Title

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Journal

Cancer Nursing, 46(2)

ISSN

0162-220X

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Publication Date

2023-03-01

DOI

10.1097/ncc.0000000000001076

Peer reviewed

HHS Public Access

Author manuscript

Cancer Nurs. Author manuscript; available in PMC 2024 January 01.

Published in final edited form as:

Cancer Nurs. 2023 ; 46(2): 92–102. doi:10.1097/NCC.0000000000001076.

Distinct Nausea Profiles Are Associated With Gastrointestinal Symptoms In Oncology Patients Receiving Chemotherapy

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Conflict of interest: The authors have no conflicts of interest to disclose.

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Abstract

Background: Unrelieved chemotherapy-induced nausea (CIN) occurs 48% of patients undergoing chemotherapy and is one of the most debilitating symptoms that patients report.

Objective: Identify subgroups of patients with distinct CIN profiles and determine how these subgroups differed on demographic and clinical characteristics; severity, frequency, and distress of CIN; and the co-occurrence of common gastrointestinal symptoms.

Methods: Patients (n=1343) completed demographic questionnaire and Memorial Symptom Assessment Scale six times over two cycles of chemotherapy. Latent class analysis was used to identify subgroups of patients with distinct CIN profiles. Differences among these subgroups were evaluated using parametric and nonparametric statistics.

Results: Four distinct CIN profiles were identified: none (40.8%), increasing-decreasing (21.5%), decreasing (8.9%), and high (28.8%). Compared to the none class, patients in the high class were: younger; had a lower annual household income; had child care responsibilities; had a lower KPS score and a higher SCQ score; and were more likely to have received chemotherapy on a 14-day cycle and a highly emetogenic chemotherapy regimen. In addition, patients in the high class reported high occurrence rates for dry mouth, feeling bloated, diarrhea, lack of appetite, abdominal cramps, difficulty swallowing, mouth sores, weight loss, and change in the way food tastes.

Conclusions: Given that 60% of the patients reported moderate to high CIN occurrence rates confirms that this unrelieved symptom is a significant clinical problem.

Implications for Practice: Nurses need to evaluate patients' level of adherence with their anti-emetic regimen and make appropriate referrals for physical therapy, psychological services; and dietary counseling.

INTRODUCTION

Despite current evidence-based antiemetic interventions, persistent chemotherapy-induced nausea (CIN) continues to be one of the most debilitating symptoms reported by oncology patients.[1, 2] In our recent study,[3] 48% of patients reported unresolved CIN, in the week following their second or third cycle of chemotherapy and the majority rated it as severe and very distressing. Persistent CIN can lead to dehydration, nutritional deficits, decrements in quality of life, and even discontinuation of treatment.[4]

Based on findings from cross-sectional studies, risk factors for CIN include: age >60 years,[5–7] female gender,[6–8] lower functional status,[3] highly emetogenic chemotherapy regimens,[3, 5, 6, 8] and higher serum albumin levels.[5] While the occurrence of CIN during

the first cycle of chemotherapy is a risk factor in future cycles,[4] only four longitudinal studies have evaluated for changes in the occurrence of CIN over time.[4, 9–11] Of note, in two of our longitudinal studies, [10, 11] a large amount of inter-individual variability was found in the occurrence of CIN over two cycles of chemotherapy. Across the thirteen studies listed above, the samples were fairly heterogenous in terms of age, gender, and cancer diagnoses, as well as the emetogenicity of the chemotherapy regimens.

Using hierarchical linear modeling,[10, 11] younger age, a higher comorbidity burden, lower levels of physical function, shorter cycle length, and higher emetogenicity of the chemotherapy regimen were associated with higher CIN occurrence rates. In addition, higher levels of sleep disturbance, depression, and morning fatigue[11] and the occurrence of vomiting, lack of appetite, constipation, feeling bloated, and difficulty swallowing[10] were risk factors for CIN occurrence. The positive associations between CIN and various neuropsychological and gastrointestinal symptoms support recent hypotheses that in addition to inflammation,[12] alterations in the microbiome-gut-brain-axis[13] may contribute to an increased symptom burden in oncology patients.[14, 15]

While statistical approaches like hierarchical linear modeling provide some information on risk factors associated with initial levels and trajectories of CIN,[10, 11] they do not allow for the identification of subgroups of patients who are at increased risk for CIN. The use of person centered analytic approaches, like latent class analysis (LCA) allows for the identification of groups of patients with distinct CIN profiles.

While LCA was used to identify distinct symptom profiles associated with chemotherapy-induced diarrhea,[16] no studies have used this approach with CIN. Therefore, the purposes of this study, in a sample of oncology outpatients with breast, gastrointestinal, gynecological, or lung cancer (n=1343), were to identify subgroups of patients with distinct CIN profiles and determine how these subgroups differed in terms of a comprehensive list of demographic and clinical characteristics; severity, frequency, and distress of CIN; and the co-occurrence of common gastrointestinal symptoms.

METHODS

Patients and settings

This analysis is part of a larger, longitudinal study of the symptom experience of oncology outpatients receiving chemotherapy.[17] The conceptual framework that guided the parent study was the Theory of Symptom Management developed by faculty members at the University of California, San Francisco.[18] Eligible patients were ≥18 years; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; 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 programs.

Study procedures

The study was approved by the Institutional Review Board at each of the study sites. Of the 2234 patients approached, 1343 consented to participate and provided evaluable data on CIN for this analysis. Patients' refusal to participate was primarily due to being overwhelmed with their cancer treatment. Eligible patients were approached in the infusion unit during their first or second cycle of chemotherapy to discuss participation in the study. Patients completed paper and pencil questionnaires in their homes six times over the next two cycles of chemotherapy, namely: prior to chemotherapy administration (Assessments 1 and 4), approximately 1 week after chemotherapy administration (Assessments 2 and 5), and approximately 2 weeks after chemotherapy administration (Assessments 3 and 6). The questionnaire administration times were adjusted to account for the cycle length of the chemotherapy (i.e., 14, 21, or 28 days).

Instruments

Demographic and clinical characteristics ––—Patients completed a demographic questionnaire, Karnofsky Performance Status (KPS) scale,[19] Self-Administered Comorbidity Questionnaire (SCQ),[20] Alcohol Use Disorders Identification Test,[21] and a smoking history questionnaire. Medical records were reviewed for disease and treatment information.

Assessment of CIN occurrence ––—The nausea item from the Memorial Symptom Assessment Scale (MSAS) was used to assess for the occurrence of CIN at each of the six assessments. The MSAS is a valid and reliable symptom assessment instrument in oncology patients that evaluates the occurrence, severity, frequency, and distress of 32 common symptoms.[22]

Assessment of additional gastrointestinal symptoms ––—A modified version of the MSAS was used to evaluate the occurrence of eleven common gastrointestinal symptoms associated with chemotherapy or the cancer itself: dry mouth, feeling bloated, vomiting, diarrhea, lack of appetite, abdominal cramps, difficulty swallowing, mouth sores, weight loss, constipation, and change in the way food tastes. Data from the enrollment assessment were used to evaluate the co-occurrence of these common gastrointestinal symptoms with the distinct CIN profiles.

Coding of the chemotherapy regimens

Given the diversity in the patients' cancer diagnoses and absolute number of different chemotherapy regimens, the regimens were coded as follows: received only chemotherapy, received only targeted therapy, or received both chemotherapy and targeted therapy. In addition, the MAX2 score was used to evaluate the toxicity of the various chemotherapy regimens.[23] A MAX2 score is the average of the most frequent grade 4 hematologic toxicity and the most frequent grade 3 to 4 non-hematologic toxicity reported in publications of a chemotherapy regimen. The score correlates with the overall risk of severe toxicity for that regimen.

Coding of the emetogenicity of the chemotherapy regimens

Using the Multinational Association for Supportive Care in Cancer guidelines,[24] each chemotherapy drug was classified as having: minimal, low, moderate, or high emetogenic potential. Emetogenicity of the regimen was categorized into one of three groups (i.e., low/minimal, moderate, high) based on the chemotherapy drug with highest emetogenic potential.

Coding of the antiemetic regimens

Each prescribed antiemetic was coded as either a neurokinin-1 (NK-1) receptor antagonist, a serotonin receptor antagonist, a dopamine receptor antagonist, prochlorperazine, lorazepam, or a steroid. The antiemetic regimens were coded into one of four groups: none (i.e., no antiemetics administered); steroid alone or serotonin receptor antagonist alone; serotonin receptor antagonist and steroid; or NK-1 receptor antagonist and two other antiemetics.

Data analyses

Descriptive statistics and frequency distributions were generated for sample characteristics at enrollment using the Statistical Package for the Social Sciences version 27 (IBM Corporation, Armonk, NY). As was done for diarrhea,[16] unconditional LCA was used to identify the profiles of CIN occurrence that characterized unobserved subgroups of patients (i.e., latent classes) over the six assessments.[25] Prior to performing the LCA, patients who responded “no” to the nausea item on the MSAS for five or six assessments (i.e., these patients did not experience nausea across the two cycles of chemotherapy) were identified and labeled as the “none” class (n=548). Then, the LCA was performed using data from the remaining 795 patients.

Estimation was carried out with full information maximum likelihood with standard errors and a Chi-square test that are robust to non-normality and non-independence of observations (“estimator=MLR”) using a logit link because the items are binary. Model fit was evaluated to identify the solution that best characterized the observed latent class structure with the Bayesian Information Criterion (BIC), Vuong-Lo-Mendell-Rubin likelihood ratio test (VLRM), entropy, and latent class percentages that were large enough to be reliable (i.e., likely to replicate in new samples).[26] Missing data were accommodated with the use of the Expectation-Maximization (EM) algorithm.[27] Mixture models, like LCA, are known to produce solutions at local maxima. Therefore, our models were fit with from 800 to 2,400 random starts. This approach ensured that the estimated model was replicated many times and was not due to a local maximum. Estimation was done with Mplus Version 8.2. [26]

Differences among the latent classes in demographic, clinical, and gastrointestinal symptom characteristics at enrollment were evaluated using analysis of variance and Kruskal-Wallis or Chi Square tests with Bonferroni corrected post hoc contrasts. The comprehensive list of demographic, clinical, and symptom characteristics was created based on a review of the extant literature. A corrected p-value of <.008 (i.e., .05/6 possible pairwise contrasts) was considered statistically significant.

RESULTS

Latent class analysis

The 548 patients (40.8%) who had ≤1 occurrence of CIN over the six assessments were labeled as the none class. As described in Table 1, for the remaining 795 patients whose data were entered into the LCA, a three class solution was selected. As shown in Figure 1, the trajectories for the occurrence of CIN differed among the latent classes. For the increasing-decreasing class (21.5%), the CIN occurrence rate increased from the first to the second assessment, decreased at the third assessment, increased again at the fourth and fifth assessments before decreasing at the sixth assessment. For the decreasing class (8.9%), the occurrence rate for CIN increased slightly from the first to the second assessment, then gradually decreased over the remaining four assessments. For the high class (28.8%), the occurrence rates for CIN remained consistently high over the six assessments.

Demographic and clinical characteristics

As shown in Table 2, compared to the none class, patients in the high class were significantly younger; more likely to have a lower annual household income; and to have child care responsibilities. In addition, they had a lower KPS score, a higher SCQ score, and were more likely to self-report diagnoses of ulcer/stomach disease, anemia or blood disease, or depression. In terms of chemotherapy regimen, compared to the none class, patients in the high class were more likely to have received: only chemotherapy; chemotherapy on a 14-day cycle; and a highly emetogenic chemotherapy regimen. In addition, compared to the none class, patients in the high class were less likely to have received only targeted therapy. Compared to the increasing-decreasing class, patients in the high class had a lower KPS score, were less likely to exercise on a regular basis, were more likely to have gastrointestinal cancer, and were less likely to have gynecological cancer.

Compared to the none class, patients in the increasing-decreasing class were younger and more likely to be female. In addition, they had a higher MAX2 score, a lower KPS score, were more likely to self-report a diagnosis of depression, and were less likely to receive a minimal/low emetogenic chemotherapy regimen. Compared to the none class, patients in the decreasing class had a lower KPS score.

Frequency, Severity, and Distress of CIN

Significant differences were found among the three classes who reported CIN, in the frequency, severity, and distress of nausea at enrollment (Figures 2A-C; all $p<0.05$). For all three dimensions of the symptom experience, post hoc contrasts found that compared to the increasing-decreasing and the decreasing classes, patients in the high class reported a higher frequency of, a worst severity of, and higher distress from CIN.

Occurrence of GI symptoms

As shown in Table 3, compared to none class, patients in the other three classes reported higher occurrence rates for vomiting and diarrhea. Compared to none and increasing-decreasing classes, patients in the high class reported higher occurrence rates for dry mouth, feeling bloated, abdominal cramps, difficulty swallowing, and mouth sores. Compared to

none class, patients in the decreasing and high classes reported higher occurrence rates for lack of appetite, weight loss, constipation, and change in the way food tastes. Compared to increasing-decreasing class, patients in the high class reported higher occurrence rates for vomiting, lack of appetite, weight loss, constipation, and change in the way food tastes.

DISCUSSION

This study is the first to use LCA to identify subgroups of patients with distinct CIN profiles; determine how these subgroups differed on demographic and clinical characteristics; categorize the severity, frequency, and distress of CIN; and describe differences in the co-occurrence of common gastrointestinal symptoms. While previous reports suggest that between 30% and 60% of patients experience CIN,[28, 29] our data confirm rates on the higher side of this range (i.e., 59.2%). Of note, patients in the high class (28.8%) had persistently high occurrence rates of CIN for almost two months. While 77.9% of the patients in the high class were receiving combination antiemetic regimens, their frequency, severity, and distress ratings for CIN were in the moderate to severe ranges (Figure 2). While patients' level of adherence with their antiemetic regimen was not evaluated, our findings suggest that persistent CIN remains a clinically significant problem that warrants follow-up phone calls to assess its occurrence and to provide tailored pharmacologic and/or non-pharmacologic interventions.

One of the goals of our LCA was to determine common and distinct risk factors associated with membership in the mild, moderate, and high CIN classes. Table 4 summarizes the demographic, clinical, and gastrointestinal symptom characteristics associated with the three nausea classes compared to the none class. The remainder of the discussion elaborates on these differences.

Demographic characteristics associated with worse CIN profiles

While patients in the increasing-decreasing and high classes were more likely to be younger, findings regarding age differences in the occurrence and severity of CIN are inconsistent.[5–7] In terms of gender differences, only the increasing-decreasing class had a higher percentage of females compared to the none class. To resolve these inconsistent findings, future research needs to evaluate for age differences (e.g., < 65 years versus ≥65 years of age) within chemotherapy regimens and for gender differences within cancer types that effect men and women equally (e.g., colorectal cancer). Equally important, patients' adherence with their antiemetic regimens needs to be included as a covariate in these analyses.

While not identified as a risk factor in previous studies, compared to none class, patients in the high class were more likely to report a lower annual household income. One potential explanation that warrants confirmation is that these patients were not able to afford their antiemetic regimens. In addition, patients in the high class were more likely to report child care responsibilities. Again, reasons for this association warrant additional investigation. However, consistent with previous reports,[30, 31] compared to the increasing-decreasing class, patients in the high class were less likely to exercise on a regular basis. Given that resistance training and breathing exercises are known to decrease CIN occurrence,[30, 31] clinicians can recommend these non-pharmacologic interventions to patients with persistent CIN.

Clinical characteristics associated with worse CIN profiles

Compared to our none class, patients in the other three classes were more likely to have a poorer functional status. While most of the research on the impact of CIN has documented decrements in quality of life,[32] our findings are consistent with previous studies that demonstrated associations between CIN and decreases in physical function.[32, 33] In addition, in a study that evaluated the efficacy of a breathing exercise intervention to decrease nausea and improve functional status in breast cancer patients receiving chemotherapy,[31] women who received the intervention reported fewer episodes of nausea and improvements in physical function scores. The theoretical underpinning for this breathing exercise was that it would reduce patients' level of stress and associated anxiety. Given the positive results of this small, randomized clinical trial (n = 60), clinicians can recommend this easy and cost effective nonpharmacologic intervention to decrease CIN.

While not described previously, compared to the none class, patients in the high class had higher SCQ scores. Specifically, patients in the high class were more likely to self-report diagnoses of ulcer or stomach disease, anemia or blood disease, and depression. Support for this association comes from a meta-analysis of the efficacy and safety of platinum-containing regimens in patients with lung cancer [34] that found that these regimens were associated not only with the occurrence of CIN but with other comorbidities (e.g., anemia) and decrements in physical function. These findings suggest that clinicians need to assess for and manage co-occurring medical conditions and provide referrals for physical therapy to improve functional status.

While we could not evaluate for differences in CIN occurrence associated with specific chemotherapy regimens because of the extreme heterogeneity in the regimens even within a single cancer diagnosis, compared to the none class, patients in the increasing-decreasing class were more likely to have a higher MAX2 score. This association is consistent with previous work that suggests that more toxic chemotherapy regimens increase the occurrence of CIN.[35] While previous studies have focused on altered drug transport [2] and elimination [2] pathways as underlying mechanisms for this association, future studies need to evaluate other potential mechanisms (e.g., role of the gut microbiome in metabolism of chemotherapy drugs).[36] In terms of chemotherapy cycle length, compared with the none class, a larger percentage of patients in the high class (37.8% vs. 53.0%) received chemotherapy on a 14-day cycle. Given the increased exposure to the drugs and potential for repeated episodes of CIN, a shorter duration between chemotherapy infusions appears to be a risk factor for CIN occurrence.[37]

Given the heterogeneity in our patients' chemotherapy regimens, we categorized them based on their emetogenicity and type (i.e., only chemotherapy, only targeted therapy, or both chemotherapy and targeted therapy). Compared to the none class, patients in the high class were more likely to receive only chemotherapy (65.5% vs. 76.0%) and highly emetogenic chemotherapy (14.6% vs. 25.5%). These findings are consistent with a study that reported that patients with breast cancer who received highly emetogenic chemotherapy were at increased risk for CIN.[5] Clinicians need to monitor patients' level of adherence with antiemetic regimens; instruct them on proper administration procedures; and recommend additional non-pharmacologic interventions.

Gastrointestinal symptoms associated with worse CIN profiles

Consistent with a single report,[38] compared to our none class, a higher percentage of patients in the high class reported the occurrence of all of the gastrointestinal symptoms that were evaluated in this study (Table 4). Potential explanations for this very high gastrointestinal symptom burden comes from our previous gene expression studies with the same sample.[13, 39] Results from these analyses suggest that perturbations in pathways involved in mucosal inflammation, disruption in the gut microbiome, apoptosis, and endocytosis are associated with CIN occurrence. In addition, previous work suggests that chemotherapy-related disruption of the gut microbiome is associated with mouth sores,[40, 41] dry mouth,[42] and change in the way food tastes.[43] Gut microbiome diversity decreases during chemotherapy treatment.[36] The gut microbiome composition profile shifts towards an increase in *Bacteroidetes* and *Proteobacteria* and a decrease in *Firmicutes* and *Actinobacteria*.[36] These changes may increase pro-inflammatory processes that result in CIN and other gastrointestinal symptoms.[44] Future studies need to evaluate for differences in gut microbiome composition profiles among patients with distinct CIN profiles. These studies may help to identify interventions to decrease CIN and other gastrointestinal symptoms.

Compared to the none class, patients in the other three classes were more likely to report vomiting and diarrhea. Co-occurrence of these symptoms across the three latent classes may be a result of chemotherapy-induced damage to the mucosal lining of the gastrointestingal tract.[13] Chemotherapy generates free radicals that stimulate enterochromaffin cells in the lining of the stomach to release excessive amounts of serotonin.[45] In addition, the free radicals cause mucosal inflammation along the entire gastrointestinal tract.[13] This biological hypothesis is supported by the fact that these three symptoms often co-occur as part of a gastrointestinal symptom cluster.[46]

Compared to the none class, patients in the decreasing and high classes were more likely to report the occurrence of lack of appetite, weight loss, constipation, and change in the way food tastes. The co-occurrence of these symptoms is supported by findings from patients with breast [47] and ovarian [48] cancer that demonstrated that these four symptoms were part of a symptom cluster. Additional reasons for the co-occurrence of these four symptoms include the patient's antiemetic regimen, [49] as well as the direct effects of chemotherapy on the oral mucosa.[50] Future studies need to investigate associations between specific antiemetic regimens, as well as patient's adherence with these regimens and the co-occurrence of gastrointestinal symptoms.

Limitations

Several limitations warrant consideration. In our study, a number of risk factors were not assessed including: occurrence of CIN during the first cycle of chemotherapy,[4] motion sickness,[5] and migraines.[2, 5] Future studies need to assess for these risk factors as well as those identified in the current study within the context of specific chemotherapy regimens and dosing schedules. In addition, future studies should enroll patients prior to and follow them through the completion of chemotherapy; enroll patients who are chemotherapy naïve; evaluate patients' level of adherence with antiemetic regimens; account for dose reductions;

and evaluate for emergency room visits and hospitalizations. Future studies need to evaluate for distinct CIN profiles in patients who do and do not receive anti-emetics that were prescribed using evidenced-based guidelines and tailored to the emetogenicity of their chemotherapy regimen. Equally important, given that this study collected data on only those anti-emetics that were administered in the infusion unit, future research needs to evaluate for differences among the distinct nausea profiles in the use of as needed anti-emetics, as well as the dose and duration of the anti-emetics that the patients took at home. Additional research is warranted to replicate our CIN profiles; validate the co-occurrence of multiple gastrointestinal symptoms; and examine relationships between CIN profiles and changes in gut microbiome composition.

Implications for Practice

Despite these limitations, the current study is the first to identify subgroups of oncology patients with distinct nausea profiles. Given that almost 60% of the patients in this study reported moderate to high CIN occurrence rates confirms that this unrelieved symptom is a significant clinical problem. This high occurrence rate for over two months in almost 30% of the patients (i.e., high class) suggests that clinicians need to: perform routine assessments of nausea between chemotherapy cycles; provide detailed information to patients on how to administer their anti-emetics and to contact their clinicians if they experience persistent nausea; and to adjust patients' anti-emetic regimens to reduce this debilitating symptom.

The current study identified a number of modifiable (e.g., poorer physical function) and non-modifiable (e.g., younger age, female gender) risk factors for CIN occurrence. Based on the assessment of these risk factors, appropriate referrals can be made. For example, patients with child care responsibilities should be provided with information on social services. Patients with a diagnosis of depression warrant referral for psychological services. Patients with decrements in physical function need a referral for physical therapy. Finally, given the co-occurrence of multiple gastrointestinal symptoms with CIN, nutritional counseling needs to be provided to these patients.

Acknowledgments:

This study was supported by a grant from the National Cancer Institute (CA134900). Dr. Miaskowski is an American Cancer Society Clinical Research Professor. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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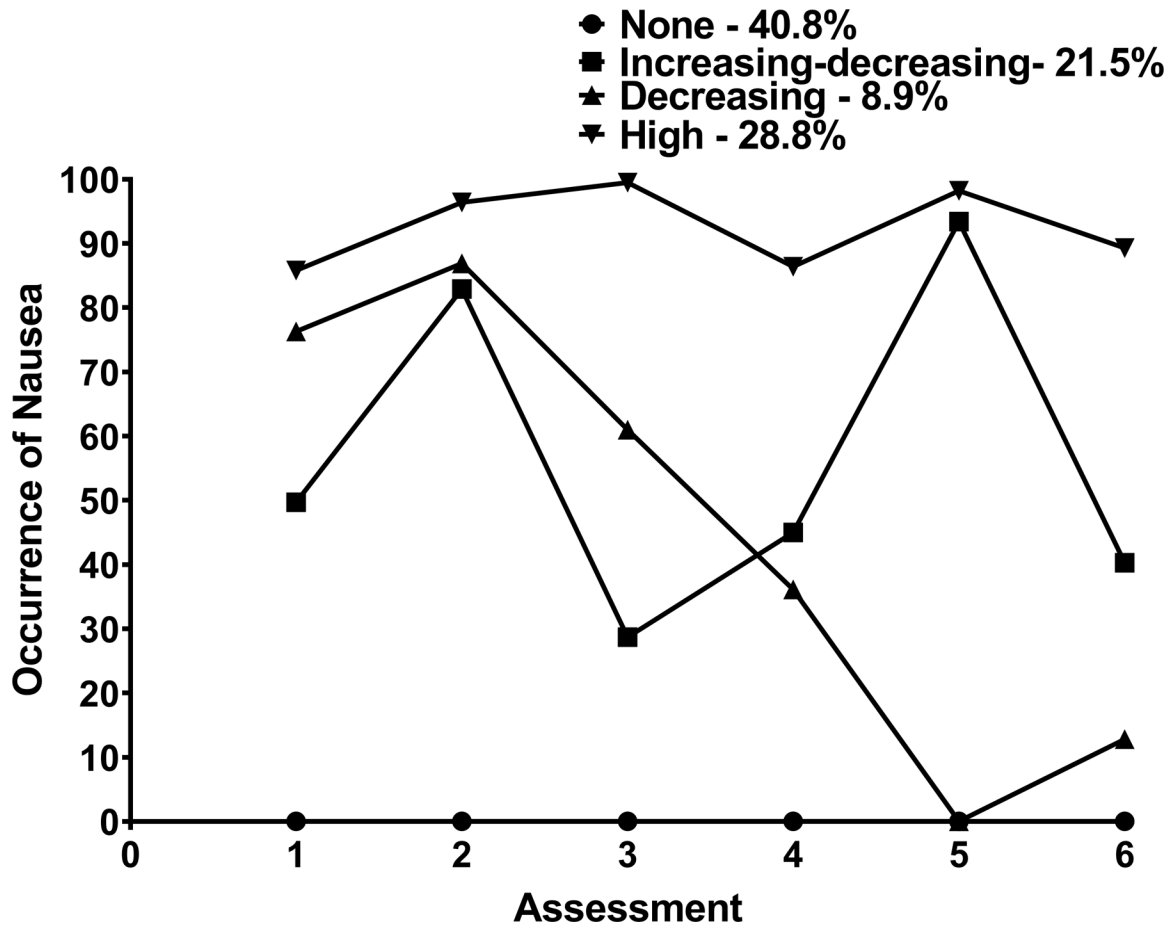

Figure 1 –.
Chemotherapy-induced nausea trajectories for patients in each of the latent classes.

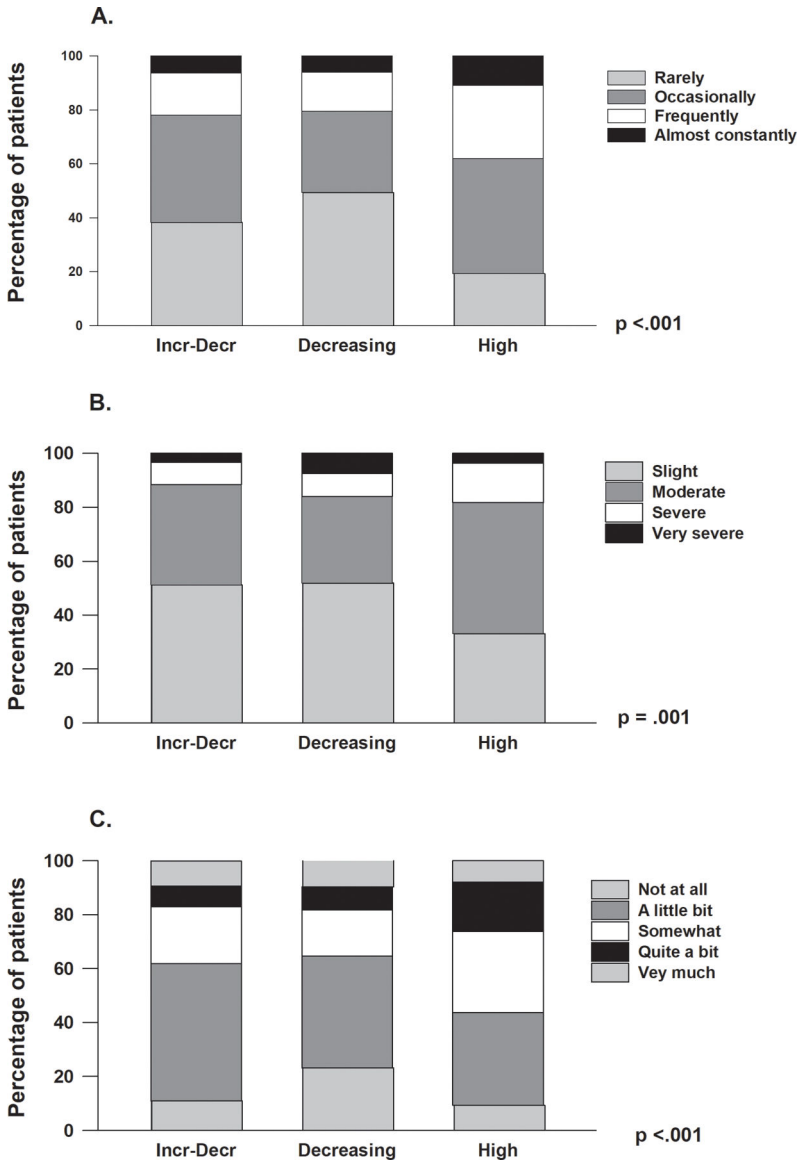

Figure 2 –.

Percentage of patients in the increasing-decreasing, decreasing, and high classes who rated the frequency (a), severity (b), and distress (c) associated with chemotherapy-induced nausea at enrollment (i.e., prior to their second or third dose of chemotherapy). For frequency (a), post hoc contrasts found that compared with the increasing-decreasing and decreasing classes, the patients in the high class reported a higher frequency of CIN. For severity (b), post hoc contrasts found that compared with the increasing-decreasing and decreasing classes, the patients in the high class had more severe CIN. In addition, compared with the increasing-decreasing class, patients in the decreasing class had more severe CIN. For distress (c), post hoc contrasts found that compared with increasing-decreasing and decreasing classes, patients in the high class reported higher distress ratings for CIN (all $p<.05$).

Table 1.

Nausea Occurrence: Latent Profile Solutions and Fit Indices for One through Four Classes

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	−2497.83	5007.67	5035.74	n/a	n/a
2 Class	−2345.34	4716.69	4777.51	0.63	304.98[d]
3 Class[a]	−2314.80	4669.61	4763.17	0.70	61.08[c]
4 Class	−2298.03	4650.07	4776.38	0.68	33.54[b]

Baseline entropy and VLMR are not applicable for the one-class solution.

[a]The 3-class solution was selected because the BIC for that solution was lower than the BIC for the 2-class and 4-class solutions. In addition, the VLMR was significant for the 3-class solution, indicating that three classes fit the data better than two classes. Although the VLMR was significant for the 4-class solution, the BIC for the 4-class solution was larger than for the 3-class solution, indicating that too many classes had been extracted.

[b]$p < .05$

[c]$p < .01$

[d]$p < .00005$

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LL, log-likelihood; n/a, not applicable; ns, not significant; VLMR, Vuong-Lo-Mendell-Rubin likelihood ratio test for the K vs. K-1 model.

Table 2.

Differences in Demographic and Clinical Characteristics Among the Nausea Latent Classes

Characteristic	None (0) 40.8% (n=548)	Increasing-decreasing (1) 21.5% (n=289)	Decreasing (2) 8.9% (n=119)	High (3) 28.8% (n=387)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	60.0 (12.1)	54.6 (12.4)	58.1 (12.5)	54.9 (11.8)	F = 18.75, p <0.001 0 > 1 and 3; 2 > 1
Education (years)	16.3 (3.1)	16.4 (2.9)	16.0 (2.7)	16.0 (3.1)	F = 1.43, p = 0.232
Body mass index (kg/m^2)	26.2 (5.5)	25.6 (5.5)	26.3 (5.8)	26.6 (6.1)	F = 2.01, p = 0.111
Alcohol Use Disorders Identification Test score	3.1 (2.3)	2.9 (2.5)	2.9 (3.1)	2.9 (2.5)	F = 0.36, p = 0.781
Karnofsky Performance Status score	83.1 (11.9)	80.5 (12.1)	78.5 (12.0)	75.7 (12.6)	F = 27.23, p <0.001 0 > 1, 2 and 3; 1 > 3
Number of comorbid conditions	2.4 (1.4)	2.3 (1.3)	2.4 (1.5)	2.6 (1.5)	F = 2.87, p = 0.036 No significant pw contrasts
Self-administered Comorbidity Questionnaire score	5.2 (3.0)	5.2 (2.9)	5.8 (3.5)	6.0 (3.5)	F = 4.90, p = 0.002 0 < 3
Time since diagnosis (years)	2.2 (4.3)	1.7 (3.4)	2.3 (4.4)	1.7 (3.4)	KW, p = 0.134
Time since diagnosis (years, median)	0.44	0.40	0.54	0.40	
Number of prior cancer treatments	1.7 (1.6)	1.5 (1.4)	1.9 (1.7)	1.5 (1.5)	F = 2.90, p = 0.034 No significant pw contrasts
Number of metastatic sites including lymph node involvement[a]	1.3 (1.3)	1.2 (1.2)	1.1 (1.1)	1.2 (1.2)	F = 1.52, p = 0.207
Number of metastatic sites excluding lymph node involvement	0.9 (1.1)	0.7 (1.0)	0.7 (0.9)	0.7 (1.0)	F = 2.96, p = 0.031 No significant pw contrasts
MAX2 score	0.17 (0.09)	0.18 (0.08)	0.18 (0.08)	0.18 (0.07)	F = 4.16, p 0.006 0 < 1
	% (n)	% (n)	% (n)	% (n)	

Characteristic	None (0) 40.8% (n=548)	Increasing-decreasing (1) 21.5% (n=289)	Decreasing (2) 8.9% (n=119)	High (3) 28.8% (n=387)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Gender (% female)	72.9 (399)	85.5 (247)	80.7 (96)	78.0 (302)	X^2 =17.88, p <0.001 0 < 1
Self-reported ethnicity					X^2 =17.78, p = 0.038
White	70.1 (379)	69.0 (198)	71.6 (83)	68.3 (261)	NS
Asian or Pacific Islander	12.4 (67)	13.6 (39)	12.1 (14)	12.6 (48)	NS
Black	8.3 (45)	5.6 (16)	12.1 (14)	5.2 (20)	NS
Hispanic, Mixed, or Other	9.2 (50)	11.8 (34)	4.3 (5)	13.9 (53)	2 < 3
Married or partnered (% yes)	67.3 (363)	64.8 (186)	59.0 (69)	61.9 (236)	X^2 = 4.57, p = 0.206
Lives alone (% yes)	19.3 (104)	20.6 (59)	29.7 (35)	22.5 (86)	X^2 = 6.58, p = 0.087
Currently employed (% yes)	36.3 (197)	38.6 (110)	29.3 (34)	32.5 (125)	X^2 = 4.74, p = 0.192
Annual household income					
Less than $30,000[b]	13.9 (67)	16.6 (43)	21.7 (23)	24.9 (88)	KW, p = 0.005 0 > 3
$30,000 to $70,000	21.2 (102)	20.8 (54)	24.5 (26)	20.3 (72)	
$70,000 to $100,000	18.9 (91)	16.2 (42)	18.9 (20)	14.1 (50)	
Greater than $100,000	46.1 (222)	46.3 (120)	34.9 (37)	40.7 (144)	
Child care responsibilities (% yes)	17.8 (96)	22.7 (64)	19.0 (22)	28.6 (108)	X^2 = 15.59, p = 0.001 0 < 3
Elder care responsibilities (% yes)	7.7 (38)	6.7 (18)	8.3 (9)	9.2 (32)	X^2 = 1.38, p = 0.711
Past or current history of smoking (% yes)	37.6 (202)	28.8 (82)	39.8 (47)	35.7 (136)	X^2 =7.66, p = 0.054
Exercise on a regular basis (% yes)	70.4 (381)	77.7 (220)	71.3 (82)	65.8 (246)	X^2 = 11.20, p = 0.011 1 > 3
Specific comorbid conditions (% yes)					
Heart disease	6.9 (38)	3.5 (10)	4.2 (5)	6.2 (24)	X^2 = 4.90, p = 0.179
High blood pressure	32.7 (179)	25.6 (74)	34.5 (41)	28.9 (112)	X^2 = 5.78, p = 0.123

Characteristic	None (0) 40.8% (n=548)	Increasing-decreasing (1) 21.5% (n=289)	Decreasing (2) 8.9% (n=119)	High (3) 28.8% (n=387)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Lung disease	13.1 (72)	7.6 (22)	10.9 (13)	11.9 (46)	$X^2 = 5.87$, p = 0.118
Diabetes	8.0 (44)	6.2 (18)	14.3 (17)	11.1 (43)	$X^2 = 9.42$, p = 0.024 No significant pw contrasts
Ulcer or stomach disease	3.5 (19)	4.2 (12)	2.5 (3)	8.0 (31)	$X^2 = 12.37$, p = 0.006 0 < 3
Kidney disease	0.5 (3)	3.1 (9)	0.0 (0)	1.8 (7)	$X^2 = 11.08$, p = 0.011
Liver disease	6.8 (37)	5.5 (16)	6.7 (8)	6.7 (26)	$X^2 = 0.54$, p = 0.910
Anemia or blood disease	9.1 (50)	13.5 (39)	13.4 (16)	15.2 (59)	$X^2 = 8.81$, p = 0.032 0 < 3
Depression	14.1 (77)	21.8 (63)	15.1 (18)	25.6 (99)	$X^2 = 22.11$, p <0.001 0 < 1 and 3
Osteoarthritis	13.9 (76)	11.1 (32)	11.8 (14)	10.9 (42)	$X^2 = 2.44$, p = 0.486
Back pain	23.7 (130)	23.9 (69)	28.6 (34)	29.2 (113)	$X^2 = 4.61$, p = 0.203
Rheumatoid arthritis	4.2 (23)	2.8 (8)	0.8 (1)	2.8 (11)	$X^2 = 4.23$, p = 0.238
Cancer diagnosis					$X^2 = 21.00$, p = 0.013
Breast cancer	39.2 (215)	41.9 (121)	43.7 (52)	39.3 (152)	NS
Gastrointestinal cancer	31.2 (171)	24.2 (70)	29.4 (35)	35.1 (136)	1 < 3
Gynecological cancer	16.8 (92)	24.2 (70)	12.6 (15)	14.5 (56)	1 > 3
Lung cancer	12.8 (70)	9.7 (28)	14.3 (17)	11.1 (43)	NS
Prior cancer treatment					$X^2 = 19.86$, p = 0.019
No prior treatment	24.2 (128)	23.9 (67)	23.1 (27)	27.2 (103)	NS
Only surgery, CTX, or RT	41.4 (219)	47.1 (132)	31.6 (37)	42.5 (161)	NS
Surgery and CTX, or surgery and RT, or CTX and RT	21.2 (112)	20.0 (56)	27.4 (32)	15.6 (59)	2 > 3
Surgery and CTX and RT	13.2 (70)	8.9 (25)	17.9 (21)	14.8 (56)	NS
Metastatic sites					
No metastasis	31.7 (170)	33.2 (95)	31.4 (37)	32.9 (126)	
Only lymph node metastasis	17.9 (96)	24.8 (71)	27.1 (32)	24.3 (93)	$X^2 = 13.42$, p = 0.145
Only metastatic disease in other sites	23.3 (125)	19.6 (56)	22.0 (26)	19.1 (73)	

Characteristic	None (0) 40.8% (n=548)	Increasing-decreasing (1) 21.5% (n=289)	Decreasing (2) 8.9% (n=119)	High (3) 28.8% (n=387)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Metastatic disease in lymph nodes and other sites	27.2 (146)	22.4 (64)	19.5 (23)	23.8 (91)	
CTX regimen					$X^2 = 20.13$, p = 0.003
Only CTX	65.5 (347)	71.2 (205)	69.5 (82)	76.0 (288)	0 < 3
Only targeted therapy	4.9 (26)	1.7 (5)	3.4 (4)	1.1 (4)	0 > 3
Both CTX and targeted therapy	29.6 (157)	27.1 (78)	27.1 (32)	23.0 (87)	NS
Cycle length					
14 day cycle	37.8 (204)	33.1 (95)	48.3 (57)	53.0 (202)	KW = 29.73, p <0.001 0 and 1 < 3 1 > 2
21 day cycle	53.5 (289)	60.3 (173)	46.6 (55)	40.4 (154)	
28 day cycle	8.7 (47)	6.6 (19)	5.1 (6)	6.6 (25)	
Emetogenicity of the CTX regimen					
Minimal/low	24.4 (132)	13.2 (38)	22.0 (26)	16.5 (63)	KW = 25.23, p <0.001 0 < 1 and 3
Moderate	61.0 (330)	66.2 (190)	58.5 (69)	58.0 (221)	
High	14.6 (79)	20.6 (59)	19.5 (23)	25.5 (97)	
Antiemetic regimen					$X^2 = 29.33$, p = 0.001
None	10.1 (53)	4.6 (13)	3.4 (4)	5.9 (22)	0 > 1
Steroid alone or serotonin receptor anatagonist alone	23.4 (123)	20.9 (59)	19.7 (23)	16.2 (60)	NS
Serotonin receptor antagonist and steroid	46.8 (246)	49.3 (139)	50.4 (59)	46.9 (174)	NS
NK-1 receptor antagonist and two other antiemetics	19.8 (104)	25.2 (71)	26.5 (31)	31.0 (115)	NS

[a] Total number of metastatic sites evaluated was 9.

[b] Reference group

Abbreviations: CTX, chemotherapy; kg, kilograms; KW, Kruskal Wallis; m^2, meters squared; NK-1, neurokinin-1; NS, not significant; pw, pairwise; RT, radiation therapy; SD, standard deviation.

Table 3.

Differences in the Occurrence of Gastrointestinal Symptoms Among the Nausea Latent Classes

Occurrence of symptoms	None (0) 40.8% (n=548)	Increasing-Decreasing (1) 21.5% (n=289)	Decreasing (2) 8.9% (n=119)	High (3) 28.8% (n=387)	Statistics
	% (n)	% (n)	% (n)	% (n)	
Dry mouth	38.6 (209)	43.9 (126)	47.5 (56)	55.5 (212)	X^2 = 26.40, p <0.001 0 and 1 < 3
Feeling bloated	23.8 (129)	35.9 (103)	33.1 (39)	44.2 (169)	X^2 =43.58, p < 0.001 0 and 1 < 3
Vomiting	3.5 (19)	11.1 (32)	16.1 (19)	24.6 (94)	X^2 = 94.17, p < 0.001 0 < 1, 2, and 3; 1 < 3
Diarrhea	21.4 (116)	32.1 (92)	35.6 (42)	37.4 (143)	X^2 = 31.61, p < 0.001 0 < 1, 2, and 3
Lack of appetite	28.8 (156)	36.9 (106)	50.0 (59)	59.7 (228)	X^2 = 94.23, p < 0.001 0 < 2 and 3; 1 < 3
Abdominal cramps	15.9 (86)	20.2 (58)	22.9 (27)	33.5 (128)	X^2 = 41.10, p <0.001 0 and 1 < 3
Difficulty swallowing	8.3 (45)	11.1 (32)	15.3 (18)	23.0 (88)	X^2 = 43.15, p < 0.001 0 and 1 < 3
Mouth sores	17.0 (92)	17.4 (50)	22.9 (27)	28.5 (109)	X^2 = 20.89, p < 0.001 0 and 1 < 3
Weight loss	20.1 (109)	20.9 (60)	33.1 (39)	33.2 (127)	X^2 = 27.23, p < 0.001 0 < 2 and 3; 1 < 3
Constipation	33.8 (183)	41.1 (118)	52.5 (62)	56.3 (215)	X^2 = 50.89, p < 0.001 0 < 2 and 3; 1 < 3
Change in way food tastes	39.5 (214)	46.7 (134)	61.0 (72)	61.8 (236)	X^2 = 51.96, p < 0.001 0 < 2 and 3; 1 < 3

Table 4.

Characteristics Associated With Membership in the Nausea Latent Classes Compared to the None Class

Characteristic	Increasing-decreasing	Decreasing	High
Demographic characteristics			
Younger age	■		■
More likely to be female	■		
More likely to have a lower annual income			■
More likely to have child care responsibilities			■
Clinical characteristics			
More likely to have a lower KPS score	■	■	■
More likely to have a higher SCQ score			■
More likely to have a higher MAX2 score	■		
More likely to report ulcer or stomach disease			■
More likely to report anemia or blood disease			■
More likely to report depression	■		■
More likely to receive only chemotherapy			■
Less likely to receive only targeted therapy			■
More likely to receive chemotherapy on a 14-day cycle			■
More likely to receive highly emetogenic chemotherapy	■		■
Gastrointestinal symptom characteristics			
More likely to report dry mouth			■
More likely to report feeling bloated			■
More likely to report vomiting	■	■	■
More likely to report diarrhea	■	■	■
More likely to report lack of appetite		■	■
More likely to report abdominal cramps			■
More likely to report difficulty swallowing			■
More likely to report mouth sores			■
More likely to report weight loss		■	■
More likely to report constipation		■	■
More likely to report change in the way food tastes		■	■

Abbreviations: KPS, Karnofsky Performance Status; SCQ, Self-Administered Comorbidity Questionnaire.