Gastrointestinal and Neuropsychological Symptoms Are Associated With Distinct Vomiting Profiles in Patients Receiving Chemotherapy

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OBJECTIVES: To identify subgroups of patients with distinct chemotherapy-induced vomiting (CIV) profiles; determine how these subgroups differ on several demographic, clinical, and symptom characteristics; and evaluate factors associated with chemotherapy-induced nausea and CIV profiles.

SAMPLE & SETTING: Adult patients (N = 1,338) receiving cancer chemotherapy.

METHODS & VARIABLES: Data were collected on demographic, clinical, and symptom characteristics. Differences among subgroups of patients with distinct CIV profiles were evaluated using parametric and nonparametric tests.

RESULTS: Three CIV profiles (None, Decreasing, and Increasing) were identified. Compared with the None class, Decreasing and Increasing classes were more likely to have lower household income and a higher comorbidity burden, as well as to report higher rates of dry mouth, nausea, diarrhea, depression, anxiety, sleep disturbance, morning fatigue, and pain interference.

IMPLICATIONS FOR NURSING: Clinicians need to assess common and distinct risk factors for CIV and chemotherapy-induced nausea.

KEYWORDS cancer; chemotherapy; latent class analysis; nausea; vomiting
***ONF, 51*(4), 361–380.**
DOI 10.1188/24.ONF.361-380

Despite the administration of evidence-based antiemetics, about 20% of patients with cancer report chemotherapy-induced vomiting (CIV) (National Comprehensive Cancer Network [NCCN], 2023). This debilitating symptom can lead to nutritional deficits, dehydration, increased risk of vomiting in future treatment cycles, discontinuation of treatment, and worse clinical outcomes (NCCN, 2023). One of the challenges in determining the prevalence of and risk factors for CIV is that the majority of studies investigated CIV together with chemotherapy-induced nausea (CIN) as a composite symptom (chemotherapy-induced nausea and vomiting [CINV]). Although a strong correlation exists between the occurrence of CIV and CIN, the occurrence of CIN is three times higher than that of CIV (NCCN, 2023; Singh et al., 2018).

Only four cross-sectional studies evaluated for associations between demographic and clinical characteristics and the occurrence of CIV (Di Mattei et al., 2016; Hayashi et al., 2019, 2021; Naito et al., 2020). Across these studies, younger age (Hayashi et al., 2021; Naito et al., 2020), receipt of a highly emetogenic chemotherapy regimen (Di Mattei et al., 2016), body mass index of 18.5 kg/m^2 or less (Hayashi et al., 2019), and receipt of an antiemetic regimen without a neurokinin-1 receptor antagonist (Hayashi et al., 2019) were associated with increased rates of CIV. Associations between hyperemesis gravidarum and CIV are inconsistent (Di Mattei et al., 2016; Hayashi et al., 2019, 2021; Naito et al., 2020). Limitations

across these studies included an evaluation of only a limited number of risk factors, absence of information on changes in CIV occurrence over multiple cycles of chemotherapy, and no evaluation of interindividual variability in patients' symptom experience.

Studies on associations between CIV and other gastrointestinal and neuropsychological symptoms in patients receiving chemotherapy are limited. Most of these studies evaluated the composite symptom (i.e., CINV) (Molassiotis et al., 2016; Mosa et al., 2020; Singh et al., 2018). In terms of gastrointestinal symptoms, patients who had CINV were more likely to report a history of nausea/vomiting (Molassiotis et al., 2016; Mosa et al., 2020; Singh et al., 2018), lack of appetite (Saragiotto et al., 2020), dry mouth (Choi et al., 2022; Saragiotto et al., 2020), diarrhea (Saragiotto et al., 2020), and taste changes (Larsen et al., 2021). In another study (Molassiotis et al., 2013), CINV was not associated with symptom distress from lack of appetite and changes in bowel patterns.

In terms of neuropsychological symptoms, higher occurrence rates and severity of CINV were associated with higher levels of prechemotherapy anxiety (Molassiotis et al., 2016), pain (Crane et al., 2020; Molassiotis et al., 2013), depression (Whisenant et al., 2019), and sleep disturbance (Crane et al., 2020; Dranitsaris et al., 2017). Although in one study (Whisenant et al., 2019) CINV was associated with higher fatigue scores, findings were inconclusive in another study (Molassiotis et al., 2013). Of note, no studies were identified that evaluated for associations between CINV and decrements in cognitive function or energy.

In the authors' previous studies (Singh, Cooper, et al., 2023; Singh, Pituch, et al., 2023), latent class analysis (LCA) was used to identify four subgroups of patients with distinct CIN profiles (i.e., None, Increasing–Decreasing, Decreasing, and High). In these two studies, specific risk factors for the occurrence of CIN across two cycles of chemotherapy were identified. Given the paucity of research on CIV as a single symptom, the purposes of this study, in a sample of outpatients with breast, gastrointestinal, gynecologic, or lung cancer (N = 1,338), were to identify subgroups of patients with distinct CIV profiles and determine how these subgroups differed on a number of demographic and clinical characteristics; severity, frequency, and distress of CIV; and the co-occurrence of common gastrointestinal and neuropsychological symptoms. In addition, building on the authors' previous findings (Singh, Cooper, et al., 2023; Singh, Pituch, et al., 2023), the overlap among the CIN and CIV profiles, as well as common and distinct risk factors associated with the CIN and CIV profiles, are described.

Methods

Patients and Setting

This analysis is part of a larger longitudinal study of the symptom experience of outpatients with cancer receiving chemotherapy (Miaskowski et al., 2014). The theory of symptom management was used as the theoretical framework for the parent study (Weiss et al., 2023). For this analysis, the symptom (CIV) and person (demographic, clinical, and other symptom characteristics) concepts were evaluated.

Eligible patients were aged 18 years or older; had a diagnosis of breast, gastrointestinal, gynecologic, 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 Veterans Affairs hospital, and four community-based oncology programs.

Study Procedures

The study was approved by the institutional review boards at the University of California, San Francisco, and at each of the study sites. Of the 2,234 patients approached, 1,338 consented to participate and provided evaluable data for the CIV analysis. Patients' refusal to participate was primarily because of being overwhelmed with their cancer treatment. Eligible patients were approached in the infusion unit during their first or second cycle of chemotherapy by a member of the research staff and provided written informed consent. Patients completed assessments of CIV in their homes using paper questionnaires a total of six times over two cycles of chemotherapy, with assessments 1 and 4 occurring prior to chemotherapy administration, assessments 2 and 5 about one week after chemotherapy administration, and assessments 3 and 6 about two weeks after chemotherapy administration. Additional measures were completed by the patients at enrollment (i.e., prior to the second or third cycle of chemotherapy). All of the questionnaires were returned to the research office in postage-paid envelopes.

Instruments

Demographic and clinical characteristics: Patients completed the Karnofsky Performance Status Scale

(Karnofsky, 1977), a demographic questionnaire, the Self-Administered Comorbidity Questionnaire (Sangha et al., 2003), the Alcohol Use Disorders Identification Test (Babor et al., 2001), and a smoking history questionnaire. Medical records were reviewed for disease and treatment information.

Assessment of CIV: The vomiting item from the Memorial Symptom Assessment Scale (MSAS) was used to assess for the occurrence of CIV at each of the six assessments. In addition, patients with CIV provided ratings of the symptom's severity, frequency, and distress. The MSAS is a valid and reliable instrument to evaluate common symptoms associated with cancer and its treatment (Portenoy et al., 1994).

Assessment of additional gastrointestinal symptoms: A modified version of the MSAS was used to evaluate the occurrence of 11 common gastrointestinal symptoms associated with cancer and/or chemotherapy, namely the following: dry mouth, feeling bloated, nausea, diarrhea, lack of appetite, abdominal cramps, difficulty swallowing, mouth sores, weight loss, constipation, and change in the way food tastes.

Assessment of neuropsychological symptoms: An evaluation of other common symptoms was done using valid and reliable instruments. These symptoms and their respective measures were as follows: (a) depressive symptoms, measured by the Center for Epidemiological Studies–Depression Scale (Radloff, 1977); (b) trait and state anxiety, measured by the Spielberger State-Trait Anxiety Inventories (Spielberger et al., 1983); (c) cognitive function, measured by the Attentional Function Index (Cimprich et al., 2005); (d) sleep disturbance, measured by the General Sleep Disturbance Scale (Fletcher et al., 2008); (e) morning and evening fatigue and energy, measured by the Lee Fatigue Scale (Lee et al., 1991); and (f) pain, measured by the Brief Pain Inventory (Daut et al., 1983).

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: (a) received only chemotherapy, (b) received only targeted therapy, and (c) received chemotherapy and targeted therapy. In addition, the MAX2 score was used to evaluate the toxicity of the various chemotherapy regimens (Extermann et al., 2004). A MAX2 score is the average of the most frequent grade 4 hematologic toxicity and the most frequent grade 3 to grade 4 nonhematologic toxicity reported in publications of a chemotherapy regimen. This score, which can range from 0 to 1, correlates with the overall risk of severe toxicity from that regimen.

Coding of the Emetogenicity of the Chemotherapy Regimens

Using the Multinational Association for Supportive Care in Cancer guidelines (Roila et al., 2016), 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 (low/minimal, moderate, or high) based on the chemotherapy drug with the highest emetogenic potential.

Coding of the Antiemetic Regimens

Each prescribed antiemetic drug was coded as either an neurokinin-1 receptor antagonist, a serotonin

TABLE 1. Latent Profile Solutions and Fit Indices for 1 Through 3 Classes for the Occurrence of Chemotherapy-Induced Vomiting

Model	LL	AIC	BIC	Entropy	VLMR
1 class	−725.6	1463.2	1482.9	N/A	N/A
2 class[a]	−693.95	1413.9	1456.58	0.56	63.3*
3 class	−676.91	1393.83	1459.49	0.69	NS

* $p < 0.001$
[a]The 2-class solution was selected because the BIC was lower than the BIC for the 1-class and 3-class solutions. In addition, the VLMR was significant for the 2-class solution, indicating that 2 classes fit the data better than one class. Finally, the VLMR was not significant for the 3-class solution, indicating that too many classes had been extracted.
AIC—Akaike 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 versus K–1 model
Note. Baseline entropy and VLMR are N/A for the 1-class solution.

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

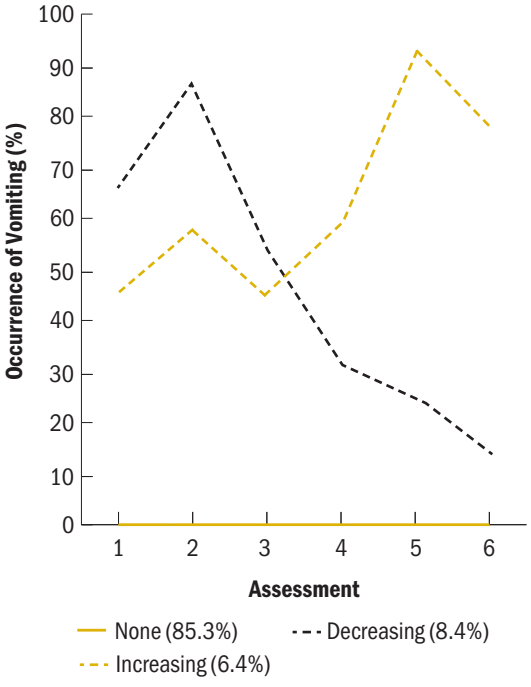
Data Analyses

LCA was used to identify the profiles of CIV occurrence that characterized unobserved subgroups of patients (i.e., latent classes) over the six assessments. Prior to performing the LCA, patients who responded "no" to the vomiting item on the MSAS for five or six assessments (i.e., patients who did not experience vomiting across the two cycles of chemotherapy) were identified and labeled as the None class (n = 1,141). Then, the LCA was performed using data from the remaining 197 patients using Mplus, version 8.2 (Muthén & Muthén, 1998–2017).

Estimation was carried out with full information maximum likelihood with standard errors and a chi-square test that are robust to non-normality and nonindependence 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, Vuong–Lo–Mendell–Rubin likelihood ratio test, entropy, and latent class percentages that were large enough to be reliable (i.e., likely to replicate in new samples) (Muthén & Muthén, 1998–2017). Missing data were accommodated with the use of the expectation–maximization algorithm (Muthén & Shedden, 1999).

Descriptive statistics and frequency distributions were generated for sample characteristics at enrollment using IBM SPSS Statistics, version 29.0. Differences among the CIV latent classes in demographic, clinical, gastrointestinal, and neuropsychological symptom characteristics at enrollment were evaluated using parametric and nonparametric tests. A Bonferroni-corrected p value of less than 0.0167 (i.e., 0.05/3 possible pairwise contrasts) was considered statistically significant.

FIGURE 1. Chemotherapy-Induced Vomiting Trajectories for Patients in Each of the Latent Classes



Results

LCA

In the current study, 1,141 patients (85.3%) who had one or fewer occurrences of CIV over the six assessments were labeled as the None class. For the remaining 197 patients whose data were entered into the LCA, a two-class solution was selected (see Table 1). As shown in Figure 1, the trajectories for the occurrence of CIV differed between these two latent classes. For the Decreasing class (n = 112, 8.4%), the occurrence rate for CIV increased from the first to the second assessment, then gradually decreased over the remaining four assessments. For the Increasing class (n = 85, 6.4%), the CIV occurrence rate increased from the first to the second assessment, decreased at the third assessment, and increased again at the fourth and fifth assessments before decreasing at the sixth assessment. No significant differences were found between the two classes who reported CIV in the frequency, severity, and distress of vomiting at enrollment (see Figure 2).

Demographic and Clinical Characteristics

Compared with the None class, the Decreasing class was significantly younger, had fewer years of education, was less likely to be employed, was more likely to have a lower annual household income, and was less likely to exercise on a regular basis (see Table 2). In addition, they had a lower Karnofsky Performance Status Scale score and a higher Self-Administered

Comorbidity Questionnaire score, and were more likely to self-report diagnoses of lung disease, diabetes, or kidney disease.

Compared with the None class, the Increasing class was less likely to be married or partnered, more likely to live alone, and more likely to have a lower annual household income. In addition, they had a lower Karnofsky Performance Status Scale score, a higher number of comorbid conditions, a higher Self-Administered Comorbidity Questionnaire score, and a higher number of metastatic sites, and were more likely to self-report a diagnosis of lung disease, back pain, or rheumatoid arthritis.

Occurrence of Gastrointestinal Symptoms

Compared with the None class, patients in the other two classes reported higher occurrence rates for dry mouth, nausea, diarrhea, lack of appetite, and difficulty swallowing (see Table 3). Compared with the None class, the Decreasing class reported higher occurrence rates for abdominal cramps, weight loss, and change in the way food tastes. Compared with the None class, the Increasing class reported a higher occurrence rate for constipation.

Severity of Neuropsychological Symptoms

Compared with the None class, the other two classes reported significantly higher severity scores for depression, state anxiety, sleep disturbance, morning fatigue, and pain interference, as well as higher occurrence rates for cancer and noncancer pain (see Table 4). Compared with the None class, the Decreasing class reported higher levels of trait anxiety. Although this trend was similar for the Increasing class, the trait anxiety score was not significantly different from the None class, most likely because of its small sample size. Compared with the None class, the Increasing class reported higher levels of evening fatigue and worse pain intensity.

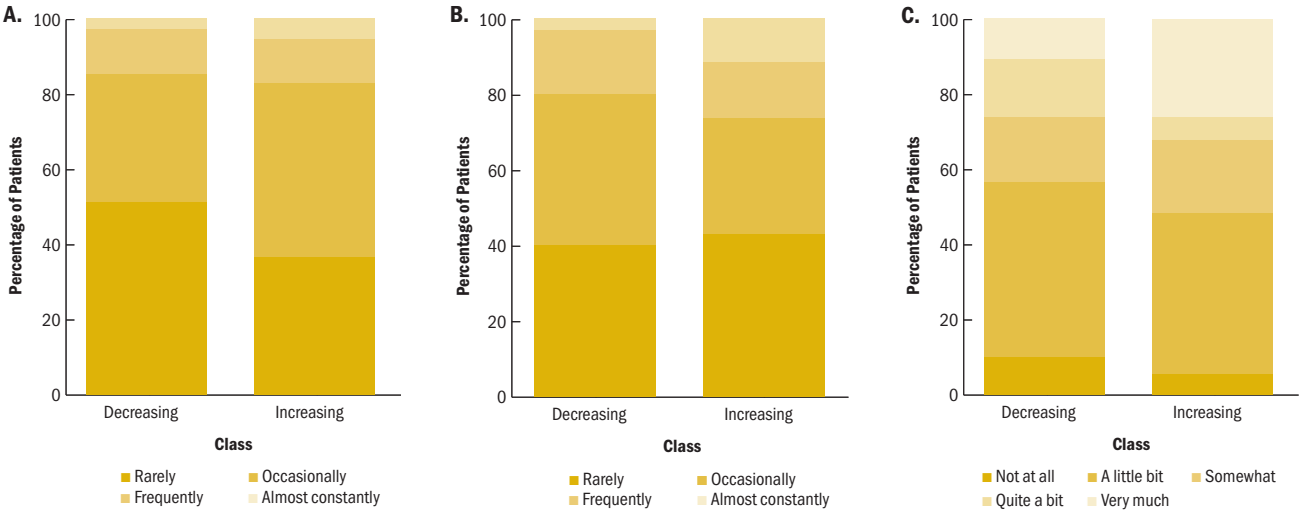
Overlap Between CIV and CIN Profiles

Of the 1,338 patients in both LCAs, 40% were in the None classes for CIV and CIN. Of the 1,141 patients who were in the CIV None class, 46.9% were in the CIN None class, 20.9% in the CIN Increasing–Decreasing class, 8.3% in the CIN Decreasing class, and 23.9% in the CIN High class. The distribution of CIV classes within the three highest CIN classes, along with common and distinct risk factors, is presented in Table 5.

Discussion

This study is the first to use LCA to identify subgroups of patients with distinct CIV profiles, compare the overlap between the CIV and CIN profiles (assessed using the nausea item on the MSAS) (Singh,

FIGURE 2. Percentage of Patients in the Decreasing and Increasing Classes Who Rated the Frequency (A), Severity (B), and Distress (C) Associated With Chemotherapy-Induced Vomiting at Enrollment (i.e., Prior to Their Second or Third Cycle of Chemotherapy)



Note. No significant differences were found between the 2 classes who reported CIV in the frequency, severity, and distress of vomiting at enrollment.

TABLE 2. Differences in Demographic and Clinical Characteristics Among the Vomiting Latent Classes

	None (0) (N = 1,141, 85.3%)		Decreasing (1) (N = 112, 8.4%)		Increasing (2) (N = 85, 6.4%)		
Characteristic	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**	**Statistics**
Age (years)	57.7	12.3	53.2	13.1	54.8	10.9	F = 8.58, p < 0.001; 0 > 1
Education (years)	16.3	3.1	15.5	2.6	15.8	2.7	F = 4.71, p = 0.009; 0 > 1
Body mass index (kg/m^2)	26.2	5.6	26.1	6	26.7	6	F = 0.38, p = 0.685
AUDIT score	3	2.4	3.1	2.8	2.7	2.6	F = 0.33, p = 0.72
Karnofsky Performance Status Scale score	80.8	12.1	75	14.2	75.8	13.7	F = 15.72, p < 0.001; 0 > 1 and 2
Number of comorbid conditions	2.4	1.4	2.6	1.6	2.8	1.8	F = 5.38, p = 0.005; 0 < 2
SCQ score	5.3	3	6.4	3.9	6.5	4.1	F = 10.8, p < 0.001; 0 < 1 and 2
Time since diagnosis (years)	2	4	1.9	3.2	1.6	3	KW = 1.7, p = 0.427
Number of prior cancer treatments	1.6	1.5	1.5	1.6	1.6	1.5	F = 0.16, p = 0.853
Number of metastatic sites including lymph node involvement[a]	1.2	1.2	1.1	1.2	1.6	1.3	F = 3.45, p = 0.032; 0 < 2
Number of metastatic sites excluding lymph node involvement	0.8	1	0.7	1	1.1	1.2	F = 3.27, p = 0.038; 0 < 2
MAX2 score	0.18	0.08	0.16	0.07	0.17	0.08	F = 2, p = 0.136
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**Statistics**
Gender							
Female	886	78	86	77	68	80	χ^2 = 0.31, p = 0.857
Self-reported ethnicity							χ^2 =11.65, p = 0.07
Asian or Pacific Islander	135	12	20	18	10	12	
Black	80	7	9	8	6	7	
Hispanic, mixed, or other	111	10	15	14	15	18	
White	802	71	65	60	53	63	
Married or partnered							
Yes	746	66	61	56	43	51	χ^2 = 11.47, p = 0.003; 0 > 2
Lives alone							
Yes	231	21	25	23	28	33	χ^2 = 7.66, p = 0.022; 0 < 2
Currently employed							
Yes	421	37	23	21	21	25	χ^2 = 15.71, p < 0.001; 0 > 1
Annual household income ($)							KW = 33.91, p < 0.001; 0 > 1 and 2
Less than 30,000[b]	163	16	29	31	28	36	
30,000–70,000	206	20	26	28	20	26	
70,000–100,000	185	18	14	15	4	5	

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TABLE 2. Differences in Demographic and Clinical Characteristics Among the Vomiting Latent Classes *(Continued)*

Characteristic	None (0) (N = 1,141, 85.3%) n	%	Decreasing (1) (N = 112, 8.4%) n	%	Increasing (2) (N = 85, 6.4%) n	%	Statistics
Annual household income ($) *(continued)*							KW = 33.91, p < 0.001; 0 > 1 and 2
Greater than 100,000	473	46	25	27	25	33	
Childcare responsibilities							
Yes	240	22	30	27	20	24	χ^2 = 1.97, p = 0.374
Eldercare responsibilities							
Yes	80	8	9	9	7	9	χ^2 = 0.14, p = 0.931
Past or current history of smoking							
Yes	396	35	37	34	32	38	χ^2 = 0.34, p = 0.844
Exercise on a regular basis							
Yes	805	72	67	61	54	65	χ^2 = 7.58, p = 0.023; 0 > 1
Specific comorbid conditions							
Heart disease	64	6	5	5	8	9	χ^2 = 2.48, p = 0.289
High blood pressure	349	31	31	28	25	29	χ^2 = 0.44, p = 0.802
Lung disease	115	10	20	18	16	19	χ^2 = 11.32, p = 0.003; 0 < 1 and 2
Diabetes	92	8	17	15	12	14	χ^2 = 9.12, p = 0.01; 0 < 1
Ulcer or stomach disease	48	4	9	8	8	9	χ^2 = 7.31, p = 0.026
Kidney disease	13	1	5	5	1	1	χ^2 = 8.09, p = 0.017; 0 < 1
Liver disease	77	7	5	5	4	5	χ^2 = 1.33, p = 0.514
Anemia or blood disease	139	12	14	13	11	13	χ^2 = 0.05, p = 0.976
Depression	210	18	26	23	21	25	χ^2 = 3.29, p = 0.193
Osteoarthritis	138	12	16	14	9	11	χ^2 = 0.67, p = 0.714
Back pain	279	25	33	30	32	38	χ^2 = 8.11, p = 0.017; 0 < 2
Rheumatoid arthritis	31	3	5	5	7	8	χ^2 = 8.36, p = 0.015; 0 < 2
Cancer diagnosis							χ^2 = 11.51, p = 0.074
Breast cancer	478	42	35	31	26	31	
Gastrointestinal cancer	341	30	41	37	27	32	
Gynecologic cancer	197	17	20	18	16	19	
Lung cancer	125	11	16	14	16	19	
Prior cancer treatment							χ^2 = 6.43, p = 0.377
No prior treatment	267	24	35	32	23	27	
Only surgery, CTX, or RT	478	43	37	34	32	38	
Surgery and CTX, or surgery and RT, or CTX and RT	222	20	21	19	15	18	
Surgery, CTX, and RT	141	13	16	15	14	17	
Metastatic sites							χ^2 = 8.53, p = 0.202
No metastasis	365	33	43	39	19	22	
Only lymph node metastasis	254	23	17	15	20	24	

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TABLE 2. Differences in Demographic and Clinical Characteristics Among the Vomiting Latent Classes *(Continued)*

Characteristic	None (0) (N = 1,141, 85.3%) n	%	Decreasing (1) (N = 112, 8.4%) n	%	Increasing (2) (N = 85, 6.4%) n	%	Statistics
Metastatic sites *(continued)*							$\chi^2 = 8.53$, p = 0.202
Only metastatic disease in other sites	234	21	22	20	23	27	
Metastatic disease in lymph nodes and other sites	271	24	29	26	23	27	
CTX regimen							$\chi^2 = 8.35$, p = 0.08
Only CTX	793	71	71	63	55	65	
Only targeted therapy	36	3	1	1	2	2	
Both CTX and targeted therapy	285	26	40	36	28	33	
Cycle length							KW = 0.03, p = 0.987
14-day cycle	475	42	47	42	36	44	
21-day cycle	579	51	54	49	38	46	
28-day cycle	79	7	10	9	8	10	
Emetogenicity of the CTX regimen							KW = 0.22, p = 0.896
Minimal/low	225	20	15	14	19	23	
Moderate	685	60	79	71	46	56	
High	224	20	17	15	17	21	
Antiemetic regimen							$\chi^2 = 9.15$, p = 0.166
None	83	8	3	3	6	8	
Steroid alone or serotonin receptor antagonist alone	230	21	17	15	18	23	
Serotonin receptor antagonist and steroid	530	48	56	51	32	41	
NK-1 receptor antagonist and 2 other antiemetics	263	24	35	32	23	29	

[a] The total number of metastatic sites evaluated was 9.
[b] Reference group
AUDIT— Alcohol Use Disorders Identification Test; CTX—chemotherapy; KW—Kruskal–Wallis; NK-1—neurokinin-1; RT—radiation therapy; SCQ—Self-Administered Comorbidity Questionnaire

Cooper, et al., 2023; Singh, Pituch, et al., 2023), and evaluate for common and distinct risk factors for CIV and/or CIN. Based on previously reported CIV occurrence rates of 13%–33% (Singh et al., 2018), the 15% found in the current study is at the lower end of this range. In addition, compared with the authors' previous LCA of CIN in this sample (Singh, Pituch, et al., 2023), a High CIV profile was not identified in the current study. In addition, across the three highest CIN classes, more than 70% of the patients did not report CIV. Taken together, these findings suggest that although the administration of evidence-based antiemetic regimens has reduced the occurrence of CIV, CIN remains a significant clinical problem.

The remainder of the Discussion highlights the common and distinct risk factors associated with membership across the two highest vomiting classes and the three highest nausea classes. The information presented in Table 5 is based on comparisons of the highest classes with the None classes for vomiting and nausea, respectively (Singh, Cooper, et al., 2023; Singh, Pituch, et al., 2023).

Demographic Characteristics

Of the nine demographic risk factors listed in Table 5, although seven were associated with membership in one or more of the CIV classes, only four were associated with CIN. Across the two symptoms, younger

age and lower annual income were the two common risk factors.

Findings regarding associations between age and CIV and CIN are inconsistent. Two studies support this study's findings that younger age is a risk factor for both symptoms (Hayashi et al., 2021; Naito et al., 2020). However, in a study of patients with gynecologic cancer (Di Mattei et al., 2016), younger age was a risk factor for CIN but not CIV. Although the current study is the first to report that lower income was associated with the worst CIV and CIN profiles, in one study of pregnant women (Mukherjee et al., 2017), a higher poverty level was associated with increases in the occurrence of nausea and vomiting. One potential explanation for this finding is that the more effective antiemetics are expensive, and financial difficulties and/or insurance coverage may hinder patients' access to these regimens.

In terms of specific demographic risk factors for CIV, although this study found that having fewer years of education was associated with membership in the Decreasing class, in another study (Pirri et al., 2011), no association was found. In terms of marital status and living alone, although not evaluated in patients receiving chemotherapy, pregnant women who were unmarried and lived alone were more likely to report severe nausea and vomiting (Markl et al., 2008; Mukherjee et al., 2017). Patients with higher levels of support may be able to delegate care responsibilities and focus on self-care interventions (e.g., adherence to an antiemetic regimen) to decrease CIV (Oh et al., 2020).

TABLE 3. Differences in the Occurrence of Gastrointestinal Symptoms Among the Vomiting Latent Classes

	None (N = 1,141, 85.3%)		Decreasing (N = 112, 8.4%)		Increasing (N = 85, 6.4%)		
Symptoms	n	%	n	%	n	%	Statistics
Dry mouth	490	43	64	58	49	60	$\chi^2 = 15.9$, $p < 0.001$; 0 < 1 and 2
Feeling bloated	361	32	45	41	34	42	$\chi^2 = 6.26$, $p = 0.044$; no significant pairwise contrasts
Nausea	486	43	88	79	57	70	$\chi^2 = 71.03$, $p < 0.001$; 0 < 1 and 2
Diarrhea	314	28	45	41	34	42	$\chi^2 = 14.01$, $p < 0.001$; 0 < 1 and 2
Lack of appetite	435	38	67	60	47	57	$\chi^2 = 29.55$, $p < 0.001$; 0 < 1 and 2
Abdominal cramps	233	21	41	37	25	31	$\chi^2 = 18.85$, $p < 0.001$; 0 < 1
Difficulty swallowing	132	12	32	29	19	23	$\chi^2 = 31.73$, $p < 0.001$; 0 < 1 and 2
Mouth sores	232	20	27	24	19	23	$\chi^2 = 1.2$, $p = 0.549$
Weight loss	264	23	48	43	23	28	$\chi^2 = 21.84$, $p < 0.001$; 0 < 1
Constipation	475	42	53	48	50	61	$\chi^2 = 12.32$, $p = 0.002$; 0 < 2
Change in the way food tastes	542	48	67	60	47	57	$\chi^2 = 8.69$, $p = 0.013$; 0 < 1

Findings regarding associations between exercise and CIV are inconsistent. In one study of patients with cancer (Andersen et al., 2006), no associations were found between CIV and low or high intensity exercise programs. However, in two studies of patients with breast cancer (Aybar et al., 2020; Raghavendra et al., 2007), breathing exercises (Aybar et al., 2020) and yoga (Raghavendra et al., 2007) decreased CIV. It is plausible that specific types of exercise may have differential effects on the occurrence of CIV.

Being female and having childcare responsibilities were the two distinct risk factors associated with the High CIN class (Singh, Pituch, et al., 2023). Although in one study (Hayashi et al., 2021), no association was

TABLE 4. Differences in Neuropsychological Symptom Severity Scores Among the Vomiting Latent Classes

Neuropsychological Symptom Scores[a]	None (0) (N = 1,141, 85.3%)		Decreasing (1) (N = 112, 8.4%)		Increasing (2) (N = 85, 6.4%)		Statistics
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	
Center for Epidemiological Studies–Depression (≥ 16)	12.3	9.3	15.6	10.8	16.9	11.4	F = 13.65, p < 0.001; 0 < 1 and 2
Trait Anxiety Inventory (≥ 32.2)	34.8	10.4	37.3	10.2	37.5	11.6	F = 5.18, p = 0.006; 0 < 1
State Anxiety Inventory (≥ 31.8)	33.3	12.1	36.4	13.1	38.9	13.9	F = 10.36, p < 0.001; 0 < 1 and 2
Attentional function (< 5 = low, 5–7.5 = moderate, > 7.5 = high)	6.5	1.8	6.1	1.9	6	1.8	F = 3.94, p = 0.02; no significant pairwise contrasts
General Sleep Disturbance Scale (≥ 43)	51.3	19.9	59.2	20.6	60	20.6	F = 13.57, p < 0.001; 0 < 1 and 2
Morning fatigue (≥ 3.2)	3	2.2	3.7	2.5	3.9	2.4	F = 9.85, p < 0.001; 0 < 1 and 2
Evening fatigue (≥ 5.6)	5.3	2.1	5.5	2.3	6	2.1	F = 4.23, p = 0.015; 0 < 2
Morning energy (≤ 6.2)	4.4	2.3	4.2	2.3	4.1	2.1	F = 1.35, p = 0.259
Evening energy (≤ 3.5)	3.6	2	3.4	2.2	3.3	2.2	F = 0.76, p = 0.468
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**Statistic**
Type of pain							χ^2 = 22.58, p < 0.001
No pain	325	29	20	19	14	17	NS
Only noncancer pain	184	16	15	14	10	12	NS
Only cancer pain	298	27	27	25	21	25	NS
Both cancer and noncancer pain	315	28	46	43	38	46	0 < 1 and 2
Characteristic	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**	**Statistic**
Worst pain intensity	6	2.5	6.1	2.9	6.9	2.8	F = 7.6, p = 0.028; 0 < 2
Number of pain locations (out of 45)	7.9	7.4	9.6	8.3	9.5	9.5	F = 2.85, p = 0.059
Pain interference	2.9	2.4	3.7	2.7	4.2	2.8	F = 11.26, p < 0.001; 0 < 1 and 2

[a] Numbers in parentheses represent clinically meaningful cut point scores for the symptom measures.
NS—not significant

TABLE 5. Characteristics Associated With Membership in the Vomiting and Nausea Latent Classes Compared With the None Classes for Vomiting and Nausea

Characteristics	Vomiting Classes		Nausea Classes		
	Decreasing (N = 112)	Increasing (N = 85)	Increasing–Decreasing (N = 289) (CIV None = 82.4%, CIV Decreasing = 10.7%, CIV Increasing = 6.9%)	Decreasing (N = 119) (CIV None = 79.8%, CIV Decreasing = 17.7%, CIV Increasing = 2.5%)	High (N = 387) (CIV None = 70.6%, CIV Decreasing = 14.7%, CIV Increasing = 14.7%)
Demographic characteristics					
Younger age	●		●		●
Less education (years)	●				
More likely to be female			●		
Less likely to be married or partnered		●			
More likely to live alone		●			
Less likely to be currently employed	●				
More likely to have a lower annual income	●	●			●
More likely to have childcare responsibilities					●
Less likely to exercise on a regular basis	●				
Clinical characteristics					
Lower Karnofsky Performance Status Scale score	●	●	●	●	●
Higher number of comorbidities		●			
Higher Self-Administered Comorbidity Questionnaire score	●	●			●
Higher number of metastatic sites		●			
More likely to have a higher MAX2 score			●		
More likely to report ulcer or stomach disease					●
More likely to report anemia or blood disease					●

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TABLE 5. Characteristics Associated With Membership in the Vomiting and Nausea Latent Classes Compared With the None Classes for Vomiting and Nausea *(Continued)*

Characteristics	Vomiting Classes		Nausea Classes		
	Decreasing (N = 112)	Increasing (N = 85)	Increasing–Decreasing (N = 289) (CIV None = 82.4%, CIV Decreasing = 10.7%, CIV Increasing = 6.9%)	Decreasing (N = 119) (CIV None = 79.8%, CIV Decreasing = 17.7%, CIV Increasing = 2.5%)	High (N = 387) (CIV None = 70.6%, CIV Decreasing = 14.7%, CIV Increasing = 14.7%)
Clinical characteristics *(continued)*					
More likely to report lung disease	●	●			
More likely to report diabetes	●				
More likely to report kidney disease	●				
More likely to report depression			●		●
More likely to report back pain		●			
More likely to report rheumatoid arthritis		●			
More likely to receive only CTX					●
Less likely to receive only targeted therapy					●
More likely to receive CTX on a 14-day cycle					●
More likely to receive highly emetogenic CTX			●		●
Gastrointestinal symptoms					
More likely to report dry mouth	●	●			●
More likely to report feeling bloated					●
More likely to report nausea	●	●			
More likely to report vomiting			●	●	●
More likely to report diarrhea	●	●	●	●	●

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TABLE 5. Characteristics Associated With Membership in the Vomiting and Nausea Latent Classes Compared With the None Classes for Vomiting and Nausea *(Continued)*

Characteristics	Vomiting Classes		Nausea Classes		
	Decreasing (N = 112)	Increasing (N = 85)	Increasing–Decreasing (N = 289) (CIV None = 82.4%, CIV Decreasing = 10.7%, CIV Increasing = 6.9%)	Decreasing (N = 119) (CIV None = 79.8%, CIV Decreasing = 17.7%, CIV Increasing = 2.5%)	High (N = 387) (CIV None = 70.6%, CIV Decreasing = 14.7%, CIV Increasing = 14.7%)
Gastrointestinal symptoms *(continued)*					
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	●			●	●
Neuropsychological symptoms					
Higher depression	●	●	●	●	●
Higher trait anxiety	●		●	●	●
Higher state anxiety	●	●	●		●
Lower attentional function			●		●
Higher sleep disturbance	●	●	●	●	●
Higher morning fatigue	●	●	●	●	●
Higher evening fatigue		●	●	●	●
Lower morning energy					●
Lower evening energy					●
More likely to report only cancer pain			●		●

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TABLE 5. Characteristics Associated With Membership in the Vomiting and Nausea Latent Classes Compared With the None Classes for Vomiting and Nausea *(Continued)*

Characteristics	Vomiting Classes		Nausea Classes		
	Decreasing (N = 112)	Increasing (N = 85)	Increasing–Decreasing (N = 289) (CIV None = 82.4%, CIV Decreasing = 10.7%, CIV Increasing = 6.9%)	Decreasing (N = 119) (CIV None = 79.8%, CIV Decreasing = 17.7%, CIV Increasing = 2.5%)	High (N = 387) (CIV None = 70.6%, CIV Decreasing = 14.7%, CIV Increasing = 14.7%)
Neuropsychological symptoms *(continued)*					
More likely to report both cancer and noncancer pain	●	●			●
Higher worst pain intensity		●			●
Higher number of pain locations					●
Higher pain interference	●	●			●

CIV—chemotherapy-induced vomiting; CTX—chemotherapy

found, in two studies of patients with cancer (Fujii et al., 2017; Iihara et al., 2016), women had higher rates and severity of CIN. Although the increased risk associated with having childcare responsibilities may be linked with being female, the increased stress associated with caring for children (Okeke et al., 2023; Pritlove & Dias, 2022) may explain this positive relationship.

Clinical Characteristics

Consistent with a previous study (Wu et al., 2019), a poorer functional status and a higher comorbidity burden were the two common clinical risk factors associated with the worst CIV and CIN profiles. Potential explanations for these associations include alterations in metabolism and elimination of chemotherapy drugs as a result of changes in gastrointestinal (Ervin et al., 2020; Singh et al., 2011) and renal (Herrstedt et al., 2022; Lyman & Sparreboom, 2013; Wu et al., 2019) function.

Although a higher overall comorbidity burden was associated with the worst profiles for both symptoms, the specific conditions differed between the CIV and CIN classes. Specifically, a higher percentage of patients in the two worst CIV profiles reported lung disease, kidney disease, diabetes, back pain, and/or rheumatoid arthritis. In contrast, patients in the High CIN class reported higher rates of ulcer or stomach disease, anemia or blood disease, and/or depression. One can hypothesize that patients with back pain and/or arthritis are taking prescription analgesics that increase their risk of vomiting (Obeng et al., 2017). In addition, in previous studies, patients with kidney disease (Lyman & Sparreboom, 2013) and lung cancer (Saragiotto et al., 2020) had higher rates of CIV. In terms of CIN, previous studies found that patients with breast (Crane et al., 2020), lung (Griesinger et al., 2019), and ovarian (Donovan et al., 2016) cancers who reported CIN were more likely to be diagnosed with depression, anemia, and/or inflammatory bowel disease.

Of note, of the 795 patients who were classified into one of the CIN profiles (Singh, Pituch, et al., 2023), 606 of these patients did not report CIV. Although in the authors' previous study of CIN (Singh, Pituch, et al., 2023), risk factors associated with the administration of chemotherapy (e.g., 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) were identified, none of these characteristics were associated with CIV. One plausible explanation for these findings is that the receipt of an evidence-based antiemetic regimen (NCCN, 2023) decreases the occurrence of CIV but not of CIN.

Gastrointestinal Symptoms

Of the 11 gastrointestinal symptoms evaluated, diarrhea was the only symptom that was associated with all of the CIV and CIN profiles. This finding may be attributed to chemotherapy-induced damage to the mucosal lining of the gastrointestinal tract (Singh et al., 2020). Chemotherapy increases levels of free radicals that damage the enterochromaffin cells within the stomach (Hesketh, 2008). These free radicals trigger inflammatory processes along the mucosal lining of the entire gastrointestinal tract (Singh et al., 2020).

As noted in Table 5, patients in the High CIN class reported higher rates for all 11 of the gastrointestinal symptoms. Compared with the None class, the Decreasing and Increasing CIV classes reported higher rates of dry mouth, nausea, diarrhea, lack of appetite, and difficulty swallowing. However, no differences in the occurrence rates for these symptoms were found between the two CIV classes. In addition, the common symptoms for the Decreasing and High CIN classes were vomiting, lack of appetite, weight loss, constipation, and change in the way food tastes. Studies of patients undergoing chemotherapy for gastrointestinal (Sánchez-Lara et al., 2013), lung (Sánchez-Lara et al., 2013), breast (Sánchez-Lara et al., 2013), and ovarian (Huang et al., 2016) cancers support the co-occurrence of lack of appetite (Huang et al., 2016; Sánchez-Lara et al., 2013), nausea (Huang et al., 2016; Sánchez-Lara et al., 2013), vomiting (Huang et al., 2016; Sánchez-Lara et al., 2013), change in the way food tastes (Huang et al., 2016), and weight loss (Huang et al., 2016; Sánchez-Lara et al., 2013), given that these symptoms are often part of a gastrointestinal symptom cluster.

Based on the findings from the authors' previous transcriptomics studies (Singh et al., 2020, 2021), this high gastrointestinal symptom burden may be related to chemotherapy-mediated disruption of the gut microbiome. Gut microbiome dysbiosis perturbs several biologic pathways related to inflammatory processes, which can increase the permeability of the epithelial membrane of the entire gastrointestinal tract. In addition, chemotherapy decreases saliva secretion (Rahnama et al., 2015) and increases the abundance of the oral acidophilic microbiome (Jensen et al., 2008). These alterations are associated with dry mouth and changes in the way food tastes. Although symptoms associated with specific chemotherapy regimens were not evaluated in the current study, the combined effects of various chemotherapy drugs and an antiemetic regimen that includes serotonin and tachykinin receptor antagonists may contribute to constipation (Hanai et al., 2016). Anthracycline and cyclophosphamide–containing regimens (Zheng et al., 2015) are associated with lack of appetite, diarrhea, and mucosal inflammation. In addition, multiple doses of serotonin receptor antagonists, with an anthracycline and cyclophosphamide–containing regimen, exacerbate the occurrence of constipation and lack of appetite (Taguchi et al., 2009).

KNOWLEDGE TRANSLATION

- Patients with high occurrence rates of chemotherapy-induced vomiting reported higher occurrence rates for dry mouth, nausea, diarrhea, lack of appetite, and difficulty swallowing, and had clinically meaningful levels of depression, anxiety, sleep disturbance, and fatigue.
- These patients may need personalized interventions that include nutritional counseling and psychological interventions.
- Findings from this study suggest that although the administration of evidence-based antiemetic regimens has reduced the occurrence of chemotherapy-induced vomiting, chemotherapy-induced nausea remains a significant clinical problem.

Neuropsychological Symptoms

Of the 10 neuropsychological symptoms evaluated, higher severity scores for depression, sleep disturbance, and morning fatigue were associated with all of the CIV and CIN profiles. Specific to CIV, for the Decreasing and Increasing classes, all of these symptom scores exceeded the clinically meaningful cutoffs. It is reasonable to hypothesize that unrelieved CIV and CIN can disrupt sleep and result in higher levels of morning fatigue. Although not associated with the CIN profiles, the Decreasing and Increasing CIV classes were more likely to report cancer and noncancer pain and higher pain interference scores. As noted above, these patients may be taking analgesics that increase the risk of vomiting. The co-occurrence of these neuropsychological symptoms with CIV and/or CIN is consistent with previous studies of patients with breast (Charalambous et al., 2016, 2019; Kwekkeboom et al., 2018; Peoples et al., 2017), gastrointestinal (Kwekkeboom et al., 2018), prostate (Charalambous et al., 2016, 2019), and lung cancers (Kwekkeboom et al., 2018).

The co-occurrence of neuropsychological symptoms with the worst CIV and CIN profiles may be explained by shared biologic mechanisms. For example, alterations in the serotonergic pathway are associated with sleep disturbance (Vaseghi et al., 2022), depression (Pourhamzeh et al., 2022),

anxiety (Szuhany & Simon, 2022), pain (Huang et al., 2024), and the composite symptom of CINV (Singh et al., 2018). Another mechanism that may explain the co-occurrence of these symptoms is alteration in the microbiome–gut–brain axis (Bajic et al., 2018; Jordan et al., 2018; Singh et al., 2020). Changes in the abundance and diversity of the gut microbiome can alter the levels of gut metabolites (e.g., short-chain fatty acids). For example, emerging evidence suggests that major depressive disorder (Jiang et al., 2015) and chronic fatigue syndrome (Nagy-Szakal et al., 2017) are associated with decreases in the abundance of fecal *Faecalibacterium spp*. In addition, sleep disturbance was associated with decreases in the abundance of *Streptococcus spp.* (Jackson et al., 2015).

Limitations

Several limitations warrant consideration. Because the occurrence of nausea and vomiting during the first cycle of chemotherapy (Molassiotis et al., 2014), hyperemesis gravidarum (Naito et al., 2020), and motion sickness (Naito et al., 2020) were not assessed, these risk factors warrant evaluation in future studies. In addition, future studies need to evaluate patients' level of adherence with their antiemetic regimen and the use of other pharmacologic or nonpharmacologic interventions for CIV and CIN (e.g., ginger, cannabis) (Lyman et al., 2018). Because the majority of the patients were female and White, the generalizability of this study's findings is limited. Given the heterogeneity and multitude of chemotherapy regimens in the current study, detailed evaluations of drug-specific CIV and CIN profiles were not done. Future studies need to use latent variable modeling to determine chemotherapy regimen–specific CIV and CIN profiles.

Conclusion

This study is the first to identify a number of demographic and clinical characteristics, as well as gastrointestinal and neuropsychological symptoms, that were associated with worse CIV and/or CIN profiles. Compared with the 59.2% of patients who reported the occurrence of CIN in the authors' previous study (Singh, Pituch, et al., 2023), only 14.7% of the patients who reported CIN reported CIV. This finding demonstrates that although advances in antiemetic treatments alleviate CIV, they are considerably less effective for the management of CIN.

Implications for Practice

Given that the occurrence of both symptoms is a significant risk factor for future episodes of CIN and CIV (Dranitsaris et al., 2017), clinicians need to educate patients about the importance of adhering to their antiemetic regimen. At each chemotherapy treatment, patients need to be assessed for the occurrence of CIV and CIN, evaluated for their level of adherence with their antiemetic regimen and its efficacy, assessed for their ability to obtain and purchase the antiemetic regimen, and have adjustments made in their symptom management regimen. Equally important, an assessment of concomitant medication use is warranted to determine whether these medications increase the severity of other gastrointestinal symptoms. Finally, based on individual risk factors, referrals should be made for nutritional counseling, integrative medicine interventions, social work and financial assistance programs as needed, physical therapy, and/or psychological interventions (e.g., mindfulness-based stress reduction) (Andersen et al., 2006; Greenlee et al., 2017).

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This research was funded, in part, by a grant from the National Cancer Institute (CA134900). K.P. Singh is supported, in part, by

grants from the Louis V. Gerstner Jr. Fund at Vanguard Charitable, Institute for Social Science Research at Arizona State University, and Sigma/Western Institute of Nursing Research Grant. Miaskowski is an American Cancer Society Clinical Research Professor.

K.P. Singh, P. Singh, and Miaskowski contributed to the conceptualization and design. K.P. Singh, P. Singh, Batalini, and Miaskowski completed the data collection. Cooper, Paul, Chen, Pituch, and Miaskowski provided statistical support. K.P. Singh, Cooper, Conley, and Miaskowski provided the analysis. K.P. Singh, Ruddy, A. Singh, Pituch, Grys, P. Singh, Batalini, Hammer, Levine, Conley, and Miaskowski contributed to the manuscript preparation.

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