Title

Multiple Gastrointestinal Symptoms Are Associated With Chemotherapy-Induced Nausea in Patients With Breast Cancer

Journal

Cancer Nursing, 45(3)

ISSN

0162-220X

Authors

Singh, Komal P
Kober, Kord M
Ernst, Brenda
et al.

Publication Date

2022-05-01

DOI

10.1097/ncc.0000000000000976

Peer reviewed

HHS Public Access

Author manuscript

Cancer Nurs. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

Cancer Nurs. 2022 ; 45(3): 181–189. doi:10.1097/NCC.0000000000000976.

Multiple Gastrointestinal Symptoms Are Associated With Chemotherapy-Induced Nausea In Patients With Breast Cancer

Komal P. Singh, RN, PhD, **Kord M. Kober, PhD**, **Brenda Ernst, MD**, **Jasgit Sachdev, MD**, **Melanie Brewer, RN, DNSc, FNP-BC**, **Qiyun Zhu, PhD**, **Haiwei Gu, PhD**, **Michele Melisko, MD**, **Steven M. Paul, PhD**, **Bruce A. Cooper, PhD**, **Marilyn Hammer, RN, PhD**, **Yvette P. Conley, PhD**, **Jon D. Levine, MD, PhD**, **Christine Miaskowski, RN, PhD**

Edson College of Nursing and Health Innovation, Arizona State University, Phoenix, AZ (Dr. Singh, Dr. Brewer); School of Nursing, University of California, San Francisco, CA (Dr. Kober, Dr. Paul, Dr. Cooper, Dr. Miaskowski); Mayo Clinic Cancer Center, Phoenix, AZ (Dr. Ernst); HonorHealth Medical Group, Scottsdale, AZ (Dr. Sachdev, Dr. Brewer); Biodesign Center for Fundamental and Applied Microbiomics, Arizona State University, Tempe, AZ (Dr. Zhu); College of Health Solutions, Arizona State University, Phoenix, AZ (Dr. Gu); School of Medicine, University of California, San Francisco, CA (Dr. Melisko, Dr. Levine, Dr. Miaskowski), Dana Farber Cancer Institute, Boston, MA (Dr. Hammer); School of Nursing, University of Pittsburgh, Pittsburgh, PA (Dr. Conley)

Abstract

Background –—Unrelieved chemotherapy-induced nausea (CIN) is a significant problem for patients with breast cancer (BC).

Objective -—In a sample of patients with BC who were assessed prior to their second or third cycle of chemotherapy, study purposes were to: evaluate for the occurrence, severity, frequency, and distress associated with CIN; evaluate for differences in demographic and clinical characteristics and gastrointestinal (GI) symptom occurrence rates between patients who did and did not report CIN, and determine which demographic, clinical, and symptom characteristics were associated with the occurrence of CIN.

Methods -—Patients completed demographic, clinical questionnaires and Memorial Symptom Assessment Scale for nausea and common GI symptom assessments. Univariate analyses evaluated for differences in demographic and clinical characteristics and GI symptom occurrence between patients who did and did not report CIN. Multiple logistic regression analysis evaluated for characteristics associated with CIN.

Results -—Of the 532 patients with BC, 47.2% reported CIN occurrence. Characteristics associated with CIN group membership were: poorer functional status, receipt of chemotherapy on a 14-day cycle, higher occurrence rates of five GI symptoms (i.e., dry mouth, vomiting, constipation, change in the way food tastes, and lack of appetite (all $p<.001$)).

Correspondence: Christine Miaskowski, RN, PhD, Department of Physiological Nursing, University of California, 2 Koret Way, San Francisco, CA 94143-0610 (chris.miaskowski@ucsf.edu).

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

Conclusions -—Unrelieved CIN is a common symptom in patients with BC. This study is the first to demonstrate that five co-occurring GI symptoms were associated with CIN occurrence.

Implications for Practice –—This study identified new risk factors for CIN occurrence in patients with BC. Clinicians may be able to initiate additional interventions to alleviate CIN.

Keywords

nausea; chemotherapy; antiemetics; gastrointestinal symptoms; breast cancer

INTRODUCTION

Despite the use of evidence-based antiemetic regimens[1] and integrative therapies (e.g., acupressure, electro-acupuncture)[2] to prevent chemotherapy-induced nausea (CIN), 35% to 60% of patients with breast cancer (BC) experience this debilitating symptom.[1, 3] Persistent CIN can lead to significant declines in nutritional status,[4] physical and mental health,[2] and quality of life.[1]

Only four studies have evaluated for demographic and clinical characteristics associated with an increased risk for CIN in patients with BC.[1, 3, 5, 6] In two studies,[1, 5] CIN was evaluated as part of a composite symptom (i.e., chemotherapy-induced nausea and vomiting (CINV)). In the other two studies,[3, 6] CIN was assessed as a distinct symptom. Across these four studies,[1, 3, 5, 6] age less than 55 years was associated with an increased risk for the occurrence of CIN/CINV. In terms of clinical characteristics, in three studies,[1, 3, 6] highly emetogenic chemotherapy regimens were associated with increased rates of CIN. Additional factors that increased the risk for CIN included: having significant CIN on the day after the first cycle of chemotherapy,[6] history of motion sickness,[1, 3, 6] history of morning sickness,[1, 3] higher serum albumin levels,[3] and a body mass index (BMI) of <27.5 kilograms per meter squared (kg/m^2).[5] While these four studies provide useful information on risk factors for CIN,[1, 3, 5, 6] several limitations warrant consideration. Age was the only demographic characteristic evaluated; findings regarding alcohol intake were inconsistent;[1, 5, 6] and in three studies,[3, 5, 6] the evaluation of CIN were limited to the first week following chemotherapy.

Patients with BC undergoing chemotherapy experience multiple co-occurring gastrointestinal (GI) symptoms.[4, 7–9] Across four studies,[4, 7–9] that used a GI symptom questionnaire,[4, 8] the Common Terminology Criteria for Adverse Events (CTCAE) version 4,[7] or the Memorial Symptom Assessment Scale (MSAS),[9] the occurrence rates for the various GI symptoms, based on grand mean averages were: change in the way food tastes (53%),[7–9] dry mouth (44%),[4, 7–9] lack of appetite (38%),[8, 9] constipation (37%),[4, 8] weight loss (20%),[9] abdominal cramps (18%),[9] diarrhea (18%),[4, 8, 9] oral mucositis (16%),[4, 7] difficulty swallowing (14%),[4, 9] and vomiting (8%).[4, 8, 9] While one study identified a GI symptom cluster that remained relatively stable over one cycle of chemotherapy,[9] the other three studies[4, 7, 8] found that higher levels of GI symptoms were associated with decreases in dietary intake. No study evaluated the relative contribution of common GI symptoms to CIN occurrence.

To date, known demographic and clinical risk factors do not explain all the variance in the occurrence of CIN in patients with BC.[10] Additional demographic and clinical characteristics that were associated with other common symptoms in these patients (e.g., ethnicity,[11] living arrangements,[9] education,[12] functional status,[13, 14] and comorbidities[15]) warrant investigation as potential risk factors for CIN. In addition, treatment characteristics (e.g., cycle length, emetogenicity of chemotherapy regimen, type of antiemetic regimen) need to be evaluated. A comprehensive evaluation of demographic and clinical characteristics may provide useful information to identify high risk patients. In addition, an evaluation of common GI symptoms may help to identify modifiable risk factors for unrelieved CIN. Therefore, the purposes of this study, in a sample of patients with BC (n=532), who were assessed prior to their second or third cycle of chemotherapy, were to: evaluate for the occurrence, severity, frequency, and distress associated with CIN and evaluate for differences in demographic and clinical characteristics and GI symptom occurrence rates between patients who did and did not report CIN. Finally, we determined which demographic, clinical, and GI symptom characteristics were associated with the occurrence of CIN.

METHODS

Patients and settings

This study is part of a larger descriptive, longitudinal study that evaluated the symptom experience of oncology outpatients receiving chemotherapy and whose methods are described in detail elsewhere.[16, 17] The theoretical framework for the parent study was the Theory of Symptom Management.[18] In the parent study, patients were eligible if they: were ≥18 years of age; had a diagnosis of breast, GI, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; were not receiving concurrent radiation therapy; were able to read, write, and understand English; and provided written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. The same inclusion criteria and study procedures were used regardless of the patient's cancer diagnosis.

Study procedures

The study was approved by the Committee on Human Research at the University of California at San Francisco and by the Institutional Review Board at each of the study sites.

A total of 2234 patients were approached and 1343 consented to participate (60.1% response rate). The major reason for refusal was being too overwhelmed with their cancer treatment. Of the 1343 patients who consented, 532 had a diagnosis of BC. These patients with BC were evaluated in this study.

A research staff member approached eligible patients in the infusion unit and discussed participation in the study. Written informed consent was obtained from all of the patients. Patients were recruited during their first or second cycle of chemotherapy. Depending on

the length of their chemotherapy cycles (i.e., 14-day, 21-day, or 28-day), patients completed study questionnaires in their homes, a total of six times over two cycles of chemotherapy. Medical records were reviewed for disease and treatment information. Data from the enrollment assessment (i.e., prior to the patients' second or third cycle of chemotherapy) were used in these analyses.

Instruments

Demographic and clinical characteristics -—Demographic questionnaire obtained information on: age, gender, ethnicity, marital status, living arrangements, education, employment status, income, and past medical history. Karnofsky Performance Status (KPS) scale was used to evaluate functional status[19, 20]. Self-Administered Comorbidity Questionnaire (SCQ) evaluated the occurrence, treatment, and functional impact of thirteen common comorbid conditions.[21] Total SCQ scores range from 0 to 39. Alcohol Use Disorders Identification Test (AUDIT) evaluated alcohol consumption, alcohol dependence, and the consequences of alcohol abuse in the last 12 months.[22] Smoking questionnaire assessed smoking history.[23]

Assessment of CIN -—A modified version of MSAS was used to assess CIN.[24] Patients were asked to indicate whether or not they had experienced CIN in the past week (i.e., symptom occurrence). If they experienced CIN, they were asked to rate its frequency, severity, and distress. Patients' assessment of CIN in the week prior to their second or third cycle of chemotherapy was used to dichotomize the sample into the "CIN" and "no CIN" groups. Patients who provided a rating for occurrence, frequency, severity, and/or distress for the CIN item were coded as having CIN. Patients who indicated "no" to the occurrence item were coded as not having CIN.

Assessment of other GI symptoms –—The MSAS was used to evaluate for associations between the occurrence of CIN and the occurrence of eleven other GI symptoms, namely: 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. The validity and reliability of the MSAS are well established.[24]

Coding of the chemotherapy regimens

Using the Multinational Association of Supportive Care in Cancer (MASCC) guidelines,[25–27] each drug in the chemotherapy regimen was classified as having: minimal, low, moderate, or high emetogenic potential. The emetogenicity of the regimen was categorized into three groups (i.e., low/minimal, moderate, or high) based on the chemotherapy drug with highest emetogenic potential.

Coding of the antiemetic regimens

Each 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 four groups: none (i.e., no antiemetic administered); steroid alone or serotonin receptor antagonist alone; serotonin receptor antagonist and steroid; or NK-1 receptor antagonist and two other antiemetics (e.g., a

serotonin receptor antagonist, dopamine receptor antagonist, prochlorperazine, lorazepam and/or a steroid).

Statistical analyses

Data were analyzed using SPSS Version 27 (IBM Corporation, Armonk, NY). Descriptive statistics and frequency distributions were calculated for demographic and clinical characteristics. Appropriate parametric and nonparametric tests were used to evaluate for differences in demographic and clinical characteristics and the occurrence of GI symptoms between patients who did and did not report CIN. Multiple logistic regression analysis was used to evaluate for predictors of CIN group membership. Only those characteristics that were significantly different in the univariate analyses between patients who did and did not report CIN were evaluated in the logistic regression analysis. A backwards stepwise approach was used to create a parsimonious model. Only predictors with a p-value of <0.05 were retained in the final model.

RESULTS

CIN characteristics

Of the 532 patients with BC, 47.2% reported CIN in the week prior to their next cycle of chemotherapy. Of these 251 patients, 96.8% rated its severity, 98.4% rated its frequency, and 96.8% rated its distress. Of the patients who reported severity, frequency and distress associated with CIN: 13.2% of the patients rated the severity as “severe” and 2.9% as “very severe” (Fig. 1a); 20.2% of the patients rated its frequency as “frequently” and 10.5% as “almost constantly” (Fig 1b); 12.3% of the patients rated its distress as “quite a bit” and 8.2% as “very much” (Fig. 1c).

Differences in demographic and clinical characteristics

Compared to the no CIN group, patients with CIN were significantly younger; reported a lower annual income; and had a lower KPS score, a higher number of comorbidities, and a higher comorbidity score. Patients in the CIN group were more likely to have high blood pressure, depression, and back pain. In addition, a higher percentage of patients in the CIN group received chemotherapy on a 14-day cycle; received highly emetogenic chemotherapy; and received a NK-1 receptor antagonist and two other antiemetics (Table 1).

Differences in the occurrence of GI symptoms

Compared to the no CIN group, patients with CIN had significantly higher occurrence rates for: change in the way food tastes, dry mouth, lack of appetite, constipation, feeling bloated, diarrhea, mouth sores, weight loss, abdominal cramps, difficulty swallowing, and vomiting (Table 2).

Results of the logistic regression analysis

Characteristics that were significantly different between the two CIN groups in the univariate analyses were included in the backwards stepwise elimination model (i.e., age, KPS score, SCQ score, cycle length, emetogenicity of the chemotherapy regimen, antiemetic

regimen, and all eleven GI symptoms). While income was significantly different between the two groups, 61 patients did not report their income. Therefore, this variable was not included in the regression analysis. Consequently, data from 502 patients with BC were included in the final model.

As shown in Table 3, seven characteristics (i.e., KPS score, dry mouth, cycle length, vomiting, constipation, change in the way food tastes, and lack of appetite) were retained in the final logistic regression model ($X^2 = 166.96$, $p<.001$). Patients who had a lower KPS score and who reported the occurrence of dry mouth, vomiting, constipation, change in the way food tastes, and lack of appetite were more likely to be in the CIN group. In addition, cycle length was a significant predictor of CIN group membership. Because cycle length had three groups, three pairwise contrasts were examined to interpret the effect of cycle length. The significance criteria for each of these contrasts was .017 (.05/3). Two contrasts were significant. Compared to patients who received chemotherapy on a 21-day or 28-day cycle, patients on a 14-day cycle had a 1.92 or a 4.17 increase in the odds, respectively of being in the CIN group.

DISCUSSION

This study is the first to evaluate the relative contribution of a comprehensive list of demographic (i.e., ethnicity, living arrangements, education) and clinical (i.e., comorbidities, functional status, cycle length, emetogenicity of the chemotherapy regimen, type of antiemetic regimen) characteristics, as well as GI symptoms to the occurrence of CIN in patients with BC. Consistent with previous occurrence rates of between 33%[1] and 60%,[1, 3] 47.2% of patients in our study reported CIN. In addition, similar to other studies[8, 28], over 16% of our patients reported that their CIN was severe or very severe and over 20% reported high levels of distress. Taken together, these findings confirm that despite the administration of combination antiemetic regimens, in 74% of the patients with CIN, this unrelieved symptom remains a significant clinical problem in the week prior to the patient's next cycle of chemotherapy.

GI symptoms associated with CIN occurrence

Across numerous studies,[9, 29, 30] a GI symptom cluster, that includes CIN and many of the GI symptoms evaluated in this study, was identified in patients receiving chemotherapy. This symptom cluster is hypothesized to occur as a result of chemotherapy-induced inflammation along the entire GI tract.[31–33] Therefore, it is not surprising that patients in the CIN group reported higher occurrence rates for all eleven GI symptoms. However, dry mouth, vomiting, constipation, change in the way food tastes, and lack of appetite were the five co-occurring symptoms that were retained in the final regression model. The co-occurrence of these GI symptoms may be the result of a number of interacting mechanisms that are described below.[31, 34–36]

The administration of chemotherapy can decrease salivary secretion.[37] This decrease in saliva and the direct effects of chemotherapy on the mucosal epithelium results in dry mouth and oral mucositis.[37] In addition, chemotherapy can change the profile of the microbiome of the oral cavity.[37] For example, in a study of patients with BC who received a combination

of cyclophosphamide, epirubicin or methotrexate, and 5-flurouracil,[32] 11% developed oral candidiasis. In our study, while mouth sores were reported by 30% of the patients in the CIN group, it did not remain significant in the regression analysis. However, patients with dry mouth were 2.08 times more likely to be in the CIN group. This finding suggests that clinicians need to perform routine assessments of the oral mucosa particularly for patients who are receiving stomatotoxic chemotherapy.

Changes in the way food tastes is another co-occurring symptom that may be related to the direct effects of chemotherapy on the oral mucosa and its microbiome. Consistent with previous reports,[4, 7, 8] the occurrence of change in the way food tastes was associated with a 1.57 times increased risk of being in the CIN group. Of note, the co-occurrence of taste changes and CIN increases with repeated cycles of chemotherapy.[7] In addition, in a study of taste changes in patients with BC,[32] while CIN was not evaluated, dry mouth, oral mucositis, and an increase in acidophilic microflora co-occurred in patients with taste changes. Given these findings, the occurrence and severity of taste changes warrant investigation in future studies.

While only 20% of the patients in the CIN group reported vomiting, this symptom was associated with an 8.91 times increase in the odds of being in this group. Numerous factors may explain the higher rates of these two symptoms in our CIN group including: the natural co-occurrence of these two symptoms; a history of morning sickness;[3, 10] increased emetogenicity of the chemotherapy regimen;[10] inconsistent adherence with the antiemetic regimen;[10] and/or a number of molecular mechanisms.[31, 34, 38]

The co-occurrence of constipation was associated with a 2.05 increase in the odds of being in the CIN group. The etiology of constipation may be multifactorial in patients with BC receiving chemotherapy. One of the major side effects of antiemetic regimens that include serotonin and tachykinin receptor antagonists is constipation.[39] While not significant in the final regression model, patients in the CIN group were more likely to receive an antiemetic regimen that included a NK1-receptor antagonist. In addition, some of the most common chemotherapy regimens that patients with BC receive include drugs (e.g., taxotere) that induce constipation. The high co-occurrence rates for bloating and abdominal cramps in the CIN group may be related to constipation.

The co-occurrence of lack of appetite was associated with a 2.45 increase in the odds of being in the CIN group. Both the type of chemotherapy and the antiemetic regimen that the patient received may contribute to the development of this symptom. For example, in a study of patients with BC who received an anthracycline and cyclophosphamide regimen,[40] compared to patients who received a single dose of granisetron, patients who received multiple doses of this antiemetic were more likely to report lack of appetite. In another study,[41] an association was found between the receipt of an anthracycline and cyclophosphamide regimen and the occurrence of CIN, lack of appetite, and stomatitis.

The co-occurrence of all of these GI symptoms may be the result of chemotherapy-induced epithelial inflammation along the entire GI tract.[35, 42] In fact, in our recent study,[31] perturbations in pathways associated with mucosal inflammation and disruption of the

gut microbiome were associated with occurrence of CIN. Taken together, these findings suggest that clinicians need to assess for all of these co-occurring GI symptoms and initiate appropriate interventions to alleviate this extremely high symptom burden.

Demographic and clinical characteristics associated with CIN occurrence

This study is the first to evaluate a comprehensive list of demographic and clinical characteristics associated with the occurrence of CIN in patients with BC. While in the multivariate analyses, no demographic characteristics remained significant, KPS score and cycle length were the two clinical characteristics retained in the final model. Patients with lower functional status had an increased likelihood of being in the CIN group. The difference in KPS scores between the two CIN groups represents not only a statistically significant but a clinically meaningful difference (i.e., d = 0.56) in functional status. Given that CIN co-occurs with symptoms that have a negative impact on patients' nutritional intake, it is plausible that their functional status may be compromised. These patients may warrant referrals to a dietician for nutritional counseling.

In our univariate analysis and consistent with previous studies, a higher percentage of patients who received highly emetogenicity chemotherapy[1, 3, 6] and antiemetic regimens that contained a NK-1 antagonist[10] were in the CIN group. However, only cycle length remained significant in the multivariate model. Compared to patients who received chemotherapy on 21- and 28-day cycles, those who received chemotherapy on a 14-day cycle, were at increased risk for being in the CIN group. Several plausible explanations exist for this association. While it was not possible due to the heterogeneity of the chemotherapy regimens in this study to evaluate the relative contribution of a specific regimen to membership in the CIN group, 88.6% of the patients who received their chemotherapy on a 14-day cycle (i.e., 156 of 203) received doxorubicin and cyclophosphamide which is known to be a highly emetogenic regimen.[41] Equally plausible, this association can be partially explained by the more frequent exposure to chemotherapy. In addition, compared to patients on a 21-day, a higher percentage of patients on a 14-day cycle received highly emetogenic chemotherapy (13.2% vs 86.8%, $p < 0.001$, respectively). For patients on a 14-day cycle, behavioral interventions (e.g., systematic desensitization, progressive muscle relaxation) prior to and during chemotherapy may help decrease the occurrence of CIN.[43] In addition, future research is warranted to investigate interventions to alleviate chemotherapy-induced GI inflammatory processes that may help decrease CIN occurrence.

Limitations

Several limitations warrant consideration. Because the occurrence of CIN during the first cycle of chemotherapy is a risk factor for subsequent episodes,[1, 44] future studies can use the MASCC antiemesis tool[45] or a daily diary to assess CIN occurrence prior to the initiation and over the course of chemotherapy. In addition, future studies need to evaluate patients' level of adherence with their antiemetic regimen. In addition, future studies need evaluate the relationships between specific chemotherapy regimens and co-occurring GI symptoms and increased occurrence rates for CIN. While our study evaluated a large number of potential predictors that warrant confirmation, future studies should evaluate additional risk factors including: motion sickness,[3, 10] morning sickness,[10] and previous history of

nausea,[46] because these risk factors may be particularly important in women with BC. Given that the majority of our patients were White, college educated, and had metastatic disease, our findings may not generalize to all patients with BC receiving chemotherapy.

Conclusions

Despite these limitations, our study is the first to describe significant associations between the occurrence of multiple GI symptoms, as well as clinically meaningful demographic and clinical characteristics, and CIN in patients with BC. Based on the findings from this study, particularly in relationship to the high occurrence rates for GI symptoms, clinicians need to assess patients for nausea and these associated symptoms. Of note, the relatively high occurrence of nausea suggests that patients may not be adhering with their antiemetic regimen. Nurses need to assess the efficacy of the antiemetic regimen, as well as patients' adherence with it, and make modifications to decrease this distressing symptom. In addition, individualized treatment plans need to be developed for co-occurring symptoms, namely constipation and dry mouth.

Given the associations among dry mouth, change in the way food tastes, vomiting, constipation, and lack of appetite, as well as a lower level of physical function in the patients with CIN, a variety of interventions may help alleviate this symptom. For example, in two studies of patients receiving chemotherapy,[47, 48] the intake of fish oil supplements alleviated dry mouth[48] and improved appetite.[47] While additional research is warranted on its efficacy in decreasing CIN, fish oil maintains intestinal wall integrity and decreases gastrointestinal inflammation[49] that may contribute to the occurrence of CIN.[34] In another study that evaluated for self-care strategies patients used to manage taste changes,[50] this symptom was associated with nausea, dry mouth, and decreased appetite. Patients who were bothered my nausea reported that adding more fats or sauces to foods and eating more flavored protein foods was helpful. Given that CIN was associated with lack of appetite and changes in the way food tastes, patients' nutritional status needs to be monitored and referrals need to be made to dieticians.

Finally, clinicians can use the demographic and clinical characteristics found in this study to identify patients at increased risk for unrelieved CIN and initiate therapeutic interventions. In addition to the recommendations cited above, future research needs to investigate the underlying mechanisms associated with these risk factors, particularly the multiple co-occurring GI symptoms.

Acknowledgements:

This study was supported by a grant from the National Cancer Institute (NCI, CA134900). Dr. Miaskowski is an American Cancer Society Clinical Research Professor.

REFERENCES

1. Dranitsaris G, Mazzarello S, Smith S, Vandermeer L, Bouganim N, Clemons M. Measuring the impact of guideline-based antiemetic therapy on nausea and vomiting control in breast cancer patients with multiple risk factors. Support Care Cancer. 2016;24(4):1563–1569. [PubMed: 26381427]

2. Greenlee H, DuPont-Reyes MJ, Balneaves LG, et al. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. CA Cancer J Clin. 2017;67(3):194–232. [PubMed: 28436999]

3. Naito Y, Kai Y, Ishikawa T, et al. Chemotherapy-induced nausea and vomiting in patients with breast cancer: a prospective cohort study. Breast Cancer. 2020;27(1):122–128. [PubMed: 31407150]

4. de Vries YC, van den Berg M, de Vries JHM, et al. Differences in dietary intake during chemotherapy in breast cancer patients compared to women without cancer. Support Care Cancer. 2017;25(8):2581–2591. [PubMed: 28303381]

5. Kawazoe H, Murakami A, Yamashita M, et al. Patient-related Risk Factors for Nausea and Vomiting with Standard Antiemetics in Patients with Breast Cancer Receiving Anthracycline-based Chemotherapy: A Retrospective Observational Study. Clin Ther. 2018;40(12):2170–2179. [PubMed: 30392814]

6. Kottschade L, Novotny P, Lyss A, Mazurczak M, Loprinzi C, Barton D. Chemotherapy-induced nausea and vomiting: incidence and characteristics of persistent symptoms and future directions NCCTG N08C3 (Alliance). Support Care Cancer. 2016;24(6):2661–2667. [PubMed: 26768436]

7. Boltong A, Aranda S, Keast R, et al. A prospective cohort study of the effects of adjuvant breast cancer chemotherapy on taste function, food liking, appetite and associated nutritional outcomes. PLoS One. 2014;9(7):e103512. [PubMed: 25078776]

8. Marinho EDC, Custodio IDD, Ferreira IB, Crispim CA, Paiva CE, Maia YCP. Impact of chemotherapy on perceptions related to food intake in women with breast cancer: A prospective study. PLoS One. 2017;12(11):e0187573. [PubMed: 29190717]

9. Sullivan CW, Leutwyler H, Dunn LB, et al. Stability of symptom clusters in patients with breast cancer receiving chemotherapy. J Pain Symptom Manage. 2018;55(1):39–55. [PubMed: 28838866]

10. Clemons M, Bouganim N, Smith S, et al. Risk model-guided antiemetic prophylaxis vs physician's choice in patients receiving chemotherapy for early-stage breast cancer: A randomized clinical trial. JAMA Oncol. 2016;2(2):225–231. [PubMed: 26562292]

11. Patel TA, Colon-Otero G, Bueno Hume C, Copland JA 3rd, Perez EA. Breast cancer in Latinas: gene expression, differential response to treatments, and differential toxicities in Latinas compared with other population groups. Oncologist. 2010;15(5):466–475. [PubMed: 20427382]

12. Liu LN, Wen FH, Miaskowski C, et al. Weight change trajectory in women with breast cancer receiving chemotherapy and the effect of different regimens. J Clin Nurs. 2014;23(19–20):2757–2768. [PubMed: 24393441]

13. Dodd MJ, Cho MH, Cooper BA, Miaskowski C. The effect of symptom clusters on functional status and quality of life in women with breast cancer. Eur J Oncol Nurs. 2010;14(2):101–110. [PubMed: 19897417]

14. Li D, McCall LM, Hahn OM, et al. Identification of risk factors for toxicity in patients with hormone receptor-positive advanced breast cancer treated with bevacizumab plus letrozole: a CALGB 40503 (alliance) correlative study. Breast Cancer Res Treat. 2018;171(2):325–334. [PubMed: 29789969]

15. Edwards MJ, Campbell ID, Lawrenson RA, Kuper-Hommel MJ. Influence of comorbidity on chemotherapy use for early breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat. 2017;165(1):17–39. [PubMed: 28528451]

16. Wright F, D'Eramo Melkus G, Hammer M, et al. Trajectories of evening fatigue in oncology outpatients receiving chemotherapy. J Pain Symptom Manage. 2015;50(2):163–175. [PubMed: 25828560]

17. Wright F, D'Eramo Melkus G, Hammer M, et al. Predictors and trajectories of morning fatigue are distinct from evening fatigue. J Pain Symptom Manage. 2015;50(2):176–189. [PubMed: 25828559]

18. Humphreys J, Janson S, Donesky D, et al. A middle range theory of symptom management. In: Smith MJ, Liehr PR, eds. Middle Range Theory in Nursing. 3rd ed. New York: Springer Publishing Company; 2014:141–164.

19. Karnofsky D Performance scale. New York: Plenum Press; 1977.

20. Karnofsky D, Abelmann WH, Craver LV, Burchenal JH. The use of nitrogen mustards in the palliative treatment of carcinoma. Cancer. 1948;1:634–656.

21. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum. 2003;49(2):156–163. [PubMed: 12687505]
22. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care. Geneva, Switzerland: World Health Organization; 2001.
23. Kozlowski LT, Porter CQ, Orleans CT, Pope M, Heatherton T. Predicting smoking cessation with self-reported measures of nicotine dependence: FTQ, FTND, and HSI. Drug Alcohol Depend. 1994;34(3):211–216. [PubMed: 8033758]
24. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. Eur J Cancer. 1994;30A(9):1326–1336. [PubMed: 7999421]
25. Hesketh P, Bohlke K, Lyman G, et al. Antiemetics: American Society of Clinical Oncology Focused Guideline Update. J Clin Oncol. 2016;34(4):381–386. [PubMed: 26527784]
26. Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. Journal of Clinical Oncology. 1997;15(1):103–109. [PubMed: 8996130]
27. Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol. Sep 2016;27(suppl 5):v119–v133.
28. Liew AC, Peh KK, Tan BS, Zhao W, Tangiisuran B. Evaluation of chemotherapy-induced toxicity and health-related quality of life amongst early-stage breast cancer patients receiving Chinese herbal medicine in Malaysia. Support Care Cancer. 2019;27(12):4515–4524. [PubMed: 30911917]
29. Kim HJ, Barsevick AM, Tulman L, McDermott PA. Treatment-related symptom clusters in breast cancer: a secondary analysis. J Pain Symptom Manage. 2008;36(5):468–479. [PubMed: 18718735]
30. Nho JH, Kim SR, Park MH, Kweon SS. Symptom clusters and quality of life in breast cancer survivors after cancer treatment in a tertiary hospital in Korea. Eur J Cancer Care. 2018;27(6):e12919.
31. Singh KP, Dhruva A, Flowers E, et al. Alterations in patterns of gene expression and perturbed pathways in the gut-brain axis are associated with chemotherapy-induced nausea. J Pain Symptom Manage. 2020;59(6):1248–1259 e1245. [PubMed: 31923555]
32. Jensen SB, Mouridsen HT, Bergmann OJ, Reibel J, Brunner N, Nauntofte B. Oral mucosal lesions, microbial changes, and taste disturbances induced by adjuvant chemotherapy in breast cancer patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106(2):217–226. [PubMed: 18554960]
33. Melo ML, Brito GA, Soares RC, et al. Role of cytokines (TNF-alpha, IL-1beta and KC) in the pathogenesis of CPT-11-induced intestinal mucositis in mice: effect of pentoxifylline and thalidomide. Cancer Chemother Pharmacol. 2008;61(5):775–784. [PubMed: 17624531]
34. Singh K, Cao H, Miaskowski C, et al. Perturbations in endocytotic and apoptotic pathways are associated with chemotherapy-induced nausea. Biol Res Nurs. 2021; in press.
35. Stringer AM, Gibson RJ, Bowen JM, Keefe DM. Chemotherapy-induced modifications to gastrointestinal microflora: evidence and implications of change. Curr Drug Metab. 2009;10(1):79–83. [PubMed: 19149515]
36. Rojas C, Slusher BS. Mechanisms and latest clinical studies of new NK1 receptor antagonists for chemotherapy-induced nausea and vomiting: Rolapitant and NEPA (netupitant/palonosetron). Cancer Treat Rev. 2015;41(10):904–913. [PubMed: 26442475]
37. Rahnama M, Madej-Czerwonka B, Jastrzebska-Jamrogiewicz I, Jamrogiewicz R. Analysis of the influence of parenteral cancer chemotherapy on the health condition of oral mucosa. Contemp Oncol 2015;19(1):77–82.
38. Singh KP, Dhruva AA, Flowers E, Kober KM, Miaskowski C. A review of the literature on the relationships between genetic polymorphisms and chemotherapy-induced nausea and vomiting. Crit Rev Oncol Hematol. 2018;121:51–61. [PubMed: 29279099]

39. Hanai A, Ishiguro H, Sozu T, et al. Effects of a self-management program on antiemetic-induced constipation during chemotherapy among breast cancer patients: a randomized controlled clinical trial. Breast Cancer Res Treat. 2016;155(1):99–107. [PubMed: 26650825]
40. Taguchi K, Iihara H, Ishihara M, et al. Comparison of antiemetic efficacy between single and repeated treatments with a 5-HT3 receptor antagonist in breast cancer patients with high-risk emetogenic chemotherapy. Anticancer Research. 2009;29:1721–1726. [PubMed: 19443393]
41. Zheng R, Han S, Duan C, et al. Role of taxane and anthracycline combination regimens in the management of advanced breast cancer: a meta-analysis of randomized trials. Medicine. 2015;94(17):e803. [PubMed: 25929935]
42. Bowen JM, White I, Smith L, et al. Pre-therapy mRNA expression of TNF is associated with regimen-related gastrointestinal toxicity in patients with esophageal cancer: a pilot study. Support Care Cancer. 2015;23(11):3165–3172. [PubMed: 25814442]
43. NCCN. Antiemetics. Available at: http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf.
44. Molassiotis A, Lee PH, Burke TA, et al. Anticipatory nausea, risk factors, and its impact on chemotherapy-induced nausea and vomiting: results from the Pan European Emesis Registry Study. J Pain Symptom Manage. 2016;51(6)::987–993. [PubMed: 26891606]
45. Molassiotis A, Coventry P, Stricker C, et al. Validation and psychometric assessment of a short clinical scale to measure chemotherapy-induced nausea and vomiting: the MASCC Antiemesis Tool. J Pain Symptom Manage. 2007;34(2):148–159. [PubMed: 17509816]
46. Mosa ASM, Hossain AM, Lavoie BJ, Yoo I. Patient-related risk factors for chemotherapy-induced nausea and vomiting: A systematic review. Front Pharmacol. 2020;11:329. [PubMed: 32296333]
47. Ukovic B, Porter J. Nutrition interventions to improve the appetite of adults undergoing cancer treatment: a systematic review. Support Care Cancer. 2020;28(10):4575–4583. [PubMed: 32451701]
48. de la Rosa Oliva F, Meneses Garcia A, Ruiz Calzada H, et al. Effects of omega-3 fatty acids supplementation on neoadjuvant chemotherapy-induced toxicity in patients with locally advanced breast cancer: a randomized, controlled, double-blinded clinical trial. Nutr Hosp. 26 2019;36(4):769–776. [PubMed: 31192682]
49. Costantini L, Molinari R, Farinon B, Merendino N. Impact of Omega-3 Fatty Acids on the Gut Microbiota. Int J Mol Sci. 2017;18(12).
50. Rehwaldt M RW, Purl S, et al. Self-Care Strategies to Cope With Taste Changes After Chemotherapy. Oncol Nurs Forum. 2009;36(2):E47–E56. [PubMed: 19273394]

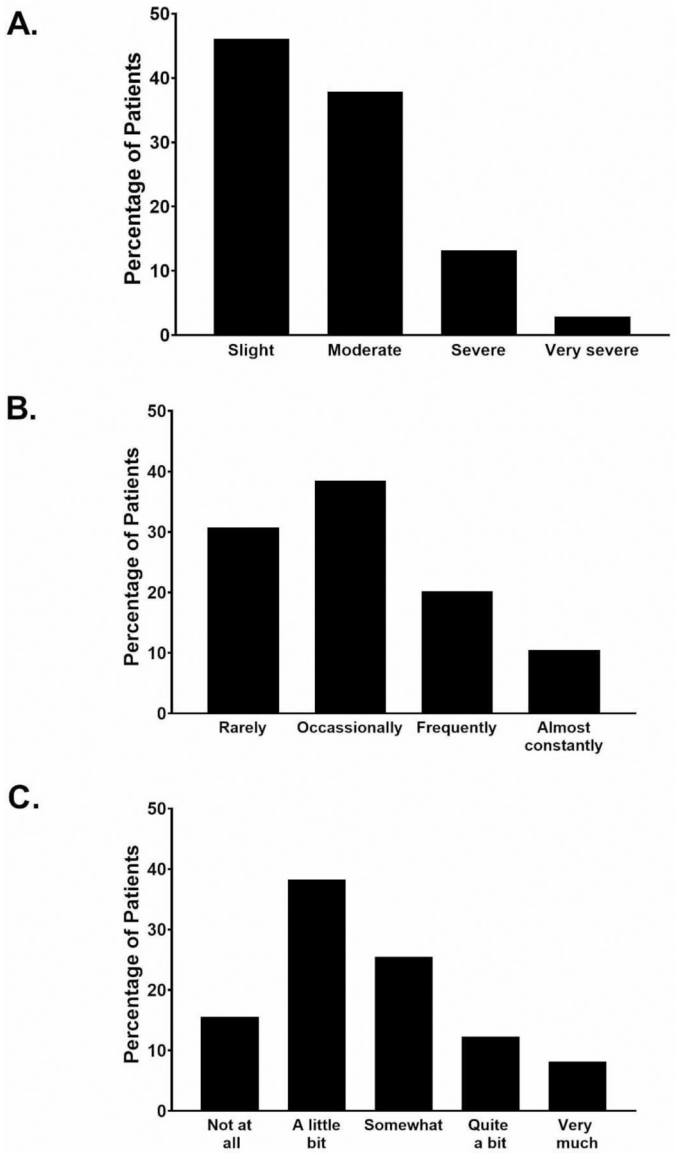

Fig. 1.

The percentage of patients with breast cancer who reported each (a) severity, (b) frequency, and (c) distress rating for chemotherapy-induced nausea on the Memorial Symptom Assessment Scale prior to their second or third cycle of chemotherapy.

Table 1.

Differences in Demographic and Clinical Characteristics Between Breast Cancer Patients With and Without Chemotherapy-Induced Nausea.

Characteristic	No Nausea (0) 52.8% (n = 281)	Nausea (1) 47.2% (n = 251)	Statistics
	Mean (SD)	Mean (SD)	
Age (years)	54.5 (11.8)	52.1 (11.2)	t = 2.43, p = .016
Education (years)	16.6 (2.9)	16.2 (2.9)	t = 1.73, p = .083
Body mass index (kg/m^2)	26.1 (5.5)	26.5 (6.2)	t = −0.81, p = .419
Karnofsky Performance Status score	83.6 (11.0)	77.1 (12.0)	t = 6.42, p < .001
Number of comorbidities	2.0 (1.3)	2.4 (1.4)	t = −3.55, p < .001
SCQ score	4.5 (2.7)	5.5 (3.0)	t = −3.94, p < .001
AUDIT score	2.9 (2.3)	2.7 (2.4)	t = 0.49, p = .624
Time since cancer diagnosis (years)	2.8 (5.3)	2.3 (4.2)	U, p = .916
Time since diagnosis (median)	0.42	0.42	
Number of prior cancer treatments	1.8 (1.8)	1.7 (1.8)	t = 0.98, p = .328
Number of metastatic sites including lymph node involvement	1.0 (1.2)	0.9 (1.3)	t = 0.12, p = .904
Number of metastatic sites excluding lymph node involvement	0.5 (1.0)	0.5 (1.0)	t = 0.59, p = .559
	% (n)	% (n)	
Ethnicity			X^2 = 4.47, p = .215
White	71.1 (199)	63.3 (157)	
Black	5.4 (15)	8.5 (21)	
Asian or Pacific Islander	13.9 (39)	15.3 (38)	
Hispanic Mixed or Other	9.6 (27)	12.9 (32)	
Married or partnered (% yes)	67.8 (187)	64.0 (158)	FE, p = .406
Lives alone (% yes)	17.0 (47)	17.7 (44)	FE, p = .908
Child care responsibilities (% yes)	28.8 (79)	32.9 (80)	FE, p = .340
Care of adult responsibilities (% yes)	8.3 (21)	8.4 (19)	FE, p = 1.000
Born prematurely (% yes)	5.9 (16)	5.9 (14)	FE, p = 1.000
Currently employed (% yes)	43.4 (121)	39.0 (97)	FE, p = .330
Income			U, p = .001
< $30,000	7.8 (19)	22.5 (51)	
$30,000 to < $70,000	18.9 (46)	17.2 (39)	
$70,000 to < $100,000	18.4 (45)	16.3 (37)	
≥ $100,000	54.9 (134)	44.1 (100)	
Specific comorbidities (% yes)			
Heart disease	4.3 (12)	2.8 (7)	FE, p = .484
High blood pressure	18.5 (52)	28.3 (71)	FE, p = .010
Lung disease	4.6 (13)	3.6 (9)	FE, p = .664
Diabetes	5.3 (15)	7.6 (19)	FE, p = .375

Ulcer or stomach disease	1.8 (5)	4.8 (12)	FE, p = .081
Kidney disease	0.7 (2)	1.2 (3)	FE, p = .671
Liver disease	4.3 (12)	4.4 (11)	FE, p = 1.000
Anemia or blood disease	11.7 (33)	17.5 (44)	FE, p = .064
Depression	16.7 (47)	28.3 (71)	FE, p = .002
Osteoarthritis	10.7 (30)	11.6 (29)	FE, p = .783
Back pain	21.0 (59)	29.9 (75)	FE, p = .021
Rheumatoid arthritis	3.2 (9)	2.4 (6)	FE, p = .611
Exercise on a regular basis (% yes)	76.9 (210)	73.3 (178)	FE, p = .359
Smoking current or history of (% yes)	31.7 (88)	25.1 (63)	FE, p = .102
Type of prior cancer treatment			$X^2 = 5.74$, p = .125
No prior treatment	24.2 (67)	31.0 (76)	
Only surgery, CTX, or RT	43.3 (120)	40.4 (99)	
Surgery & CTX, or Surgery & RT, or CTX & RT	16.2 (45)	10.6 (26)	
Surgery & CTX & RT	16.2 (45)	18.0 (44)	
CTX cycle length			$X^2 = 21.33$, p < .001
14 day cycle	29.2 (82)	48.6 (122)	0 < 1
21 day cycle	62.6 (176)	46.2 (116)	0 > 1
28 day cycle	8.2 (23)	5.2 (13)	NS
Emetogenicity of CTX			$X^2 = 16.79$, p < .001
Minimal/Low	24.9 (70)	21.1 (53)	NS
Moderate	48.8 (137)	35.9 (90)	0 > 1
High	26.3 (74)	43.0 (108)	0 < 1
Antiemetic regimens			$X^2 = 15.13$, p = .002
None	11.2 (31)	6.9 (17)	NS
Steroid alone or serotonin receptor antagonist alone	30.4 (84)	19.4 (48)	0 > 1
Serotonin receptor antagonist and steroid	30.8 (85)	34.0 (84)	NS
NK-1 receptor antagonist and two other antiemetics	27.5 (76)	39.7 (98)	0 < 1

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; CTX, chemotherapy; FE, Fisher's Exact test; kg, kilograms; m^2, meter squared; NK-1, neurokinin-1; NS, not significant; RT, radiation therapy; SCQ, Self-administered Comorbidity Questionnaire; SD, standard deviation; U, Mann-Whitney U test.

Table 2.

Differences in the Occurrence of Gastrointestinal Symptoms Between Breast Cancer Patients With and Without Chemotherapy-Induced Nausea.

Gastrointestinal Symptom (% yes)	No Nausea 52.8% (n = 281)	Nausea 47.2% (n = 251)	Statistics
	% (n)	% (n)	
Change in the way food tastes	42.0 (118)	68.5 (172)	FE, p < .001
Dry mouth	33.5 (94)	63.3 (159)	FE, p < .001
Lack of appetite	23.5 (66)	62.2 (156)	FE, p < .001
Constipation	28.1 (79)	55.0 (138)	FE, p < .001
Feeling bloated	28.8 (81)	42.2 (106)	FE, p = .001
Diarrhea	19.6 (55)	35.1 (88)	FE, p < .001
Mouth sores	16.7 (47)	29.9 (75)	FE, p < .001
Weight loss	15.3 (43)	29.5 (74)	FE, p < .001
Abdominal cramps	11.7 (33)	25.1 (63)	FE, p < .001
Difficulty swallowing	8.9 (25)	19.5 (49)	FE, p < .001
Vomiting	1.4 (4)	19.5 (49)	FE, p < .001

Abbreviation: FE, Fisher's Exact test.

Table 3.

Multiple Logistic Regression Analysis Predicting Nausea Group Membership in Breast Cancer Patients (n = 502)

Predictor	Odds Ratio	95% CI	p-value
Karnofsky Performance Status score	0.97	0.95, 0.99	.003
Dry mouth	2.08	1.34, 3.22	.001
Vomiting	8.91	2.99, 26.53	< .001
Constipation	2.05	1.34, 3.16	.001
Change in the way food tastes	1.57	1.02, 2.42	.040
Lack of appetite	2.45	1.57, 3.82	< .001
Chemotherapy cycle length			.001
14-day cycle vs 21-day cycle	1.92	1.25, 2.94	.003
14-day cycle vs 28-day cycle	4.17	1.52, 11.11	.006
21-day cycle vs 28-day cycle	2.16	0.79, 5.87	.133
Overall model fit: df = 8, X^2 = 166.96, p < .001			

Abbreviation: CI, confidence interval.