Published in final edited form as:

Support Care Cancer. 2016 June ; 24(6): 2635–2642. doi:10.1007/s00520-015-3071-4.

Nausea as a sentinel symptom for cytotoxic chemotherapy effects on the gut-brain axis among women receiving treatment for recurrent ovarian cancer: An exploratory analysis

Heidi S. Donovan, PhD, RN^{1,2}, Teresa L. Hagan, PhD, RN², Grace B. Campbell, PhD, CRRN, RN², Michelle M. Boisen, MD^{1,5}, Leah M. Rosenblum, BSN, RN², Robert P. Edwards, MD^{1,5}, Dana H. Bovbjerg, PhD^{1,3}, and Charles C. Horn, PhD^{1,4}

¹University of Pittsburgh Cancer Institute, 5115 Centre Avenue, Pittsburgh, PA 15232

²School of Nursing, University of Pittsburgh, 3500 Victoria Street, Pittsburgh, PA, 15261

³Departments of Psychiatry, Psychology, Behavioral & Community Health Sciences, and Clinical & Translational Science Institute, University of Pittsburgh, 5115 Centre Avenue, Suite 140, Pittsburgh, PA 15232

⁴Departments of Medicine and Anesthesiology, and Center for Neuroscience, University of Pittsburgh, Hillman Cancer Center – Research Pavilion G17b, 5117 Centre Avenue, Pittsburgh, PA, 15213

⁵Department of Obstetrics, Gynecology & Reproductive Sciences, University of Pittsburgh, 300 Halket Street, Pittsburgh, PA 15213

Abstract

Purpose—Nausea is a common and potentially serious effect of cytotoxic chemotherapy for recurrent ovarian cancer, and may function as a sentinel symptom reflecting adverse effects on the gut-brain axis (GBA) more generally, but research is scant. As a first exploratory test of this GBA hypothesis, we compared women reporting nausea to women not reporting nausea with regard to the severity of other commonly reported symptoms in this patient population.

Methods—A secondary analysis of data systematically collected from women in active chemotherapy treatment for recurrent ovarian cancer ($n=158$) was conducted. The Symptom Representation Questionnaire (SRQ) provided severity ratings for 22 common symptoms related to cancer and chemotherapy. Independent sample t-tests and regression analyses were used to compare women with and without nausea with regard to their experience of other symptoms.

Results—Nausea was reported by 89 (56.2%) women. Symptoms that were significantly associated with nausea in bivariate and regression analyses included: abdominal bloating, bowel disturbances, dizziness, depression, drowsiness, fatigue, headache, lack of appetite, memory

Corresponding author: Dr. Heidi S. Donovan, 415 Victoria Building, 3500 Victoria Street, Pittsburgh, PA 15261, **Phone:** 412-624-2699, **Fax:** 412-383-7227, donovanh@pitt.edu.

Conflict of Interest: The authors have no conflicts of interest to report.

Ethical approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

problems, mood swings, shortness of breath, pain, sleep disturbance, urinary problems, vomiting, and weight loss. Symptoms that were not associated with nausea included: hair loss, numbness and tingling, sexuality concerns, and weight gain.

Conclusions—Nausea experienced during chemotherapy for recurrent ovarian cancer may be an indicator of broader effects on the gut-brain axis. A better understanding of the mechanisms underlying these effects could lead to the development of novel supportive therapies to increase the tolerability and effectiveness of cancer treatment.

1. Disclosure of Potential Conflicts of Interest. The authors do not have any relationships or interests that would bias or in any way influence this study. The grant mechanisms supporting this research are:
 - a. NINR T32 NR07102
 - b. NINR F31 NR07556
 - c. Oncology Nursing Society/Ortho-Biotech; PEO Scholar Award
 - d. NCI P30 CA047904
2. Statement of Human Rights: This research study was granted exempt status by Institutional Review Boards of the University of Wisconsin and University of Pittsburgh.
3. Informed Consent: Informed consent was obtained from all individual participants included in the study.

Keywords

Chemotherapy-Induced Nausea and Vomiting; Gut-Brain Axis; Ovarian Cancer; Symptom Assessment

Introduction

The concept of a gut-brain axis (GBA) originated with research showing the action of gastrointestinal endocrine factors and extrinsic nerve pathways, primarily the vagus, on the brain in the control of digestion, metabolism and food intake [1, 2]. The concept has recently been extended to include gut microbiome modulation of GBA signaling pathways that could impact emotion, pain, and stress, as well as nutritional balance [3]. The GBA is increasingly recognized to include both afferent and efferent pathways, which provide rich opportunities for bi-directional communication and control processes [4]. A consistent and comprehensive description of symptoms linked to GBA activation does not yet exist, but there is considerable evidence for effects on appetite, nausea and vomiting, weight changes, visceral pain, and bowel symptoms (e.g., diarrhea, constipation, and cramping) [5]. Accumulating evidence also implicates additional symptoms such as depression and anxiety [6–8], cognitive/memory problems [9, 10], sleep rhythms [11], and fatigue [12, 13]. Activation of the gut-brain axis can occur anywhere along the pathway, from direct stimulation of the gut to systemic effects on the central nervous system components of the GBA [4, 14].

Cytotoxic chemotherapy continues to be the mainstay of adjuvant treatment for many cancers [15–17], but has long been recognized to have profound gastrointestinal side effects,

with virtually universal nausea and vomiting for some agents if antiemetic therapies are not used [18–21]. Even with standard-of-care prophylactic anti-emetic treatments, nausea continues to be a common experience for women receiving cytotoxic chemotherapy for recurrent ovarian cancer, with acute nausea (within 24 hours) affecting about a third of patients and delayed nausea (after 24 hours) affecting nearly two-thirds [22, 23]. To date, the biological pathways that characterize such complex nausea in relation to additional symptoms experienced by these patients have not been well characterized. As one of the most prevalent side effects experienced by patients receiving cytotoxic chemotherapy, nausea in these patients may serve as a sentinel symptom for a broader spectrum of symptoms engendered by alterations in GBA functioning.

As a first exploratory test of the possible role of the GBA in symptom experiences among patients receiving chemotherapy for recurrent ovarian cancer, we compared women reporting nausea to women not reporting nausea with regard to the severity of other commonly reported symptoms. If nausea is a marker of GBA activation, the severity of other GBA associated symptoms would be expected to be higher among women experiencing nausea compared to those who were not. To date, no other studies have systematically evaluated these relationships.

Methods

Study Design and Participants

The current study is an ancillary analysis of a sub-set of data from a symptom experience study of members of the National Ovarian Cancer Coalition (NOCC) with a history of ovarian cancer [24]. Briefly, in the previously published study the sample included 713 respondents to a survey sent to randomly selected members of the NOCC with a history of ovarian cancer. The study was granted exempt status by the Institutional Review Boards of the University of Wisconsin and University of Pittsburgh. For the current analysis, inclusion criteria included being in active chemotherapy treatment for recurrent ovarian cancer at the time of completing the symptom experience survey. One person had missing data for nausea severity and was excluded from analyses for a final sample of n=158.

Measures

The Symptom Representation Questionnaire (SRQ) was used to measure symptom severity for cancer- and treatment-related symptoms and side effects commonly reported by women with ovarian cancer [24]. Women rated the severity of 22 symptoms at their worst in the past week on an 11 point scale where 0 = “did not have the symptom” and 10 = “as bad as I can imagine.”

As previously described, the survey study queried participants regarding demographic information (e.g., age, highest level of education, income) and clinical information (e.g., stage at diagnosis, time since diagnosis, current disease status, time since most recent chemotherapy treatment, type of treatment most recently received) [24]. The emetogenic potential of chemotherapy treatments was characterized as minimal/low vs. moderate/high based on current NCCN guidelines [25].

Data Analysis

Consistent with the purposes of this exploratory study, independent sample t-tests (two-tailed) were used to compare symptom experiences between women with nausea, defined as a rating of 1 for nausea during the past week on the SRQ, and those without nausea, with significance defined as a p-value of ≤ 0.05 [26]. Simple linear regression analyses were also conducted to measure the extent to which the severity (0–10) of nausea was associated with the presence of additional symptoms. Covariates included in regression analyses were age, number of previous chemotherapy regimens, and time since most recent treatment. These covariates were selected because: older patients (> 70 years old) are known to have reduced symptom burden compared to younger patients [27–30]; a higher number of previous chemotherapy treatments may increase the potential for chemotherapy-induced symptoms [30]; and symptoms are usually most severe during the first few days after chemotherapy [31] and then decrease over time [32]. Analyses were completed using SPSS Software Version 22 (Armonk, NY: IBM Corp.).

Results

Sample

Table I provides sample demographic, disease, and treatment information for participants included in this analysis. The majority of this sample was middle-aged ($M = 55.59$ years old, $SD = 10.13$), well-educated, and financially stable. Of note, this sample was younger than the median age of 63 years at diagnosis for women with ovarian cancer in the general population [33]. Similar to most women with recurrent ovarian cancer, the sample was mostly diagnosed at Stage III (76.3%), approximately 4 years after their primary diagnosis, and had previously received more than four different chemotherapy regimens. Treatment regimens were heterogeneous across the sample and included liposomal doxorubicin, paclitaxel, and carboplatin/paclitaxel, as well as gemcitabine, topotecan, etoposide. Chemotherapy agents were used both as single agents and in combination. These regimens remain standard treatments for recurrent ovarian cancer [34]. Approximately 30% of women were receiving chemotherapy regimens classified as moderately or highly emetogenic [25]. Nausea was reported by 89 (56.2%) of participants. The mean nausea severity score was 4.11 ($SD = 2.73$) with a mode of 2 and a range of 0–9.

Women reporting nausea were compared to those not reporting nausea on demographic and disease characteristics (Table 1). The only significant differences between the two groups were for age and education. The average age for women experiencing nausea (53.82 years) was significantly lower than for women who were not experiencing nausea (57.65 years; $t_{(156)} = 2.40$; $p = 0.02$). With respect to education, women with a high school education or less had lower rates of nausea (36.4%) compared to those with higher levels of education (45.2 – 66.7%; $\chi^2_{(3)} = 9.22$; $p = 0.03$).

In independent sample t-tests, 17 of the 21 symptoms assessed were more severe among participants experiencing nausea compared to those not experiencing nausea. Table II shows the results of the t-tests and regression analyses. Hair loss, numbness/tingling, sexuality concerns, and weight gain severity scores did not significantly differ between groups. In

regression models nausea severity remained a significant predictor of 15 symptoms after controlling for age, number of previous chemotherapy regimens, and time since most recent treatment. Depression and headaches were no longer significantly related to the women's experience of nausea, but did show a trend.

Discussion

Consistent with the study hypothesis, the presence of nausea and nausea severity during cytotoxic chemotherapy for recurrent ovarian cancer were significantly related to the experience of multiple other common cancer and treatment-related symptoms, which may be related to GBA activation. Also consistent with the exploratory hypothesis, the presence of nausea and nausea severity were not significantly related to the severity of hair loss, numbness/tingling, weight gain, or sexuality concerns.

Among the set of 15 symptoms that were significantly related to nausea in both sets of analyses, several have strong evidence linking them to the GBA (e.g., abdominal bloating, bowel disturbances, vomiting) [35, 36], and others have emerging but weaker links to the GBA (e.g., sleep problems, fatigue, memory problems, and mood swings [37]). Several of the symptoms with less clear associations with GBA may be attributable to effects of chemotherapy on the gut microbiome. The microbiome is increasingly recognized to have a broad range of effects on the activities of the central nervous system, including emotional and cognitive effects that have led to a call to expand the concept of GBA to highlight a brain-gut enteric micro-biota axis [3].

Particularly in need of additional research is the role of nausea as a specific precipitating GBA-related symptom with downstream effects on other symptoms and side effects of treatment. One possible clinically significant pathway for example would link nausea as a prodrome to reduced appetite, which in turn may contribute to reductions in food consumption and weight loss, which increases risk of premature mortality [38–40]. Nausea may also be related to reductions in fluid consumption, which were not assessed in the present study. Dehydration secondary to nausea and vomiting could contribute to renal toxicities in this patient population, which can be life threatening. Rising creatinine concentrations indicating renal toxicity are one of the most common reasons for dose delays among women with ovarian cancer [41–43].

Another issue that the results of the present study highlights for additional research attention is the possible impact of chemotherapy on the functioning of the vagus nerve as a contributing factor in GBA-related symptoms. In what are now largely separate silos of research, the importance of vagal function has been implicated in studies of: microbiome influences on symptom experience [44]; appetite [45]; nausea and vomiting [46]; fatigue [47]; drowsiness and sleep problems [48]; and peripheral pain sensation [49]. It is also important to note that nausea does not require a precipitating impact on the gut; nausea can be provoked by effects in the central nervous system components of the gut-brain axis. For example, research supports the role of the area postrema in chemotherapy-induced nausea and vomiting [50]. Chemotherapy (and/or residual cancer) may produce circulating factors that act on central components of the gut-brain axis to produce nausea [51, 52].

Another interesting finding is that 70% of our sample received chemotherapy regimens of minimal to low emetogenic potential, yet 56.4% of women were still experiencing nausea an average of 16 days post-treatment. Here it is important to emphasize that emetogenic potential is based solely on incidence of vomiting – not on incidence of nausea [53, 54]. Multiple studies have documented that although current anti-emetic regimens have reduced the incidence of vomiting, the incidence of nausea, especially delayed nausea, has remained unacceptably high, and perhaps even increased [55, 56]. Indeed, the incidence of delayed nausea, even in the context of guideline consistent anti-emetic treatment remains in the range of 40–70% [57–61]. This rate is consistently underestimated by clinicians and may contribute to sub-optimal management for patients receiving low emetogenic regimens [57]. These findings suggest a chronic type of chemotherapy-induced nausea that requires additional research and increased awareness in clinical practice. One rodent model [62] suggests that chemotherapy-related nausea may persist in some individuals for up to 6 months post chemotherapy. Another explanation for the high rates of nausea in our study could be that the recurrent cancer itself contributes to the nausea. In women with recurrent ovarian cancer, chemotherapy-induced nausea may be further complicated by the presence of peritoneal or liver involvement that may cause additional nausea via direct mechanical effects on the gut, or via stimulation of biological responses (e.g., cytokines, prostaglandins) that may systemically activate the GBA [63]. This study cannot distinguish between these possible mechanistic pathways, however, it is important to note that the presence of cancer per se does not explain the variability in nausea in our sample; 42% of women with active disease were not experiencing nausea.

It is important to emphasize that our goal in this exploratory study was to provide initial evidence of GBA activation during chemotherapy for recurrent ovarian cancer and to highlight the potential importance of additional research specifically designed to better characterize the nature of these relationships and the mechanisms involved. As a secondary data analysis, the present study had several weaknesses that should be noted. Most notably, the cross-sectional nature of the original mailed survey study [23] substantially limits causal interpretation of the significant associations between nausea and other symptoms reported here. It should also be noted that the assessments included in the original survey study were not specifically designed to explore GBA symptoms, or to investigate downstream effects of such symptoms, and were intentionally kept brief to minimize respondent burden. The self-report survey did not allow determination of whether nausea was related to cytotoxic chemotherapy administration, or to the cancer itself. The women in this sample were younger (55 years) than the typical age of diagnosis (63 years old).

Younger women in this sample and in other studies [64] are at higher risk for nausea. Future studies should evaluate whether age has a general influence on GBA activation among patients with cancer. Finally, access to medical record data was not requested from respondents to corroborate their self-reports of treatments received. Findings should be interpreted cautiously since patients' understanding of the details of their disease and treatment, while generally accurate, may be imperfect [65–67].

If future research confirms the results of this initial study and the hypothesized impact of cytotoxic chemotherapy on the GBA, it would have important implications for the

development of novel supportive therapies to increase the tolerability and effectiveness of cancer treatment for this patient population. By addressing chemotherapy-induced effects on the GBA, it may be possible to eliminate an entire cluster of symptoms, which would not only improve recurrent ovarian cancer patients' quality of life, but also might have a significant impact on morbidity and mortality.

Acknowledgments

Funding: This study was supported by NINR T32 NR07102, NINR F31 NR07556, Oncology Nursing Society/Ortho-Biotech; PEO Scholar Award, and NCI P30 CA047904.

References

- Schwartz GJ. The role of gastrointestinal vagal afferents in the control of food intake: current prospects. *Nutrition*. 2000; 16:866–873. [PubMed: 11054591]
- Track NS. The gastrointestinal endocrine system. *Can Med Assoc J*. 1980; 122:287–292. [PubMed: 6989456]
- Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci*. 2012; 13:701–712. [PubMed: 22968153]
- Keightley PC, Koloski NA, Talley NJ. Pathways in gut-brain communication: evidence for distinct gut-to-brain and brain-to-gut syndromes. *Aust N Z J Psychiatry*. 2015; 49:207–214. [PubMed: 25710826]
- Rhee SH, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain–gut–enteric microbiota axis. *Nat Rev Gastroenterol Hepatol*. 2009; 6:306–314. [PubMed: 19404271]
- Slyepchenko A, Carvalho AF, Cha DS, Kasper S, McIntyre RS. Gut emotions-mechanisms of action of probiotics as novel therapeutic targets for depression and anxiety disorders. *CNS & Neurol Disord Drug Targets*. 2014; 13:1770–1786.
- Klarer M, Arnold M, Günther L, et al. Gut vagal afferents differentially modulate innate anxiety and learned fear. *J Neurosci*. 2014; 34:7067–7076. [PubMed: 24849343]
- Foster JA, Neufeld KAM. Gut–brain axis: how the microbiome influences anxiety and depression. *Trends Neurosci*. 2013; 36:305–312. [PubMed: 23384445]
- Tillisch K. The effects of gut microbiota on CNS function in humans. *Gut Microbes*. 2014; 5:404–410. [PubMed: 24838095]
- Miyazaki K, Itoh N, Yamamoto S, et al. Dietary heat-killed *Lactobacillus brevis* SBC8803 promotes voluntary wheel-running and affects sleep rhythms in mice. *Life Sci*. 2014; 111:47–52. [PubMed: 25058921]
- Davari S, Talaei SA, Alaei H. Probiotics treatment improves diabetes-induced impairment of synaptic activity and cognitive function: Behavioral and electrophysiological proofs for microbiome–gut–brain axis. *Neuroscience*. 2013; 240:287–296. [PubMed: 23500100]
- Mayer EA, Knight R, Mazmanian SK, Cryan JF, Tillisch K. Gut microbes and the brain: paradigm shift in neuroscience. *J Neurosci*. 2014; 34:15490–15496. [PubMed: 25392516]
- Rao AV, Basted AC, Beaulne TM, et al. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathog*. 2009; 1:1–6. [PubMed: 19338677]
- De Palma G, Collins SM, Bercik P, Verdu EF. The microbiota-gut-brain axis in gastrointestinal disorders: stressed bugs, stressed brain or both? *J Physiol*. 2014; 15:2989–2997. [PubMed: 24756641]
- Fung-Kee-Fung M, Oliver T, Elit L, et al. Optimal chemotherapy treatment for women with recurrent ovarian cancer. *Curr Oncol*. 2007; 14:195–208. [PubMed: 17938703]
- Kelland L. The resurgence of platinum-based cancer chemotherapy. *Nat Rev Cancer*. 2007; 7:573–584. [PubMed: 17625587]
- Luvero D, Milani A, Ledermann JA. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. *Ther Adv Med Oncol*. 2014; 6:229–239. [PubMed: 25342990]

18. Hesketh PJ. Chemotherapy-induced nausea and vomiting. *N Engl J Med*. 2008; 358:2482–2494. [PubMed: 18525044]
19. Francis P, Rowinsky E, Schneider J, et al. Phase I feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: a Gynecologic Oncology Group pilot study. *J Clin Oncol*. 1995; 13:2961–2967. [PubMed: 8523061]
20. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2011; 29:4189–4198. [PubMed: 21947834]
21. Warr D. Prognostic factors for chemotherapy induced nausea and vomiting. *Eur J Pharmacol*. 2014; 722:192–196. [PubMed: 24157977]
22. Cohen L, de Moor CA, Eisenberg P, Ming EE, Hu H. Chemotherapy-induced nausea and vomiting —incidence and impact on patient quality of life at community oncology settings. *Support Care Cancer*. 2007; 15:497–503. [PubMed: 17103197]
23. Fernandez-Ortega P, Caloto MT, Chirveches E, et al. Chemotherapy-induced nausea and vomiting in clinical practice: impact on patients' quality of life. *Support Care Cancer*. 2012; 20:3141–3148. [PubMed: 22460057]
24. Donovan HS, Ward S, Sherwood P, Serlin RC. Evaluation of the Symptom Representation Questionnaire (SRQ) for assessing cancer-related symptoms. *J Pain Symptom Manage*. 2008; 35:242–257. [PubMed: 18201866]
25. National Comprehensive Cancer Network. [Accessed December 4, 2015] NCCN Clinical Practice Guidelines in Oncology; v.2.2015: Antiemesis. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf
26. McDonald, JH. Handbook of biological statistics. 3rd. Baltimore, Maryland: Sparky House Publishing; 2014.
27. Cataldo JK, Paul S, Cooper B, et al. Differences in the symptom experience of older versus younger oncology outpatients: a cross-sectional study. *BMC Cancer*. 2013; 13:6. [PubMed: 23281602]
28. Miaskowski C, Dunn L, Ritchie C, et al. Latent class analysis reveals distinct subgroups of patients based on symptom occurrence and demographic and clinical characteristics. *J Pain Symptom Manage*. 2015; 50:28–37. [PubMed: 25647419]
29. Ritchie C, Dunn LB, Paul SM, et al. Differences in the symptom experience of older oncology outpatients. *J Pain Symptom Manage*. 2014; 47:697–709. [PubMed: 23916681]
30. Roscoe JA, Morrow GR, Colagiuri B, et al. Insight in the prediction of chemotherapy-induced nausea. *Support Care Cancer*. 2010; 18:869–876. [PubMed: 19701781]
31. Giesinger JM, Wintner LM, Zabernigg A, et al. Assessing quality of life on the day of chemotherapy administration underestimates patients' true symptom burden. *BMC Cancer*. 2014; 14:758. [PubMed: 25305067]
32. Meraner V, Gamper EM, Grahmann A, et al. Monitoring physical and psychosocial symptom trajectories in ovarian cancer patients receiving chemotherapy. *BMC Cancer*. 2012; 12:77. [PubMed: 22373218]
33. Howlader, N.; Noone, AM.; Krapcho, M.; Garshell, J.; Miller, D.; Altekruse, SF.; Kosary, CL.; Yu, M.; Ruhl, J.; Tatalovich, Z.; Mariotto, A.; Lewis, DR.; Chen, HS.; Feuer, EJ.; Cronin, KA., editors. SEER Cancer Statistics Review, 1975–2012. Bethesda, MD: National Cancer Institute; http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015. Ovarian cancer statistics accessed at <http://seer.cancer.gov/statfacts/html/ovary.html> on 12/04/2015
34. National Comprehensive Cancer Network. [Accessed 8/13/15] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Ovarian cancer: including fallopian tube cancer and primary peritoneal cancer. Version 2.2015. 2015. http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf
35. Mayer EA. Gut feelings: the emerging biology of gut-brain communication. *Nat Rev Neurosci*. 2011; 12:453–466. [PubMed: 21750565]
36. Rao AV, Bested AC, Beaulne TM, et al. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathog*. 2009; 1:1–6. [PubMed: 19338677]

37. Klarer M, Arnold M, Günther L, et al. Gut vagal afferents differentially modulate innate anxiety and learned fear. *J Neurosci.* 2014; 34:7067–7076.
38. Hess LM, Barakat R, Tian C, Ozols RF, Alberts DS. Weight change during chemotherapy as a potential prognostic factor for stage III epithelial ovarian carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2007; 107:260–265. [PubMed: 17675142]
39. Skírnisdóttir I, Sorbe B. Body mass index as a prognostic factor in epithelial ovarian cancer and correlation with clinico-pathological factors. *Acta Obstet Gynecol Scand.* 2010; 89:101–107. [PubMed: 19878086]
40. Suh DH, Kim HS, Chung HH, et al. Body mass index and survival in patients with epithelial ovarian cancer. *J Obstet Gynaecol Res.* 2012; 38:70–76. [PubMed: 21827578]
41. Lesnock JL, Richard SD, Zorn KK, et al. Completion of intraperitoneal chemotherapy in advanced ovarian cancer and catheter-related complications. *Gynecol Oncol.* 2010; 116:345–350. [PubMed: 19959211]
42. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med.* 2006; 354:34–43. [PubMed: 16394300]
43. Chan DL, Morris DL, Rao A, Chua TC. Intraperitoneal chemotherapy in ovarian cancer: a review of tolerance and efficacy. *Cancer Manage Res.* 2012; 4:413–422.
44. Forsythe P, Bienenstock J, Kunze WA. Vagal pathways for microbiome-brain-gut axis communication. *Adv Exp Med Biol.* 2014; 817:115–133. [PubMed: 24997031]
45. Berthoud HR. Vagal and hormonal gut-brain communication: from satiation to satisfaction. *Neurogastroenterol Motil.* 2008 May; 201(Suppl):64–72. [PubMed: 18402643]
46. Horn CC. Measuring the nausea-to-emesis continuum in non-human animals: refocusing on gastrointestinal vagal signaling. *Exp Brain Res.* 2014; 232:2471–2481. [PubMed: 24862507]
47. VanElzakker MB. Chronic fatigue syndrome from vagus nerve infection: a psychoneuroimmunological hypothesis. *Med Hypotheses.* 2013; 81:414–423. [PubMed: 23790471]
48. Tsai HJ, Kuo TB, Lee GS, Yang CC. Efficacy of paced breathing for insomnia: enhances vagal activity and improves sleep quality. *Psychophysiology.* 2015; 52:388–396. [PubMed: 25234581]
49. Laqua R, Leutzow B, Wendt M, Usichenko T. Transcutaneous vagal nerve stimulation may elicit anti- and pro-nociceptive effects under experimentally-induced pain – A crossover placebo-controlled investigation. *Autonomic Neuroscience.* 2014; 185:120–122. [PubMed: 25135040]
50. Percie du Sert N, Rudd JA, Moss R, Andrews PL. The delayed phase of cisplatin-induced emesis is mediated by the area postrema and not the abdominal visceral innervation in the ferret. *Neurosci Lett.* 2009; 465:16–20. [PubMed: 19733218]
51. Takahashi T, Nakamura Y, Tsuya A, Murakami H, Endo M, Yamamoto N. Pharmacokinetics of aprepitant and dexamethasone after administration of chemotherapeutic agents and effects of plasma substance P concentration on chemotherapy-induced nausea and vomiting in Japanese cancer patients. *Cancer Chemother Pharmacol.* 2011; 68:653–659. [PubMed: 21125277]
52. Higa GM, Auber ML, Altaia R, Piktet D, Kurian S, Hobbs G, Landreth K. 5-Hydroxyindoleacetic acid and substance P profiles in patients receiving emetogenic chemotherapy. *J Oncol Pharm Pract.* 2006; 12:201–209. Erratum in: *J Oncol Pharm Pract.* 2007 Mar;13(1):59-60. [PubMed: 17156592]
53. Gralla RJ, Osoba D, Kris MG, Kirkbride P, Hesketh PJ, Chinnery LW, Clark-Snow R, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. *J Clin Oncol.* 1999; 17:2971–2971. [PubMed: 10561376]
54. Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, Aapro MS, Gandara D, Lindley CM. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol.* 1997; 15:103–109. [PubMed: 8996130]
55. Roscoe JA, Morrow GR, Hickok JT, et al. Nausea and vomiting remain a significant clinical problem: Trends over time in controlling chemotherapy-induced nausea and vomiting in 1413 patients treated in community clinical practices. *J Pain Sympt Manage.* 2000; 20:113–121.
56. Bloechl-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. *J Clin Oncol.* 2006; 24:4472–4478. [PubMed: 16983116]

57. Grunberg SM, Deuson RR, Mavros P, Geling O, Hansen M, Cruciani G, Daugaard G. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. *Cancer*. 2004; 100:2261–2668. [PubMed: 15139073]
58. Aapro M, Molassiotis A, Dicato M, Peláez I, Rodríguez-Lescure Á, Pastorelli D. PEER investigators. The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). *Ann. Oncol*. 2012;mds021.
59. Farrell C, Brearley SG, Pilling M, Molassiotis A. The impact of chemotherapy-related nausea on patients' nutritional status, psychological distress and quality of life. *Support Care Cancer*. 2013; 21:59–66. [PubMed: 22610269]
60. Pirri C, Bayliss E, Trotter J, Olver IN, Katris P, Drummond P, Bennett R. Nausea still the poor relation in antiemetic therapy? The impact on cancer patients' quality of life and psychological adjustment of nausea, vomiting and appetite loss, individually and concurrently as part of a symptom cluster. *Support Care Cancer*. 2013; 21:735–748. [PubMed: 22976921]
61. Tamura K, Aiba K, Saeki T, Nakanishi Y, Kamura T, Baba H, Kitajima M. Testing the effectiveness of antiemetic guidelines: results of a prospective registry by the CINV Study Group of Japan. *Int J Cancer Oncol*. 2015:1–11.
62. Sallam HS, Song J, Chen JZ. Electroacupuncture via Chronically Implanted Electrodes: Potential Treatment for Chemotherapy-Induced Delayed Emesis. *Neuromodulation*. 2015; 18:494–498. [PubMed: 25913051]
63. Hursti TJ, Avall-Lundqvist E, Börjeson S, Fredrikson M, Fürst CJ, Steineck G, Peterson C. Impact of tumour burden on chemotherapy-induced nausea and vomiting. *Br J Cancer*. 1996; 74:1114–1119. [PubMed: 8855984]
64. Molassiotis A, Stamataki Z, Kontopantelis E. Development and preliminary validation of a risk prediction model for chemotherapy-related nausea and vomiting. *Support Care Cancer*. 2013; 21:2759–2767. [PubMed: 23715816]
65. Liu Y, Diamant AL, Thind A, Maly RC. Validity of self-reports of breast cancer treatment in low-income, medically underserved women with breast cancer. *Breast Cancer Res Treat*. 2010; 119:745–751. [PubMed: 19551500]
66. McCarthy AM, McGuire E, Bristol M, Fredricks T, Domchek SM, Armstrong K. Agreement of self-reported hormone receptor status with cancer registry data in young breast cancer patients. *Cancer Epidemiol*. 2013; 37:601–605.
67. Gupta V, Gu K, Chen Z, Lu W, Shu XO, Zheng Y. Concordance of self-reported and medical chart information on cancer diagnosis and treatment. *BMC Med Res. Methodol*. 2011; 11:72. [PubMed: 21592352]

Table I**Sociodemographic and Cancer Characteristics (n=158)**

Sample Characteristics			
	n(%) Total	n(%) with nausea	n(%) no nausea
Sociodemographic			
Ethnicity			
Non-Hispanic White	148 (93.7)	82 (55.4)	64 (44.6)
Other (Black/African American, Asian, Hispanic)	10 (6.3)	7 (70.0)	3 (30.0)
		$\chi^2_{(1)} = 0.81$; p=0.37	
Marital Status			
Married/Life Partner	123 (77.8)	66 (53.7)	57 (46.3)
Other	35 (22.2)	23 (65.7)	12 (34.3)
		$\chi^2_{(1)} = 1.61$; p=0.21	
Education			
High school or less	22 (13.9)	8 (36.4)	14 (63.6)
Some college	64 (40.5)	42 (65.6)	22 (34.4)
College degree	42 (26.6)	19 (45.2)	23 (54.8)
Post-graduate training	30 (19.0)	20 (66.7)	10 (33.3)
		$\chi^2_{(3)} = 9.22$; p=0.03	
Annual income (n=146; 12 refusals)			
< \$30,000	27 (18.6)	18 (66.7)	9 (33.3)
\$30 – \$59,000	48 (33.1)	29 (60.4)	19 (39.6)
\$60 – \$89,000	40 (27.6)	20 (50.0)	20 (50.0)
\$90,000	30 (20.7)	15 (50.0)	15 (50.0)
		$\chi^2_{(3)} = 2.64$; p=0.45	
	m (SD) Total	m (SD) with nausea	m (SD) no nausea
Age (M and SD)	55.49 (10.09)	53.82 (10.13)	57.65 (9.68)*
		$t_{(156)} = 2.40$; p=0.02	
Cancer			
Months since diagnosis (M and SD)	45.73 (26.37)	45.65 (24.63)	45.84 (28.66)
		$t_{(156)} = 0.05$; p=0.97	
# of new chemotherapy regimens (M and SD)	4.40 (2.37)	4.60 (2.56)	4.13 (2.09)
		$t_{(152)} = -1.21$; p=0.23	
Days from last chemotherapy (M and SD)	16.54 (12.26)	16.27 (12.53)	16.88 (11.99)
		$t_{(148)} = 0.30$; p=0.77	
	n(%) Total	n(%) with nausea	n(%) no nausea
Emetogenicity of Current Treatments (n=152; 6 missing or unknown)			

Sample Characteristics			
	n(%) Total	n(%) with nausea	n(%) no nausea
Minimal to Low	107 (70.4)	61 (57.0)	46 (43.0)
Moderate to High	45 (29.6)	24 (53.3)	21 (46.7)
$\chi^2_{(1)} 2.74; p=0.68$			
Current evidence of disease (n=155; 6 = unknown)			
No	8 (5.2)	3 (37.5)	5 (62.5)
Yes	145 (94.8)	85 (57.8)	62 (42.2)
Fisher's ; p=0.29 Exact			

Table II

Comparisons Between Women Experiencing and Not Experiencing Nausea

Symptom	Nausea (n=89)		No Nausea (n=69)		Statistics		β (p)	R^2
	Mean	(SD)	Mean	(SD)	t	p		
Abdominal bloating	2.82	(2.95)	1.48	(2.65)	2.97	.003	0.22 (.011)	.04
Bowel disturbances	5.29	(2.87)	3.09	(3.10)	4.63	<.001	0.32 (<.001)	.09
Depression	2.90	(2.56)	1.97	(2.53)	2.27	.025	0.15 (.080)	.02
Dizziness	1.47	(2.02)	0.68	(1.44)	2.76	.007	0.23 (.007)	.05
Drowsiness	3.87	(2.75)	2.09	(2.58)	4.14	<.001	0.38 (<.001)	.13
Fatigue	6.47	(2.54)	4.13	(2.76)	5.54	<.001	0.41 (<.001)	.16
Hair loss	4.01	(4.27)	3.21	(3.93)	1.21	.229	0.16 (.070)	.02
Headaches	2.04	(2.83)	1.09	(1.81)	2.45	.015	0.16 (.070)	.02
Hot flashes	3.46	(3.58)	1.96	(2.49)	2.98	.003	0.19 (.020)	.04
Lack of appetite	3.92	(3.25)	0.90	(2.02)	6.78	<.001	0.48 (<.001)	.22
Memory problems	3.39	(2.61)	2.41	(2.52)	2.40	.018	0.19 (.025)	.03
Mood swings	3.22	(2.77)	1.59	(2.32)	3.99	<.001	0.28 (.001)	.07
Numbness/ Tingling	3.04	(3.35)	3.03	(2.98)	0.03	.975	0.07 (.394)	.01
Pain	3.36	(3.18)	1.93	(2.60)	3.04	.003	0.17 (.044)	.03
Sexuality concerns	2.80	(3.45)	2.43	(3.50)	0.65	.520	0.03 (.730)	.001
Shortness of breath	2.67	(2.63)	1.43	(2.08)	3.22	.002	0.28 (.001)	.07
Sleep disturbances	4.66	(3.23)	2.80	(2.86)	3.79	<.001	0.27 (.001)	.07
Urinary problems	2.37	(3.14)	0.91	(2.04)	3.35	.001	0.25 (.003)	.06
Vomiting	1.53	(2.84)	0.29	(1.50)	3.29	.001	0.20 (.019)	.04
Weight gain	1.93	(3.03)	1.40	(2.24)	1.22	.226	0.63 (.467)	.004
Weight loss	2.02	(2.89)	0.81	(2.15)	2.89	.004	0.23 (.006)	.05

Covariates for the regression analyses included age, number of previous chemotherapy regimens, and time since most recent treatment.

Highlighted symptoms show significant relationships with nausea in bivariate and regression analyses.