European Journal of Cancer Care

Original Article

# The symptom phenotype of oncology outpatients remains relatively stable from prior to through 1 week following chemotherapy

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MIASKOWSKI C., COOPER B.A., AOUIZERAT B., MELISKO M., CHEN L.-M., DUNN L., HU X., KOBER K.M., MASTICK J., LEVINE J.D., HAMMER M., WRIGHT F., HARRIS J., ARMES J., FURLONG E., FOX P., REAM E., MAGUIRE R. & KEARNEY N. (2017) *European Journal of Cancer Care* **26**, e12437, doi: 10.1111/ecc.12437

**The symptom phenotype of oncology outpatients remains relatively stable from prior to through 1 week following chemotherapy**

Some oncology outpatients experience a higher number of and more severe symptoms during chemotherapy (CTX). However, little is known about whether this high risk phenotype persists over time. Latent transition analysis (LTA) was used to examine the probability that patients remained in the same symptom class when assessed prior to the administration of and following their next dose of CTX. For the patients whose class membership remained consistent, differences in demographic and clinical characteristics, and quality of life (QOL) were evaluated. The Memorial Symptom Assessment Scale (MSAS) was used to evaluate symptom burden. LTA was used to identify subgroups of patients with distinct symptom experiences based on the

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Accepted 26 November 2015
DOI: 10.1111/ecc.12437

occurrence of the MSAS symptoms. Of the 906 patients evaluated, 83.9% were classified in the same symptom occurrence class at both assessments. Of these 760 patients, 25.0% were classified as Low–Low, 44.1% as Moderate–Moderate and 30.9% as High–High. Compared to the Low–Low class, the other two classes were younger, more likely to be women and to report child care responsibilities, and had a lower functional status and a higher comorbidity scores. The two higher classes reported lower QOL scores. The use of LTA could assist clinicians to identify higher risk patients and initiate more aggressive interventions.

*Keywords:* cancer, chemotherapy, latent transition analysis, symptoms, predictive risk modelling, quality of life.

## INTRODUCTION

Patients receiving chemotherapy (CTX) report an average of 10 co-occurring symptoms (Esther Kim *et al.* 2009). However, in several studies (Miaskowski *et al.* 2006; Pud *et al.* 2008; Dodd *et al.* 2010, 2011; Illi *et al.* 2012), a significant amount of inter-individual variability was found in patients' experiences with various multiple co-occurring symptoms. All five of these studies evaluated for subgroups of patients based on self-reports of the four most common symptoms associated with cancer and its treatment (i.e. pain, fatigue, sleep disturbance, depression). A consistent finding across all five studies was the identification of a subgroup of patients with low levels of all four symptoms and a subgroup of patients with high levels of all four symptoms. Equally important, patients in the 'all high' subgroup reported worse functional status and poorer quality of life (QOL) outcomes.

While the aforementioned studies were limited to only four co-occurring symptoms, newer work has used the Memorial Symptom Assessment Scale (MSAS) (Portenoy *et al.* 1994) to identify high-risk patients based on the occurrence of 32 symptoms (Ferreira *et al.* 2008; Gwede *et al.* 2008; Miaskowski *et al.*, 2015). In two of these studies (Ferreira *et al.* 2008; Gwede *et al.* 2008), two distinct symptom subgroups were identified. In the third study (Miaskowski *et al.*, 2015), four distinct symptom subgroups were found. Across these three studies, patients in the subgroup with the highest symptom occurrence rates reported decrements in functional status and QOL. Of note, across all eight studies cited above, clinical characteristics were not associated with subgroup membership. Variations in the total number of patient subgroups may be related to the heterogeneous nature of the samples in terms of cancer diagnoses and types of treatments, the number of symptoms evaluated, the dimension of the symptom experience (e.g. occurrence, severity) used to create the subgroups and the statistical procedures used to identify the subgroups.

Recently, our research team reported on the use of latent class analysis (LCA) to identify three distinct groups of patients (i.e. latent classes) based on the relative occurrence rates for 25 symptoms on the MSAS prior to receiving their next cycle of CTX (Miaskowski *et al.* 2014a). Of the 582 patients evaluated, 36.1% were categorised in the low class (i.e. mean of 5.7 symptoms); 50.0% were in the moderate class (i.e. mean of 12.9 symptoms); and 13.9% were in the all high class (i.e. mean of 20.3 symptoms). Of note, patients in the all high class were significantly younger and more likely to be women and non-White, and had lower levels of social support, lower socioeconomic status, poorer functional status and a higher level of comorbidity. As noted previously, no other clinical characteristics were associated with latent class membership. At the conclusion of this paper, we suggested that the use of LCA may provide an effective way to identify patients with a higher symptom burden or a high-risk symptom phenotype (Miaskowski *et al.* 2014a).

A question that remains unanswered is whether or not this high-risk symptom phenotype persists following the administration of CTX. In other words, do patients who were classified, using LCA, into the low, moderate and high classes remain in those symptom classes following the administration of their next dose of CTX? To answer this research question, we used latent transition analysis (LTA) (Lanza *et al.* 2003; Collins & Lanza 2010), to examine the probability that patients remained in the same class at their initial (i.e. prior to the administration of CTX) and subsequent (i.e. following the administration of their next dose of CTX) assessment. For the patients whose class membership remained consistent over the two time points, differences in demographic and clinical characteristics, as well as QOL outcomes were evaluated.

## PATIENTS AND METHODS

### Patients and settings

This study is part of an ongoing, longitudinal study of the symptom experience of oncology outpatients receiving

CTX (Miaskowski *et al.* 2014a). Eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal (GI), gynaecological (GYN) or lung cancer; had received CTX within the preceding 4 weeks; were scheduled to receive at least two additional cycles of CTX; were able to read, write and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programmes. A total of 1505 patients were approached and 906 consented to participate (60.2% response rate). The major reason for refusal was being overwhelmed with their cancer treatment.

### Instruments

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status and income. The Karnofsky Performance Status (KPS) scale (Karnofsky 1977) was used to evaluate patients' functional status. The Self-administered Comorbidity Questionnaire (SCQ) (Sangha *et al.* 2003) evaluated the occurrence, treatment and functional impact of common comorbid conditions (e.g. diabetes, arthritis).

The MSAS was used to evaluate the occurrence, severity, frequency and distress of 32 symptoms commonly associated with cancer and its treatment. The MSAS is a self-report questionnaire designed to measure the multidimensional experience of symptoms. Patients were asked to indicate 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 frequency of occurrence, severity and distress. The reliability and validity of the MSAS is well established in studies of oncology inpatients and outpatients (Portenoy *et al.* 1994).

Quality of life (QOL) was evaluated using generic [i.e. Medical Outcomes Study-Short Form-12 (SF-12)] (Ware *et al.* 1996) and disease-specific [i.e. Quality of Life Scale-Patient Version (QOL-PV)] measures (Ferrell *et al.* 1995; Dow *et al.* 1996). Both measures have well-established validity and reliability. Higher scores on both measures indicate a better QOL.

### Study procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Board at each of the study sites. From February 2010 to December 2013, all eligible patients were approached by the research staff in the infusion unit to discuss participation in the study. Written informed consent was obtained from all patients. Depending on the length of their CTX cycles, patients completed questionnaires in their homes, a total of six times over 2 cycles of CTX (i.e. prior to CTX administration (Time 1 and 4), approximately 1 week after CTX administration (Time 2 and 5), approximately 2 weeks after CTX administration (Time 3 and 6). For this analysis, symptom occurrence data from the Time 1 (i.e. recovery from previous cycle) and Time 2 (i.e. acute symptoms) assessments were analysed. Patients were asked to report on their symptom experience for the previous week. Medical records were reviewed for disease and treatment information.

### Data analysis

#### *Latent class analysis*

Latent class analysis identifies latent classes based on an observed response pattern using categorical variables (Vermunt & Magdison 2002; Lanza *et al.* 2003; Nylund *et al.* 2007a; Collins & Lanza 2010). Prior to identifying the LTA model that described patients' transitions from classes at Time 1 to classes at Time 2, separate LCAs were done to identify subgroups of patients with similar symptom experiences at each of the two assessments. These analyses provided an estimate of the number of classes that might be expected at each assessment, so as to inform the LTA modelling of the class transitions.

The LCAs and LTA were done using the symptom occurrence data from the MSAS. In order to have a sufficient number of patients with each symptom to perform the LCA and LTA, we identified the MSAS symptoms that occurred in at least 40% of the patients. This criterion was selected to provide assurance that sufficient information was available to identify classes that were not sample-specific, due to infrequent reports of symptoms. A total of 25 of 32 symptoms from the MSAS occurred in >40% of the patients. Following the identification of the number of latent classes at each assessment with LCA, the estimation of latent transition classes was performed.

The final number of latent classes for each LCA was selected based on the Bayesian information criterion (BIC), the Vuong, Lo, Mendel, and Rubin (VLMR) likelihood ratio test, and entropy. Typically, the best fitting LCA model has the lowest BIC. This BIC criterion can be supplemented by an evaluation of the VLMR (Nylund *et al.* 2007b) which tests whether a model with K classes fits the data better than a model with one fewer class (the K-1 class model). If the VLMR is significant, it supports

the K-class model as fitting the data better. If it is not significant, it indicates that too many classes were extracted and that the K-1 class model fits the data better than the K-class model. In addition, well-fitting models produce entropy values of ≥0.80 (Celeux & Soromenho 1996). Finally, well-fitting models 'make sense' conceptually and the estimated classes differ as might be expected on variables not used in the generation of the model. Because the VLMR is not available for LTA, the best fitting model was determined based on its BIC and entropy values.

*Latent transition analysis*

Latent transition analysis allows for the identification of individuals who transition from latent classes at one point in time, to the same latent classes at a subsequent point in time, as well as individuals who move to different classes (Lanza *et al.* 2003; Nylund *et al.* 2007a; Collins & Lanza 2010). Symptom occurrence data from the MSAS was used to identify the latent classes of patients with similar symptom experiences at two time points during their CTX cycle (i.e. Time 1 – week prior to CTX administration and Time 2 – week following CTX administration).

The LCA and LTA models were estimated using Mplus™ Version 7 (Muthen & Muthen 1998-2014). Estimation was carried out with robust maximum-likelihood and the expectation–maximisation algorithm (Muthen & Shedden 1999). Given that the observed variables were dichotomies, estimation was carried out with a logit link. To protect against solutions that were identified based on a local maximum, from 800 to as many as 6000 random starts were used in the estimation of the model. This approach ensured that the best fitting log-likelihood was replicated with multiple models (Muthen & Muthen 1998-2014).

Differences in demographic and clinical characteristics and QOL outcomes among the LTA classes, were evaluated using analyses of variance, Kruskal–Wallis or chi-squared tests with Bonferroni corrected *post hoc* contrasts, using SPSS version 22 (IBM, Armonk, NY). A $P < 0.05$ was considered statistically significant. All comparisons among the classes used actual values. Adjustments were not made for missing data. Therefore, the cohort for each of these analyses was dependent on the largest set of complete data among groups.

## RESULTS

### Latent class analyses

A total of 906 patients completed the MSAS at Time 1 and Time 2. A separate LCA was done for each time point. As shown in Table S1, a three-class solution fit the data best at each time point. For both time points, the BIC was lower for the three-class compared to the two-class solution and the VLMR was significant. While the BIC for the four-class solution was smaller, the VLMR was not significant. These consistent results for the two time points suggested an upper limit to the number of classes that might be found over the two assessments with the LTA. The probability of occurrence of the 25 MSAS symptoms for the three-class solutions for the Time 1 and Time 2 assessments are illustrated in Figures 1A and B respectively.

### Latent transition analysis

First, the LTA models were fit with two classes at each of the two assessments. Then the models were fit with three classes at each of the two time points. To ensure that the LTA classes at the two times were comparable, the LTA models were fit assuming measurement invariance for latent class indicators at each time.

As shown in Table S2, the BIC was smaller for the three-to-three-class LTA and entropy remained above 0.80. As shown in Table 1, an LTA solution with three classes at each assessment produces nine classes in the joint distribution. An inspection of Table 1 shows that the proportion of cases in the off-diagonal classes is much smaller than for the classes on the diagonal and that five of the off-diagonal classes consist of less than 3% of the sample. Therefore, we did not estimate models beyond three classes at each assessment.

As shown in Table 1C, of the 906 patients who had evaluable data at Time 1 and Time 2, 760 (83.9%) were classified in the same symptom occurrence classes at both assessments. Of these 760 patients, based on the relative occurrence rates for the 25 MSAS symptoms across the latent classes, 25.0% were classified as Low–Low, 44.1% as Moderate–Moderate and 30.9% as High–High (Figure 2).

### Differences in patient characteristics among the three consistent LTA classes

Table 2 summarises the differences in demographic and clinical characteristics among the three consistent LTA classes. Compared to the Low–Low class, patients in the High–High and Moderate–Moderate classes were significantly younger, more likely to be women, more likely to report having child care responsibilities, and had a lower KPS score and a higher comorbidity score. In terms of specific comorbid conditions, compared to the Low–Low class, a higher percentage of patients in the High–High

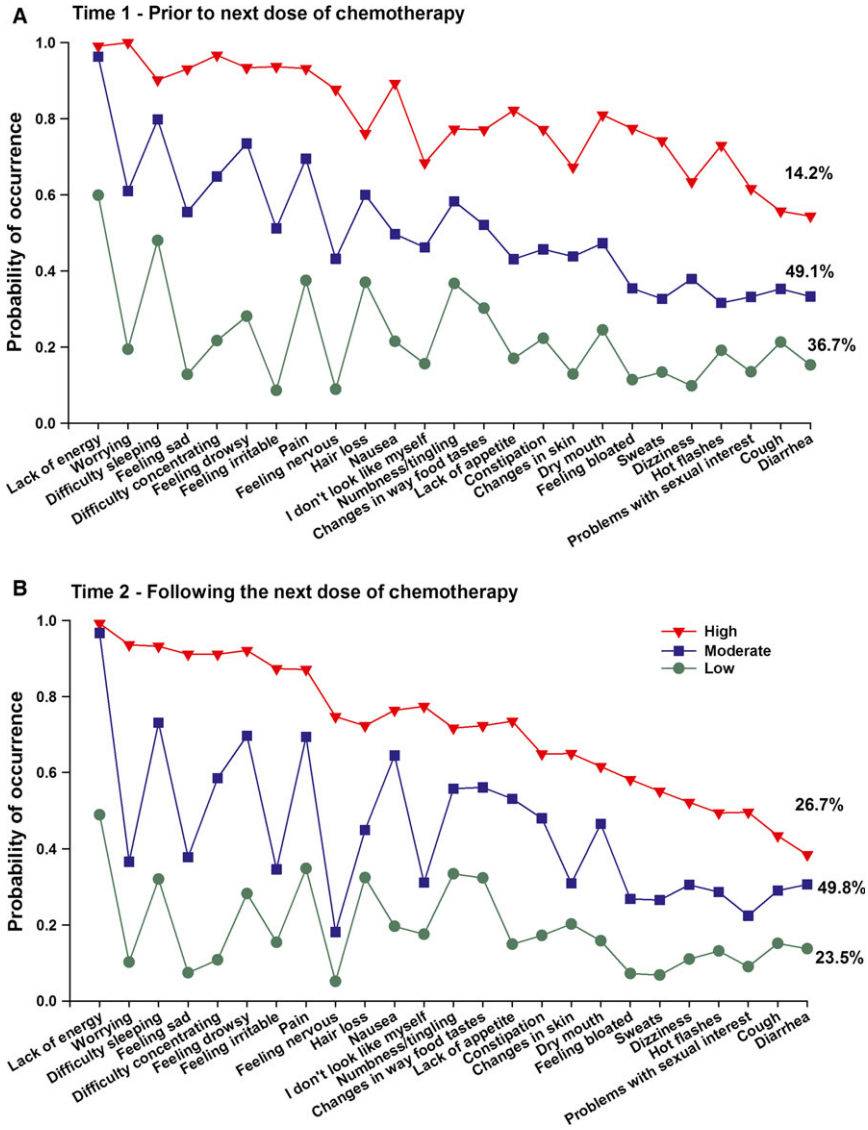


**Figure 1.** (A) Probability of symptom occurrence for each of the latent classes for the 25 symptoms on the Memorial Symptom Assessment Scale that occurred in ≥40% of the total sample ($n$ = 906) at Time 1 (i.e. prior to next dose of chemotherapy). (B) Probability of symptom occurrence for each of the latent classes for the 25 symptoms on the Memorial Symptom Assessment Scale that occurred in ≥40% of the total sample ($n$ = 906) at Time 2 (i.e. following next dose of chemotherapy). The percentages on each figure indicate the percentage of patients in each of the latent classes.

class reported the occurrence of anaemia, depression and back pain. With the exception of the KPS and comorbidity scores, as well as cancer diagnosis, none of the other clinical characteristics (i.e. time since diagnosis, types and number of prior treatments, presence or number of metastatic sites) differed among the LTA classes. For cancer diagnosis, pairwise contrasts found that compared to the High–High class, a higher percentage of patients in the Low–Low class had a GI cancer. Patients in the High–High class reported the occurrence of a significantly higher number of MSAS symptoms (19.3 ± 4.2) than patients in the Moderate class (12.4 ± 3.0). Patients in the Moderate–Moderate class reported a significantly higher number of symptoms than patients in the Low–Low class (5.5 ± 2.7).

### Differences in quality of life scores among the latent classes

As shown in Table 3, except for the spiritual well-being subscale, *post hoc* contrasts revealed that patients in the High–High class reported significantly lower scores on the QOL-PV subscale and total scores than patients in the Moderate–Moderate class. Patients in the Moderate–

**Table 1.** Latent transition class counts and proportions for three-to-three classes using symptom occurrence ratings for Time 1 to Time 2

| Time | Class | Count | Proportion |
|---|---|---|---|
| A. Three-class to three-class solution | | | |
| 1 | 1 | 264.73 | 0.292 |
| | 2 | 374.81 | 0.414 |
| | 3 | 266.45 | 0.294 |
| 2 | 1 | 251.18 | 0.277 |
| | 2 | 434.76 | 0.480 |
| | 3 | 220.06 | 0.243 |

| T1 class | T2 class | Count | Proportion |
|---|---|---|---|
| B. Three-class to three-class pattern | | | |
| 1 | 1 | 224.39 | 0.248 |
| 1 | 2 | 35.33 | 0.039 |
| 1 | 3 | 5.01 | 0.006 |
| 2 | 1 | 22.77 | 0.025 |
| 2 | 2 | 318.08 | 0.351 |
| 2 | 3 | 33.97 | 0.037 |
| 3 | 1 | 4.02 | 0.004 |
| 3 | 2 | 81.34 | 0.090 |
| 3 | 3 | 181.08 | 0.200 |

| Class | Latent class pattern | Number of patients | Percentage of patients | Class names |
|---|---|---|---|---|
| C. Actual classification of patients based on their most likely latent class pattern from Time 1 to Time 2 | | | | |
| 1 | 1 – 1 | 235 | 25.94 | High–High |
| 2 | 1 – 2 | 25 | 2.76 | High–Moderate |
| 3 | 1 – 3 | 3 | 0.33 | High–Low |
| 4 | 2 – 1 | 13 | 1.43 | Moderate–High |
| 5 | 2 – 2 | 335 | 36.98 | Moderate–Moderate |
| 6 | 2 – 3 | 27 | 2.98 | Moderate–Low |
| 7 | 3 – 1 | 3 | 0.33 | Low–High |
| 8 | 3 – 2 | 75 | 8.28 | Low–Moderate |
| 9 | 3 – 3 | 190 | 20.97 | Low–Low |

Moderate class reported significantly lower QOL-PV scores than patients in the Low–Low class.

In terms of the SF-12 subscale and physical component summary scores (PCS) and mental component summary scores, except for the physical functioning and PCS scores, *post hoc* contrasts revealed the same pattern of between group differences in QOL scores (i.e. High–High < Moderate–Moderate < Low–Low). For the physical functioning and PCS scores, the pattern of between class differences was Moderate–Moderate class and High–High class < Low–Low class.

## DISCUSSION

To our knowledge, this study is the first to use LTA to evaluate for a stable symptom phenotype based on patients' experiences with 25 common symptoms before and following a dose of CTX. Consistent with our previous report that used LCA to evaluate 582 patients in the current sample prior to their next dose of CTX (Miaskowski *et al.* 2014a), three distinct subgroups of patients with consistent symptom experiences were identified by LTA. In addition, the mean number of symptoms reported by each latent class is relatively consistent across both studies. While in the previous study, as well as in the Time 1 LCA done with this larger sample (Fig. 1A), approximately 14% of the patients were categorised in the all high class, in the current LTA study, using both the pre-treatment and post-treatment assessments, 30.9% of the patients were categorised in the High–High class (Figure 2). This finding suggests that two or more assessments may be warranted to categorise those patients who are in a 'stable' lower or higher risk symptom phenotype. In addition, it should be noted that 75% of the patients in this study experienced moderate to high occurrence rates for 25 common symptoms from prior to through the first week following their dose of CTX.

As shown in Table 1, for 83.9% of the patients ($n$ = 760), their most likely latent class pattern remained the same from Time 1 to Time 2. In terms of patients who transitioned from a lower to a higher symptom class, 9.7% went up one class and 0.3% went up two classes. In terms of patients whose transition pattern was the opposite, 5.7% went down one class and 0.3% went down two classes. Given the small sample sizes for each of these groups, one cannot readily evaluate the exact reasons for these different patterns of transition.

As shown in Table 4 and consistent with previous reports of multiple co-occurring symptoms in oncology outpatients (Kirkova *et al.* 2012; Trudel-Fitzgerald *et al.* 2012; Oksholm *et al.* 2015), the six symptoms that were among the top 11 in occurrence rates across the three LTA classes were lack of energy (0.512–0.976), difficulty sleeping (0.401–0.946), pain (0.341–0.855), hair loss (0.338–0.733), feeling drowsy (0.255–0.877) and nausea (0.184–0.727). Of note, lack of energy, difficulty sleeping, anxiety and pain are symptoms commonly associated with cytokine-induced sickness behaviour (Dantzer *et al.* 2008; Myers 2008; Wang *et al.* 2010; Illi *et al.* 2012). However, while depression is often reported to be a symptom associated with sickness behaviour (Dantzer 2006; Harrison *et al.* 2009; Walker *et al.* 2014), it (i.e. feeling sad on the MSAS) was only found in the top 11 occurring symptoms in patients in the High–High class. In fact, in the High–High class, worrying (0.946), feeling irritable (0.895) and feeling nervous (0.758) had very high occurrence rates. None of the four psychological symptoms were found in the top 11 occurring symptoms in the other two LTA classes. This finding suggests that in addition to interven-

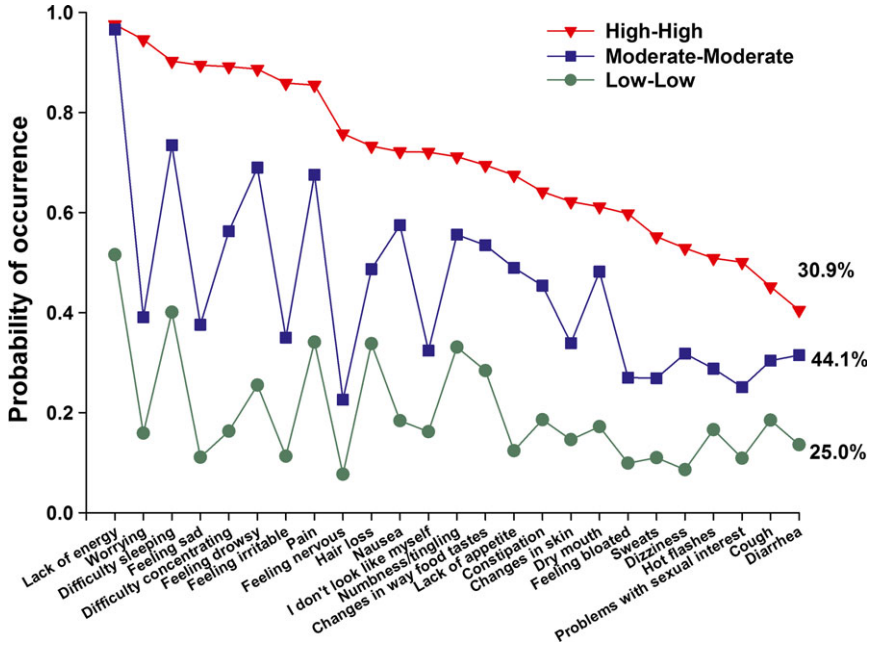


**Figure 2.** Probability of symptom occurrence for each of the latent transition classes for the 25 symptoms on the Memorial Symptom Assessment Scale that occurred in ≥40% of the total sample ($n$ = 760). The percentages on each figure indicate the percentage of patients in each of the latent classes.

tions to treat physical symptoms, patients in the High–High class require more in-depth mental health evaluation and more proactive and aggressive management of their psychological symptoms. This approach is warranted given the substantial body of evidence that has documented the negative long-term sequelae of ongoing and high levels of psychological distress in cancer patients (Stanton *et al.* 2015).

Consistent with our previous report in the same sample (Miaskowski *et al.* 2014a) as well as reports by others (Ferreira *et al.* 2008; Gwede *et al.* 2008), KPS and SCQ scores were associated with LTA class membership. While associations between a higher symptom burden and a higher level of comorbidity, as well as poorer functional status, are reported consistently in oncology patients (Miaskowski *et al.* 2006; Ferreira *et al.* 2008; Gwede *et al.* 2008; Pud *et al.* 2008; Dodd *et al.* 2010, 2011), additional research is warranted to further explicate these relationships. For example, the most common comorbid conditions in this sample were high blood pressure (31.2%), back pain (26.4%) and depression (20.1%). Many of the chronic conditions listed in Table 2 are associated with both acute and chronic symptoms. Therefore, future studies need to assess the impact of the symptoms associated with cancer and its treatment, as well as the symptoms associated with other chronic conditions, on latent class membership. In addition, future longitudinal studies need to evaluate, using statistical procedures like parallel process growth modelling (Cheong *et al.* 2003; Rose *et al.* 2009), whether increases in symptom burden are associated with decreases in functional status or vice versa. Similar approaches could be used to evaluate for changes in patients' symptom burden in relationship with changes in their comorbidity profiles.

While the majority of the characteristics associated with cancer and its treatment did not predict LTA class membership, compared to the High–High class, a relatively higher percentage of patients with GI cancer were in the Low–Low class. The exact reasons for this difference are not readily apparent and warrant investigation in future studies.

Compared to the Low–Low class, patients in the Moderate–Moderate and High–High classes were almost a half or a whole decade younger respectively. While the association between younger age and higher symptom burden is reported in previous studies (Illi *et al.* 2012; Cataldo *et al.* 2013; Miaskowski *et al.* 2014a; Ritchie *et al.* 2014), the underlying physiological and psychological mechanisms for this association remain to be determined. However, because recent evidence suggests that an overlap exists between molecular mechanisms that govern both ageing and cancer (Coppede 2013; Kong *et al.* 2013; Teschendorff *et al.* 2013; Menck & Munford 2014), patients with cancer may experience 'premature biological ageing' that is associated with a higher symptom burden. Alternatively, 'chronologically' older patients may receive lower doses of

**Table 2.** Differences in demographic and clinical characteristics among the three latent transition analysis classes ($n$ = 760)

| Characteristic | Low–Low (1) ($n$ = 190), 25.0% Mean (SD) | Moderate–Moderate (2) ($n$ = 335), 44.1% Mean (SD) | High–High (3) ($n$ = 235), 30.9% Mean (SD) | Statistics |
|---|---|---|---|---|
| Age (years) | 61.4 (10.6) | 57.0 (11.9) | 54.3 (12.1) | $F$ = 19.9, $P$ < 0.0001<br>1 > 2 > 3 |
| Education (years) | 15.7 (3.2) | 16.5 (2.8) | 16.1 (3.0) | $F$ = 4.34, $P$ = 0.013<br>1 < 2 |
| Body mass index (kg/m$^2$) | 26.1 (5.6) | 26.3 (5.8) | 25.9 (5.6) | $F$ = 0.30, $P$ = 0.741 |
| Karnofsky Performance Status score | 87.4 (9.7) | 79.7 (11.8) | 74.8 (12.0) | $F$ = 58.25, $P$ < 0.0001<br>1 > 2 > 3 |
| Self-administered Comorbidity Questionnaire score | 4.5 (2.5) | 5.5 (3.1) | 6.4 (3.3) | $F$ = 19.85, $P$ < 0.0001<br>1<2 < 3 |
| Time since diagnosis (mean in years) | 1.9 (3.2) | 2.1 (3.7) | 2.1 (4.1) | KW, $P$ = 0.871 |
| Time since diagnosis (median in years) | 0.44 | 0.44 | 0.44 | |
| Number of prior cancer treatments | 1.6 (1.6) | 1.7 (1.5) | 1.8 (1.5) | $F$ = 1.34, $P$ = 0.263 |
| Number of metastatic sites including lymph node involvement* | 1.3 (1.2) | 1.2 (1.2) | 1.2 (1.2) | $F$ = 0.42, $P$ = 0.656 |
| Number of metastatic sites excluding lymph node involvement | 0.9 (1.1) | 0.8 (1.1) | 0.8 (1.0) | $F$ = 0.74, $P$ = 0.477 |
| Mean number of MSAS symptoms (out of 32) | 5.5 (2.7) | 12.4 (3.0) | 19.3 (4.2) | $F$ = 880.63, $P$ <0.0001<br>1 < 2 < 3 |
| | % ($n$) | % ($n$) | % ($n$) | |
| Gender (% female) | 68.9 (131) | 78.2 (262) | 89.8 (211) | $\chi^2$ = 31.96, $P$ < 0.0001<br>1 < 2 < 3 |
| Self-reported ethnicity | | | | |
| White | 71.0 (130) | 72.9 (240) | 68.4 (158) | $\chi^2$ = 1.37, $P$ = 0.505 |
| Non-White | 29.0 (53) | 27.1 (89) | 31.6 (73) | |
| Married or partnered (% yes) | 70.1 (131) | 67.1 (222) | 62.7 (146) | $\chi^2$ = 2.64, $P$ = 0.266 |
| Lives alone (% yes) | 17.0 (32) | 19.9 (66) | 23.9 (56) | $\chi^2$ = 3.16, $P$ = 0.206 |
| Currently employed (% yes) | 37.2 (70) | 37.4 (125) | 28.6 (67) | $\chi^2$ = 5.43, $P$ = 0.066 |
| Annual household income | | | | |
| Less than $30 000 | 16.7 (27) | 15.9 (49) | 22.0 (46) | KW=9.47, $P$ = 0.230 |
| $30 000 to $70 000 | 24.1 (39) | 22.7 (70) | 18.7 (39) | |
| $70 000 to $100 000 | 17.9 (29) | 13.6 (42) | 19.6 (41) | |
| Greater than $100 000 | 41.4 (67) | 47.9 (148) | 39.7 (83) | |
| Child care responsibilities (% yes) | 15.7 (29) | 24.0 (79) | 29.1 (67) | $\chi^2$ = 10.40, $P$ = 0.006<br>1 < 2 and 3 |
| Elder care responsibilities (% yes) | 6.9 (12) | 9.9 (30) | 7.0 (15) | $\chi^2$ = 1.95, $P$ = 0.378 |
| Common comorbidities (% yes) | | | | |
| Heart disease | 4.7 (9) | 5.7 (19) | 4.3 (10) | $\chi^2$ = 0.62, $P$ = 0.733 |
| High blood pressure | 34.7 (66) | 31.9 (107) | 27.2 (64) | $\chi^2$ = 2.92, $P$ = 0.233 |
| Lung disease | 12.6 (24) | 11.0 (37) | 11.9 (28) | $\chi^2$ = 0.31, $P$ = 0.857 |
| Diabetes | 8.4 (16) | 9.3 (31) | 7.7 (18) | $\chi^2$ = 0.45, $P$ = 0.797 |
| Ulcer or stomach disease | 2.6 (5) | 4.2 (14) | 6.4 (15) | $\chi^2$ = 3.58, $P$ = 0.167 |
| Kidney disease | 0.0 (0) | 0.9 (3) | 1.7 (4) | $\chi^2$ = 3.34, $P$ = 0.188 |
| Liver disease | 7.4 (14) | 3.3 (11) | 7.7 (18) | $\chi^2$ = 6.34, $P$ = 0.042 |
| Anaemia | 6.3 (12) | 13.1 (44) | 18.3 (43) | No significant pw contrasts |
| Depression | 5.8 (11) | 14.9 (50) | 39.1 (92) | $\chi^2$ = 13.32, $P$ = 0.001 |
| Osteoarthritis | 10.5 (20) | 9.6 (32) | 16.2 (38) | 1 < 3 |
| Back pain | 15.8 (30) | 24.8 (83) | 37.4 (88) | $\chi^2$ = 82.81, $P$ < 0.0001 |
| Rheumatoid arthritis | 3.2 (6) | 3.9 (13) | 3.4 (8) | 1<2<3 |
| Cancer diagnosis | | | | |
| Breast cancer | 34.7 (66) | 41.5 (139) | 46.0 (108) | $\chi^2$ = 23.36, $P$ = 0.001 |
| Gastrointestinal cancer | 35.8 (68) | 27.5 (92) | 21.3 (50) | 1>3 |
| Gynaecological cancer | 14.7 (28) | 16.7 (56) | 24.7 (58) | |
| Lung cancer | 14.7 (28) | 14.3 (48) | 8.1 (19) | |
| Prior cancer treatment | | | | |
| No prior treatment | 27.6 (51) | 23.4 (77) | 15.9 (37) | $\chi^2$ = 11.25, $P$ = 0.081 |
| Only surgery, CTX or RT | 35.1 (65) | 41.6 (137) | 45.9 (107) | |
| Surgery and CTX, or surgery and RT, or CTX and RT | 23.8 (44) | 20.1 (66) | 21.5 (50) | |
| Surgery and CTX and RT | 13.5 (25) | 14.9 (49) | 26.7 (39) | |

**Table 2.** *Continued*

| Characteristic | Low–Low (1) ($n$ = 190), 25.0% Mean (SD) | Moderate–Moderate (2) ($n$ = 335), 44.1% Mean (SD) | High–High (3) ($n$ = 235), 30.9% Mean (SD) | Statistics |
|---|---|---|---|---|
| Metastatic sites | | | | |
| No metastasis | 29.1 (55) | 33.3 (111) | 36.1 (84) | $\chi^2 = 6.33$, $P = 0.387$ |
| Only lymph node metastasis | 20.1 (38) | 23.1 (77) | 21.0 (49) | |
| Only metastatic disease in other sites | 28.6 (54) | 23.7 (79) | 19.7 (46) | |
| Metastatic disease in lymph nodes and other sites | 22.2 (42) | 19.8 (66) | 23.2 (54) | |

CTX, chemotherapy; KW, Kruskal–Wallis; pw, pairwise; RT, radiation therapy; SD, standard deviation.
*Total number of metastatic sites evaluated was 9.

**Table 3.** Differences in disease-specific and generic quality of life scores among the three latent transition analysis classes ($n$ = 760)

| Characteristic | Low–Low (1) ($n$ = 190), 25.0% Mean (SD) | Moderate–Moderate (2) ($n$ = 335), 44.1% Mean (SD) | High–High (3) ($n$ = 235), 30.9% Mean (SD) | Statistics |
|---|---|---|---|---|
| Multidimensional quality of life scale | | | | |
| Physical well-being | 8.1 (1.3) | 6.6 (1.6) | 5.5 (1.7) | $F = 153.26$, $P < 0.001$ 1 > 2 > 3 |
| Psychological well-being | 6.9 (1.5) | 5.7 (1.7) | 4.1 (1.5) | $F = 170.35$, $P < 0.001$ 1 > 2 > 3 |
| Social well-being | 7.1 (1.7) | 5.8 (1.8) | 4.4 (1.7) | $F = 119.97$, $P < 0.0001$ 1 > 2 > 3 |
| Spiritual well-being | 5.4 (2.2) | 5.3 (2.1) | 5.2 (2.1) | $F = 0.58$, $P = 0.562$ |
| Total QOL score | 6.9 (1.2) | 5.8 (1.3) | 4.6 (1.2) | $F = 183.88$, $P < 0.001$ 1 > 2 > 3 |
| SF12 scores | | | | |
| Physical functioning | 65.6 (34.0) | 48.0 (32.8) | 42.3 (32.5) | $F = 25.89$, $P < 0.001$ 1 > 2 and 3 |
| Role physical | 70.6 (26.2) | 51.1 (27.6) | 40.5 (26.8) | $F = 63.54$, $P < 0.001$ 1 > 2 > 3 |
| Bodily pain | 91.3 (17.9) | 76.4 (25.9) | 64.1 (29.2) | $F = 58.64$, $P < 0.0001$ 1 > 2 > 3 |
| General health | 73.1 (22.6) | 64.1 (27.3) | 51.9 (28.8) | $F = 32.58$, $P < 0.001$, 1 > 2 > 3 |
| Vitality | 62.9 (22.6) | 42.0 (24.5) | 35.0 (24.8) | $F = 72.61$, $P < 0.001$ 1 > 2 > 3 |
| Social functioning | 85.9 (21.8) | 67.1 (29.5) | 52.1 (30.3) | $F = 73.36$, $P < 0.0001$ 1 > 2 > 3 |
| Role emotional | 87.7 (22.0) | 78.2 (25.5) | 62.8 (27.8) | $F = 50.89$, $P < 0.001$ 1 > 2 > 3 |
| Mental health | 83.9 (16.9) | 74.6 (18.2) | 57.7 (20.2) | $F = 108.83$, $P < 0.001$ 1 > 2 > 3 |
| Physical Component Summary score | 46.2 (9.2) | 40.0 (10.3) | 38.3 (10.0) | $F = 33.07$, $P < 0.0001$ 1 > 2 and 3 |
| Mental Component Summary score | 55.3 (8.6) | 50.2 (9.4) | 42.5 (9.8) | $F = 92.45$, $P < 0.0001$ 1 > 2 > 3 |

SD, standard deviation.

CTX (Townsley *et al.* 2005; Kumar *et al.* 2007) or have a 'response shift' in their perception of symptoms (Schwartz & Sprangers 1999; Sprangers & Schwartz 1999).

While female gender, years of education and child care responsibilities were associated with a higher symptom burden in the current study, findings regarding these characteristics are inconsistent across studies (Miaskowski 2004; Baldwin *et al.* 2010; Cheung *et al.* 2011; Dodd *et al.* 2011; Illi *et al.* 2012; Miaskowski *et al.* 2014b). In addition, while other studies found that being a member of an ethnic minority and reporting a lower socioeconomic status were associated with more severe symptoms (Miaskowski *et al.* 2014a), these associations were not found in the current study. Additional research is warranted to confirm or refute these inconstant findings.

For both the generic- (SF-12) and disease-specific (MQOLS-PV) measures of QOL, as symptom burden increased, QOL decreased. The decrements in QOL among the three latent classes represent not only statistically significant, but clinically meaningful decreases in QOL with

**Table 4.** Probability of occurrence for the 25 MSAS symptoms for each of the three latent transition class in descending order of occurrence

| Rank order | High–High | *P* | Moderate–Moderate | *P* | Low–Low | *P* |
|---|---|---|---|---|---|---|
| 1 | Lack of energy | 0.976 | Lack of energy | 0.966 | Lack of energy | 0.512 |
| 2 | Worrying | 0.946 | Difficulty sleeping | 0.735 | Difficulty sleeping | 0.401 |
| 3 | Difficulty sleeping | 0.903 | Feeling drowsy | 0.690 | Pain | 0.341 |
| 4 | Feeling sad | 0.895 | Pain | 0.676 | Hair loss | 0.338 |
| 5 | Difficulty concentrating | 0.892 | Nausea | 0.575 | Numbness and tingling in hands/feet | 0.331 |
| 6 | Feeling drowsy | 0.887 | Difficulty concentrating | 0.563 | Changes in the way food tastes | 0.284 |
| 7 | Feeling irritable | 0.859 | Numbness and tingling in hands/feet | 0.556 | Feeling drowsy | 0.255 |
| 8 | Pain | 0.855 | Changes in the way food tastes | 0.535 | Constipation | 0.186 |
| 9 | Feeling nervous | 0.758 | Lack of appetite | 0.490 | Cough | 0.185 |
| 10 | Hair loss | 0.733 | Hair loss | 0.487 | Nausea | 0.184 |
| 11 | Nausea | 0.727 | Dry mouth | 0.482 | Dry mouth | 0.172 |
| 12 | I don't look like myself | 0.721 | Constipation | 0.454 | Hot flashes | 0.166 |
| 13 | Numbness and tingling in hands/feet | 0.712 | Worrying | 0.391 | Difficulty concentrating | 0.163 |
| 14 | Changes in the way food tastes | 0.695 | Feeling sad | 0.376 | I don't look like myself | 0.162 |
| 15 | Lack of appetite | 0.675 | Dizziness | 0.368 | Worrying | 0.159 |
| 16 | Constipation | 0.642 | Feeling irritable | 0.350 | Changes in skin | 0.146 |
| 17 | Changes in skin | 0.622 | Changes in skin | 0.339 | Diarrhoea | 0.136 |
| 18 | Dry mouth | 0.612 | I don't look like myself | 0.324 | Lack of appetite | 0.124 |
| 19 | Feeling bloated | 0.598 | Diarrhoea | 0.315 | Feeling irritable | 0.113 |
| 20 | Sweats | 0.552 | Cough | 0.304 | Feeling sad | 0.111 |
| 21 | Dizziness | 0.529 | Hot flashes | 0.288 | Sweats | 0.110 |
| 22 | Hot flashes | 0.509 | Feeling bloated | 0.270 | Problems with sexual interest | 0.109 |
| 23 | Problems with sexual interest | 0.501 | Sweats | 0.269 | Feeling bloated | 0.099 |
| 24 | Cough | 0.452 | Problems with sexual interest | 0.251 | Dizziness | 0.086 |
| 25 | Diarrhoea | 0.405 | Feeling nervous | 0.226 | Feeling nervous | 0.077 |

effect sizes ranging from 0.44 to 1.54 (Osoba 1999; Sloan *et al.* 2003). Taken together and consistent with previous reports (Ferreira *et al.* 2008; Gwede *et al.* 2008; Illi *et al.* 2012; Miaskowski *et al.* 2014a), these findings provide evidence of the significant negative impact that multiple co-occurring symptoms have on patients' ability to function and other QOL outcomes.

Several study limitations need to be acknowledged. Because patients were recruited at different points in their CTX treatment, symptom occurrence rates prior to the initiation of CTX are not available. In addition, the CTX drugs used varied based on the patients' diagnoses and stages of disease. While we cannot rule out the potential contributions of these clinical characteristics to the patients' symptom experiences, the relatively similar percentages of cancer diagnoses, evidence of metastatic disease, time since cancer diagnosis and types of previous treatments suggest that the three LTA classes were relatively similar in terms of disease and treatment characteristics. While it is possible that patients in the Low–Low class were receiving more aggressive symptom management interventions, the occurrence rates for fatigue, sleep disturbance and pain were high across the three LTA classes. Finally, it should be noted that given the fact that 40% of the patients who were approached declined to participate in this study because they were too overwhelmed with their treatment, this study may be underestimating the symptom burden of oncology patients undergoing CTX. Additional studies are needed to confirm our findings.

In the era of precision medicine (Collins & Varmus 2015) and big data (Yoo *et al.* 2014), coupled with the use of electronic medical records and smart phone technology (e.g. the ASyMS/eSMART© system that is being evaluated as part of a grant from the European Commission; Kearney *et al.* 2009; Maguire *et al.* 2015), it is conceivable that symptom data will be collected in 'real time' from oncology patients receiving CTX. The use of analytic approaches like LTA, or the development of more sophisticated algorithms using techniques like machine learning (Bastanlar & Ozuysal 2014; Yoo *et al.* 2014), will allow

clinicians to analyse patients' phenotypic and molecular data on an ongoing basis. The integration of these types of information across multiple patients will assist clinicians to identify patients at highest risk for the most severe symptom profiles and to pre-emptively or more aggressively treat their most common and severe symptoms. This type of risk profiling and aggressive symptom management should reduce oncology patients' symptom burden and improve their QOL.

## ACKNOWLEDGEMENTS

This study was funded by the National Cancer Institute (CA134900). In addition, this project received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement number 602289.

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