of 0 = no limitations to 10 = unable to do daily activity, how much did (insert symptom) limit your daily activities?' For statistical analyses, an overall symptom limitation index was created by summing all limitations reported across the 15 symptoms, for each participant, at each observation. The potential range of scores was from 0 to 150; the observed range of symptom limitations was from 0–91.

Chronic health conditions were assessed using a modified version of the Comorbidity Questionnaire (Katz *et al.*, 1996). The scale asked a series of 14 *yes* or *no* questions about the presence of various health conditions, including heart disease, hearing problems, and arthritis. A summary score was calculated on the number of *yes* responses, a higher score indicating a greater number of comorbid conditions. The Comorbidity Questionnaire has established content validity and test-retest reliability.

Emotional status was assessed using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). Higher scores indicate a greater level of depression symptomatology. The CES-D has been used extensively for studies of cancer patients,

providing reliable, valid data regarding risk for depression. In this study, coefficient alphas across observations were above 0.80.

Demographic questions included gender, age, education, race, and marital status. For the purposes of this analysis, race was coded into two categories (*majority* and *minority*); and marital status was coded into *married* and *not married*. Data regarding cancer stage and site was collected from medical records after participants signed consent forms. Cancer stage was coded as *advanced* (stages 3 and 4) or *early* (stages 1 and 2), according to the TNM staging criteria of the American Joint Committee on Cancer (1997). The sites of solid tumor cancer in participants consisted of breast, lung, colon, gynecological, lymphoma, pancreatic, or uterine. Cancer sites were combined into three groups (*breast*, *lung*, and *other*), with appropriate dummy variables created using lung as the reference category.

Analysis

Given that symptom limitations change over time, repeated assessment of each participant was required. An additional challenge was created by the time-varying interventions used in this study, which were tailored to the symptoms experienced at any given point in time, as well as to the effectiveness of previous intervention options. In order to measure longitudinal effects of interventions on symptom limitation, a two-level, hierarchical linear model (HLM) was used, which describes data that varies at two levels, in this case, both within and between individuals (Raudenbush *et al.*, 2001). Level 1 defined change within each individual. At level 1, the change from baseline values of symptom limitation was examined by creating appropriate dummy variables for each time point (baseline, and weeks 10, 20, and 32). Individual characteristics hypothesized to impact symptom limitations were included at level 2. A complete case analysis was used, i.e., if the participant had at least one time point and all individual characteristics, their data was included in the analysis.

To render the intercept of the regression line meaningful, continuous variables such as age were centered to the grand mean of the whole sample. Thus, an average patient is defined as one that has zero value for any continuous variable. Using data procured at both levels improved our ability to examine the effects of covariates that function in different ways at different levels of analysis (Raudenbush, 2001). Additionally, all continuous variables were tested for linear and quadratic effects to determine if these variables were related to symptom limitations in a nonlinear manner.

RESULTS

Sample characteristics and ratings of symptoms

Participants ranged in age from 31 to 87, with a mean of 60 and a standard deviation of 10. The majority of the participants were married, Caucasian females, who had completed some college education. The majority of the participants had advanced (stages 3 or 4) cancer (67%). The most common site of cancer was breast (38%), followed by lung (35%). The number of symptoms reported by participants ranged from 1 to 14 with a mean of 5.8 (S.D. = 2.9). The number and percent of patients experiencing symptom limitations and severity for the 15 symptoms assessed can be seen in Table 2. Vomiting and nausea were the most limiting symptoms for participants of this study.

Baseline correlations

At baseline, the highest association among age, CES-D scores, symptom limitation, and chronic health conditions occurred between symptom limitations and CES-D at $r = 0.54$, $p = 0.000$. Symptom limitations were also negatively correlated with age ($r = -0.18$, $p = 0.006$) and positively correlated with chronic health conditions ($r = 0.19$, $p = 0.004$). Age was moderately

correlated with chronic health conditions ($r = 0.32, p = 0.000$) and negatively correlated with CES-D scores ($r = -0.15, p = 0.022$).

Effects of cognitive behavioral nursing intervention over time

Various HLM models were tested, and the most parsimonious model with good data fit, as indicated by chi square statistic χ^2 , the likelihood ratio test was accepted. Initial models included age, gender, race, marital status, education, CES-D scores, site of cancer, stage of disease, chronic health conditions, and interaction terms between all variables to explain symptom limitation. Although there was a trend towards significance at week 10 for an age-by-group interaction ($p = 0.07$), it was eliminated from the final model along with gender, race, marital status, education, site of cancer, stage of disease, functional status, depression over time, and chronic health conditions, as a significance level of $\alpha = 0.05$ was not reached. (See Table 3 for the final HLM model.)

Table 4 presents the results of the HLM model predicting symptom limitations over time. Significant explanatory variables of symptom limitations were group assignment (experimental or control), and age. At the onset of the study, younger participants reported more symptom limitations than their older counterparts ($p < 0.0001$); however, this difference diminished over time and eventually reversed during the course of treatment ($p < 0.0001$) (see Figure 2).

Although in terms of their symptom limitations, both groups improved between baseline and later observations, the experimental group improved significantly more than the control group at each measurement point controlling for age (see Figure 1). At baseline, both groups had similar initial symptom limitations (24.9 and 28.8 for the control and experimental groups respectively; $p = 0.088$). Although the control group showed some improvement in symptom limitation after 10 weeks (decreasing to 18.7), the problem-solving cognitive behavioral intervention group decreased in symptom limitations to 13.5. This significance was increased by the 20-week interviews, with the intervention group reporting symptom limitations of 5.0, compared with 10.0 for the control group. So, although each group is improving, the experimental group ultimately had significantly fewer limitations from symptoms. Also, 12 weeks after the intervention ended, although both groups showed some retrograde increase in symptom limitations (to 13.1 and 10.6 for the control and experimental groups respectively), the experimental group continued to report fewer limitations. See Table 4.

DISCUSSION

Effectiveness of cognitive behavioral interventions on symptom limitations over time

The findings from this study add to a growing body of evidence of the effectiveness of cognitive behavioral interventions for individuals with cancer (Given *et al.*, 2002; Graves, 2003; Sheard and Maguire, 1999), by demonstrating the value of problem-solving cognitive behavioral interventions on symptom limitations compared to conventional care. On average, after 10 weeks, the experimental group reduced symptom limitations by a statistically significant 13 points more than the control group and maintained this advantage over the course of treatment. This expected effect was clearly seen in the differences between the experimental and control groups over time.

Explanatory variables of symptom limitations

Findings from this study indicate that along with nursing intervention, age was a significant explanatory variable. Younger cancer participants reported their symptom limitation as greater at baseline across experimental groups. This may be due to younger cancer participants' lack of experience in dealing with symptom limitations, more aggressive chemotherapy regimens

received, or to the fact that their spectrum of activities are typically more vigorous and varied and thus open to greater limitations than older participants. As the younger cancer participants progressed through the intervention, they found effective ways to compensate and reverse the limitations experienced from the symptoms, while the older cancer participants reported ongoing symptom limitations. The age-by-group interaction trend suggests that younger participants were able to benefit more from the problem-solving strategies of the nursing intervention.

One possible explanation for younger participants' decreasing symptom limitations may relate to lower comorbidities. Similar to other study findings, this study found that as age increased, more comorbidities were present with the cancer diagnosis (Yancik *et al.*, 2001b). Similarly, the lack of change in elderly cancer participants' symptom limitation may be attributed to comorbidities which, when combined with symptoms, lower the rates of improvement (Repetto *et al.*, 2001). This study's findings suggest that the additional stress imposed by cancer symptoms has a synergistic effect on the physical limitations already experienced by the elderly, reducing their ability to ameliorate those limitations through the cognitive behavioral intervention techniques.

Other research has found relationships between increased depression and quality of life (Holland *et al.*, 2001; Smith *et al.*, 2003); however, in this study depression measured over the time of the study did not predict symptom limitation. This finding may be due to the study's use of a more specific outcome measure of symptom limitation rather than a more global measure of quality of life, which may be more influenced by emotional status.

Symptom limitations

The results are consistent with the cancer literature, in which pain and fatigue are the most *common* symptoms affecting individuals with cancer (Given *et al.*, 2001; Mock, 2003; Patrick *et al.*, 2003). Although it is important for oncology nurses to know which symptoms are most prevalent with cancer, it is also important to understand the limitations which different symptoms impose on affected individuals. Previous studies indicate that the most severe symptoms are not necessarily found to be the most limiting (Jensen *et al.*, 2001; Tishelman *et al.*, 2000). In this study, the most *limiting* symptoms to participants were vomiting and nausea. Consistent with previous findings, higher symptom severity did not necessarily correspond with higher limitations experienced from the symptom. A demonstration of this phenomenon occurs with the symptom *constipation*. Although the severity rating of 5.68 indicates those who experience constipation find it severe, its limitations score of 2.61 reveals that this severe symptom does not dramatically impact their ability to maintain a normal lifestyle.

Limitations

A limitation of this study was the lack of diversity among participants, particularly regarding ethnicity, education, and socioeconomic status. Many individuals with cancer who were eligible for the study chose not to participate; therefore, the generalizability of these results cannot be determined. Continued investigation of symptom limitations in a less homogenous sample of cancer participants would provide a greater ability to generalize findings.

It cannot be determined from this research how the intervention affects the symptom limitation. It may directly relieve the symptom severity. It may also allow the participant to better cope; thus, rating the symptom as less limiting.

A further limitation to this study was the lack of an overarching framework within which to locate responses to the cancer experience. Future research could include the use of Lazarus and Folkman's Stress and Coping Theory (Folkman *et al.*, 1986; Lazarus and Folkman,

1984), as it is a classic model for describing the process by which individuals recognize, respond, and adapt to the realities of cancer- and chemotherapy-induced stresses.

The problem-solving approach of cognitive behavioral intervention could be integrated into the Stress and Coping Theory framework, as problem definition and formulation are functionally equivalent to the primary appraisal element of the Stress and Coping Theory. Similarly, the generation of alternative solutions is equivalent to the secondary appraisal element of the Stress and Coping Theory. Decision-making (the selection of specific coping resources from those available), and implementation and verification (acting upon the strategy using the selected resources, and performing analysis of the results of that action), could be viewed as occurring within the transition from secondary appraisal to observation of outcomes, and draw upon feedback from the outcomes. The actual limitations in daily activity, remaining after the individual's application of available resources to the perceived physical and emotional threats or challenges, creates a learning cycle in which the individual reassesses both the severity of specific situational inputs and the efficacy of previously selected strategies, subsequently implementing the new knowledge in further assessments and decisions.

Given that repeated measures are required to assess changes in symptom limitation, the problem of attrition cannot be ignored. Attrition not only weakens statistical precision, but may also introduce bias. Maximum likelihood estimation efficiently uses all available data to estimate models, assuring unbiased estimation of treatment effects (Little and Rubin, 2002; Schafer and Graham, 2002) if missing at random is assumed. The use of HLM was particularly suited to this research, as it allowed for the examination of various covarying effects at different levels of analysis, accounted for the time-varying intervention, and used maximum likelihood to estimate the model (Raudenbush and Bryk, 2002).

RESEARCH AND CLINICAL IMPLICATIONS

Finding measures to assess both cancer and its treatment effects continues to provide a challenge (Cleeland and Reyes-Gibby, 2002). Clinical assessment including both symptom severity and reaction to symptom limitations may be more effective than an assessment of symptom severity alone.

This study demonstrated that cognitive behavioral interventions can decrease symptom limitation, especially in younger individuals with cancer. This study also supports the use of multilevel analysis when dealing with longitudinal data. Consideration of multilevel modelling at the study design stage may help researchers select theoretically and statistically sound research methods.

Directions for future research

The body of evidence supporting cognitive behavioral nursing interventions is growing steadily. The generalizability of this evidence would benefit from research including more diversity in age, education, socioeconomic status, and ethnicity in the studied populations. Individuals with different sites of cancer experience very different symptom clusters; future studies should be planned to include sufficient sample sizes to permit assessment of symptom limitations associated with specific symptoms or symptom clusters.

To better elucidate the effectiveness of cognitive behavioral interventions using multimodal approaches, differential effects of various components of the intervention strategies need to be examined. These examinations would allow oncology health care providers to target the most effective components of cognitive behavioral interventions to reap optimal benefits in symptom control. Furthermore, examination of the common barriers to symptom interventions, and the

most effective methods for eliminating those barriers, may enable even greater control over symptom limitations for individuals with cancer.

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Figure 1.
Symptom limitations over time controlling for covariates.

Figure 2.
Age and symptom limitation at four time points.

Table 1

Baseline Week 10 Week 20 Week 32

Baseline		Week 10	Week 20	Week 32
(a) Descriptive statistics sample for experimental group				
Variable	Mean (S.D.) Min–Max			
Age	60.4 (9.7) 36–83	60.3 (9.6) 36–83	60.5 (9.8) 36–83	60.8 (10.2) 36–83
CES-D	12.1 (9.1) 0–38	10.4 (8.7) 0–38	7.0 (8.2) 0–39	7.1 (8.0) 0–31
Chronic health conditions	2.3 (1.6) 0–7			
Variable	N (%)			
N valid	118 (100%)	99 (100%)	81 (100%)	66 (100%)
Female	87 (73%)	75 (75%)	63 (78%)	52 (79%)
Married	90 (76%)	74 (74%)	59 (73%)	47 (71%)
Completed college	52 (44%)	45 (45%)	34 (42%)	27 (41%)
Caucasian	108 (90%)	90 (90%)	73 (90%)	59 (89%)
Advanced Stage Cancer	80 (67%)	64 (64%)	52 (64%)	40 (61%)
Cancer Site				
Breast	47 (39%)	42 (42%)	36 (44%)	32 (49%)
Lung	42 (35%)	31 (31%)	21 (26%)	15 (23%)
(b) Descriptive statistics sample for control group				
Variable	Mean (S.D.) Min–Max			
Age	58.7 (11.1) 31–87	58.3 (11.5) 31–87	57.5 (11.5) 31–87	57.1 (11.4) 31–87
CES-D	13.5 (9.1) 0–44	12.7 (9.2) 0–38	9.8 (9.1) 0–36	8.1 (6.9) 0–25
Chronic health conditions	2 (1.7) 0–7			
Variable	N (%)			
N valid	119 (100%)	98 (100%)	88 (100%)	77 (100%)
Female	88 (74%)	76 (77%)	71 (79%)	64 (82%)
Married	86 (72%)	72 (73%)	64 (71%)	56 (72%)
Completed college	44 (40%)	36 (36%)	34 (38%)	31 (40%)
Caucasian	108 (90%)	89 (90%)	80 (89%)	71 (91%)
Advanced Stage Cancer	81 (68%)	62 (63%)	56 (62%)	49 (63%)
Cancer Site				
Breast	46 (38%)	40 (40%)	38 (42%)	37 (47%)
Lung	42 (35%)	31 (31%)	26 (29%)	20 (26%)

Table 2

Descriptive statistics of symptom limitations and severity at baseline based on a 0 to 10 scale (10 being the worst possible)

Symptoms	No. of participants experiencing symptom	Limitation mean	Limitation standard deviation	Severity mean	Severity standard deviation
Vomiting	48	7.27	3.09	6.61	2.98
Nausea	134	5.04	3.33	4.57	2.73
Fatigue	220	4.99	2.75	4.97	2.41
Difficulty breathing	67	4.52	3.43	4.48	2.48
Fever	33	4.52	3.44	3.48	2.43
Pain	150	4.43	3.01	3.91	2.47
Insomnia	148	3.91	2.98	5.45	2.46
Coordination problems	37	3.73	3.21	3.62	2.72
Diarrhea	78	3.58	3.58	5.00	2.80
Inability to concentrate	75	3.56	2.75	4.05	2.22
Anorexia	123	3.31	3.21	5.18	2.52
Constipation	111	2.61	2.98	5.68	2.64
Cough	67	1.64	2.76	3.58	2.45
Mouth sores	29	1.41	2.65	4.18	2.51
Dry mouth	78	0.71	1.73	4.50	2.56

Table 3

HLM theoretical models

Level-1 Model: Individual Trajectory of Symptom Limitations
Symptom limitation _{ti} = $\beta_{0i} + \beta_{1i} (\text{week } 10)_{ti} + \beta_{2i} (\text{week } 20)_{ti} + \beta_{3i} (\text{week } 32)_{ti} + r_{ti}$
i = individual
t = time
Level-2 Model: Participant Characteristics
$\beta_{0i} = \gamma_{00} + \gamma_{01} (\text{control})_i + \gamma_{02} (\text{grand mean centered age})_i + u_{0i}$
$\beta_{1i} = \gamma_{10} + \gamma_{11} (\text{control})_i + \gamma_{12} (\text{grand mean centered age})_i$
$\beta_{2i} = \gamma_{20} + \gamma_{21} (\text{control})_i + \gamma_{22} (\text{grand mean centered age})_i$
$\beta_{3i} = \gamma_{30} + \gamma_{31} (\text{control})_i + \gamma_{32} (\text{grand mean centered age})_i$

Table 4

HLM results

Fixed effect	Estimate	Standard Error	T-ratio	Approximate d.f	P-value
<i>For INTRCPT1, B0</i>					
INTRCPT2, G00	28.81	3.74	7.71	191	0.000
CONTROL, G01	-3.89	2.27	-1.71	191	0.088
AGE, G02	-0.52	0.12	-4.25	191	0.000
<i>For week 10 slope, B1</i>					
INTRCPT2, G10	-15.28	4.47	-3.42	548	0.001
CONTROL, G11	9.14	2.77	3.30	548	0.001
AGE, G12	0.35	0.13	2.65	548	0.009
<i>For week 20 slope, B2</i>					
INTRCPT2, G20	-23.81	5.09	-4.68	548	0.000
CONTROL, G21	9.01	3.09	2.91	548	0.004
AGE, G22	0.58	0.14	3.99	548	0.000
<i>For week 32 slope, B3</i>					
INTRCPT2, G30	-18.19	5.45	-3.33	548	0.001
CONTROL, G31	6.40	3.33	1.92	548	0.055
AGE, G32	0.73	0.15	4.69	548	0.000
Sigma_squared	159.98				
Tau INTRCPT1,B0	147.39				
<i>Random level-1 coefficient reliability estimate:</i>					
INTRCPT 1, BO	0.69				