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PII: S0885-3924(16)00057-9

DOI: [10.1016/j.jpainsymman.2015.12.317](https://doi.org/10.1016/j.jpainsymman.2015.12.317)

Reference: JPS 9066

To appear in: *Journal of Pain and Symptom Management*

Received Date: 6 December 2015

Revised Date: 21 December 2015

Accepted Date: 24 December 2015

Please cite this article as: Molassiotis A, Lee PH, Burke TA, Dicato M, Gascon P, Roila F, Aapro M, Anticipatory Nausea, Risk Factors and Its Impact on Chemotherapy-Related Nausea and Vomiting: Results from the PEER Study, *Journal of Pain and Symptom Management* (2016), doi: 10.1016/j.jpainsymman.2015.12.317.

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Original Article

15-00807R1

**Anticipatory Nausea, Risk Factors and Its Impact on Chemotherapy-Related Nausea and Vomiting: Results from the PEER Study**

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AU: PLS EXPAND MAILING ADDRESS

**Abstract**

**Context.** Anticipatory (pre-chemotherapy) nausea (AN) is a classic conditioned symptom not responding well to current antiemetics. Minimal work has been done to assess its risk factors and impact on chemotherapy-related nausea and vomiting (CINV).

**Objectives.** To evaluate risk factors for AN and assess its impact on CINV development.

**Methods.** We analyzed data ( $n=991$ ) from a prospective observational multisite study in eight European countries over three cycles of chemotherapy. Patient/treatment characteristics were collected before chemotherapy. History of nausea/vomiting (yes/no), patient expectation of CINV (0-100mm visual analogue scale, [VAS]), and pre-chemotherapy anxiety (0-100mm VAS) also were collected before chemotherapy. A patient-completed diary during each chemotherapy cycle obtained information on AN in the 24 hours before chemotherapy administration, and nausea and vomiting (episodes of vomiting and severity of nausea) daily for five days after administration of chemotherapy (0-100mm VAS).

**Results.** AN was reported by 8.3-13.8% of patients, increasing in frequency and intensity over each cycle. Every 1mm increase in AN on the VAS was significantly associated with 2-13% of increase in the likelihood of CINV (all  $P < 0.05$ ). Key predictors of AN in cycle 1 included metastatic disease and pre-chemotherapy anxiety. However, predictors of AN in subsequent cycles included pre-chemotherapy anxiety, and AN and CINV experience in the previous cycle,

the latter being the strongest predictor (odds ratio 3.30 to 4.09 for CINV outcomes over the cycles).

**Conclusion.** AN is a challenging symptom and its prevention needs to consider better CINV prevention in the previous cycles as well as managing pre-chemotherapy anxiety.

**Key Words:** anticipatory nausea, pre-chemotherapy nausea, chemotherapy-related nausea and vomiting, cancer, antiemetics

**Running title:** Predictors of Anticipatory Nausea

**Accepted for publication:** December 24, 2015.

## Introduction

Anticipatory nausea and vomiting (ANV) are psychologically-linked variations of chemotherapy-induced nausea and vomiting (CINV). The mechanism behind its development is a Pavlovian classical conditioning. Reviews suggest that ANV may occur in 20-30% of patients depending on the chemotherapy cycle patients are receiving [1,2], although more recent studies in Asian populations show a lower prevalence of 4.8-10.3% [3,4]. ANV is typically unresponsive to antiemetic medication [2]. The best approach to preventing ANV may be the optimal management of CINV in previous cycles of chemotherapy [1] and, if needed, current guidelines propose the use of psychological therapies or benzodiazepines as treatment options [1]. Most researched psychological therapies include progressive muscle relaxation therapy with guided imagery, systematic desensitization and hypnosis [1]. A number of factors place patients at higher risk of ANV, including younger age, experiencing CINV in previous cycle, expectation of CINV, motion sickness, and female gender [1,2]. ANV is a risk factor for CINV, and this has been observed in several studies in the past, including a European multi-country study of 991 patients [5,6]; an Australian study of 200 patients [7] and an Asian Pacific study of 598 patients [3]. It is also clear that ANV contributes to significant declines in quality of life outcomes, even after adjusting for age, sex, performance status and psychological distress [4].

The very limited number of studies assessing risk factors for ANV consider anticipatory

nausea and anticipatory vomiting as a single symptom, even though nausea seems to be a more difficult symptom to manage and is more common than vomiting in the era of newer antiemetics. Results are not always consistent and the impact of anticipatory nausea on CINV has not been fully appreciated in the literature.

Recently we have published data related to predictors of CINV from a large multisite multi-country prospective observational study over three cycles of chemotherapy ( $n=991$ ) [6] showing that anticipatory (pre-chemotherapy) nausea (AN) was a predictor of complete CINV response in the acute, delayed and overall phases alongside the use of antiemetics inconsistent with international guidelines, younger age, and incomplete CINV response in an earlier cycle. In this paper, we explored further the predictors and impact of AN in the development of CINV with the same data.

## **Methods**

### ***Design and Sample***

This was a large prospective observational evaluation of AN over three cycles of chemotherapy across eight European countries, as part of a larger study [5] and the methodology has been previously detailed [6]. In summary, adult patients receiving highly- and moderately-emetogenic chemotherapy with no vomiting in the prior 24hrs, not using steroids and with no brain metastasis were recruited.

### *Assessment Measures*

Nausea and significant nausea were defined as  $\geq 5$  mm and  $\geq 25$ mm, respectively, on a 0-100 visual analogue scale. Overall CINV was defined as having either nausea or emesis. Data were collected through a case report form by the clinicians for the sociodemographic and clinical characteristics, and by patients regarding pre-chemotherapy AN experience, and nausea and vomiting (episodes of vomiting and severity of nausea on a 0-100mm VAS). Other data obtained included history of nausea/vomiting (yes/no), patient expectation of CINV (0-100mm VAS), and pre-chemotherapy anxiety (0-100mm VAS). Ethical approvals were obtained from each participating hospital and patients signed a consent form before participation to the study. Patients were provided with a daily diary and recording their nausea, vomiting and anxiety experience over six days (the 24hrs prior to chemotherapy and the five days during and post-chemotherapy). Diaries were returned by patients through a pre-paid self-addressed envelope or at their next chemotherapy visit. Definitions for nausea and vomiting were provided in the diary. Sample size, according to the power calculations of the primary outcome in the larger study was calculated to be 1200. However, for a regression analysis of predictors, Harris [8] proposes a minimum of 30 cases per predictor variable, suggesting that the sample for the current exploratory analysis was adequate.

### *Statistical Analysis*

Descriptive statistics including mean and standard deviation for the visual analogue scale, as well as the frequency and prevalence of pre-chemotherapy nausea and emesis were used to summarize the data. We examined the effects of age, sex, emetogenicity of chemotherapy, metastatic disease, history of nausea, alcohol intake, anxiety over last 24 hours, perception about nausea, and the overall CINV and pre-chemotherapy (anticipatory) nausea VAS at the previous cycle on subsequent cycle pre-chemotherapy nausea using logistic regression. The effects of pre-chemotherapy nausea in VAS on acute nausea, delayed nausea, and acute emesis were investigated using logistic regression. Both crude effects and effects adjusted for the above list of variables were evaluated. Analyses were repeated for each cycle. All analyses were conducted in SPSS version 22, and  $P$ -value of  $<0.05$  indicated significant results.

## **Results**

### *Sample Characteristics*

While 1128 patients were recruited, 991 provided evaluable data at the end of cycle 1, 888 for cycle 2 and 769 for cycle 3. The most common reason for exclusion was that patients did not complete the six-day diary during their chemotherapy cycle. The sample had a mean age of 56.7 (SD=11.4) years; females comprised 72.9% of the sample and breast cancer was the most common diagnosis (53%). Highly-emetogenic chemotherapy was the regimen given to 189 patients, female AC (anthracycline-cyclophosphamide) chemotherapy was given to 463 patients



and moderately-emetogenic chemotherapy was given to 339 patients. Full details of the patient characteristics are presented elsewhere [6].

### ***Prevalence of Anticipatory Nausea***

Table 1 shows that pre-chemotherapy (anticipatory) nausea ( $AN \geq 5\text{mm}$ ) was evident in 8.3-13.8% of patients over the three cycles. Significant anticipatory nausea ( $AN \geq 25\text{mm}$ ) was reported by 2.0-4.8% of the patients. Intensity was mild in most of the cases. Both prevalence and intensity increased over each subsequent chemotherapy cycle (Table 1), and significant AN more than doubled by cycle 3 and intensity of AN also doubled by cycle 3. CINV, however (particularly nausea, both acute and delayed) was much higher than AN with fairly similar prevalence across the three chemotherapy cycles.

### ***Impact of AN on CINV***

In a logistic regression of the crude impact of AN on acute and delayed nausea and vomiting, AN was significantly linked with the development of CINV, showing higher impact in nausea as opposed to vomiting, and in the second and third cycles as opposed to the first cycle. As can be seen in Table 2, for every 1mm (in the 0-100 VAS) increase in AN there was a 3%, 12% and 13% increase in acute nausea in the first, second and third cycle respectively. The same pattern was observed in all other CINV outcomes, with impact being more on nausea variables rather than vomiting variables.

***Risk Factors for AN***

A number of patient and treatment characteristics were included in a multivariate logistic regression to assess potential risk factors for AN. In the first cycle, only metastatic disease and higher level anxiety before the chemotherapy were AN predictors. However, in the second and third cycles, the effect of metastatic disease disappeared and gave place to CINV in the previous cycle as the strongest predictor alongside AN in the previous cycle and higher anxiety pre-chemotherapy (Table 3). For example, those with CINV experience in the previous cycle had 3.7 times (cycle 2) and 3.3 times (cycle 3) more chances to develop AN in the subsequent cycle than those that had no CINV experience. These chances were even higher when ‘significant AN’ was concerned. Pre-chemotherapy anxiety was modestly correlated with AN in cycle 1 ( $r=0.15$ ,  $P<0.001$ ), but correlations increased in cycle 2 ( $r=0.37$ ,  $P<0.001$ ) and cycle 3 ( $r=0.38$ ,  $P<0.001$ ), further supporting the notion that AN and anticipatory anxiety significantly increased over subsequent cycles of chemotherapy.

***Risk Factors for CINV***

Exploring the potential predictors of CINV, Table 4 shows that AN had a significant impact in acute nausea, delayed nausea and acute and delayed vomiting. This consistent predictor was part of a larger set of variables (risk factors) for CINV. Such risk factors for CINV included use of female AC chemotherapy, history of nausea/vomiting, younger age, anxiety before

chemotherapy, expectation of CINV and presence of AN, with some minor variation from cycle to cycle and from phase of symptom to phase of symptom (Table 4). However, the strongest predictor of CINV in a cycle was CINV experience in the previous cycle.

## Discussion

This is the largest study to date assessing AN in patients receiving chemotherapy, using a prospective design in a multisite study. Key findings indicate that AN is prevalent in about 8-14% of patients, with higher prevalence in later cycles of chemotherapy. The intensity of AN was mild. A consistent predictor of AN was pre-chemotherapy anxiety, with CINV in the previous cycle being the key additional factor in subsequent cycles of chemotherapy.

The prevalence of AN in this study is lower than that reported in past studies and reviews on the topic (20-30%) [1] and even lower when “significant AN” only is assessed, but all these studies (or the studies reviewed in the past) are at least 10-20 years old. The only recent study in Australasian countries [3] shows a prevalence of 4.8-8.3%, which is closer to our findings. The difference in the two studies is in the definitions used. We have used a 100mm VAS and defined AN as that of  $\geq 5$ mm and significant AN that of  $\geq 25$ mm, whereas the latter study used “clinically significant” AN as  $>3$  on a 0-10 scale. Hence, the definitions of clinically significant nausea in the two studies are slightly different. This overall decrease in ANV symptoms may be attributed to the use of more effective antiemetics in the past decade (i.e. decreasing significantly the CINV

experience being strongly linked with ANV symptoms) as well as more patient education and support. In the era of more potent antiemetics, better symptom education and more familiarity of the public with chemotherapy, rates of AN are lower than in the past decades.

The impact of AN on CINV outcomes is significant, as the chances of a patient developing CINV significantly increases for every slight increase in the experience of AN, as shown in Table 2. This is a new finding, and suggests that preventing AN may have a positive outcome in the experience of CINV. In cycle 1, anxiety (alongside metastatic disease which may also be linked with more anxiety) is the key predictor of AN. This, coupled with the fact that AN increases over each cycle of chemotherapy, clearly supports the notion of AN being a classical conditioned effect. The picture of AN predictors is more complicated beyond the first cycle of chemotherapy, where new (and strong) predictors include, additionally to pre-chemotherapy anxiety, experiencing CINV in the previous cycle. Nevertheless, other commonly reported risk factors for CINV seem to play no role in the development in AN. As AN is a very difficult symptom to prevent, efforts should be diverted to manage CINV well. Indeed experts in the field suggest that the best approach to managing AN is to manage well CINV in the previous cycle [1]. Regrettably many clinicians do not use guideline recommended preventative antiemetics and expose patients to a much higher risk of experiencing CINV [5]. Furthermore, as AN is strongly linked with pre-chemotherapy anxiety, psychological (behavioral) therapies or use of benzodiazepines are

recommended from international clinical guidelines [1].

AN is also a key predictor of CINV in a complex interrelationship of uncontrolled CINV leading to more AN in subsequent cycles and AN increasing the risk of CINV in the next cycle. As seen in Table 4, AN contributes to higher level of CINV risk in subsequent cycles. Hence, this is a variable that needs to be considered in risk assessment for CINV and antiemetics adjusted accordingly. Nevertheless, uncontrolled CINV in the previous cycle is the key factor for CINV in the subsequent cycle, increasing the likelihood of CINV by 6.5 times in cycle 2 and 14 times in cycle 3. Currently CINV prevention is based on level of emetogenicity of the chemotherapy used, ignoring individual variation in the development of CINV. Considering the many factors that can contribute to the development of CINV, a risk-guided antiemetic prophylaxis, where patients with higher risk are treated with the next higher level of antiemetic prophylaxis may be a more effective approach to preventing CINV. Indeed we have a recent such example albeit not including patients with AN, which showed in a large randomized trial that risk assessment-based regimens, i.e., adding dexamethasone and olanzapine in the subsequent cycle to the previous antiemetic regimen if patients continued to experience nausea/vomiting, were more effective than using physician-based choice of antiemetics [9]. Such an approach could consider ways to manage AN as part of a CINV antiemetic protocol, where the addition of benzodiazepines or behavioral treatment could be added to the antiemetic regimen if patients experience anticipatory

symptoms. It is unclear currently if clinicians consistently assess anticipatory symptoms and how they prevent them, hence standardizing this practice could have beneficial outcomes for patients.

Despite our study being fully powered, when many analyses are performed, some results may be significant by chance, and this should be considered when the results of this study are interpreted. Nevertheless, the management of AN is challenging and based on minimal and low quality evidence. As this study shows that it is a prevalent and complex symptom, future research should be directed in testing effective interventions for managing this symptom. We should also explore more concretely the link between anxiety and nausea, particularly when these symptoms develop before any chemotherapy is administered. As anxiety is a key predictor of AN, psychological therapies to minimize anxiety should be offered, supporting current clinical guidelines for the prevention of AN [1]. The impact of AN on patients' quality of life is another area of future research, although the differentiation of AN's and CINV's impact on quality of life will be problematic.

#### **Disclosures and Acknowledgments**

The observational study was funded by Merck Sharpe & Dohme Corp., but the analysis was done and the manuscript written independently without company support. Conflicts of Interest:

AM: research funding and consultancies: Merck & Co. Ltd.

PHL: no conflict of interest declared

TAB: employee of Merck & Co. Ltd.

MD: consultancy: Merck & Co. Ltd.

PG: Merck & Co. Ltd.

FR: consultancies: Merck & Co. Ltd.

MA: consultancies and grant support: Helsinn & Eisai; consultancies: Tesaro; Taiho;

Mundipharma; Merck & Co. Ltd.

The authors thank all the PEER (Pan European Emesis Registry) study chief investigators for their contribution to the data collection. A full list of names can be found in [doi:10.1016/j.jpainsymman.2013.06.012](https://doi.org/10.1016/j.jpainsymman.2013.06.012).

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**Table 1. Descriptive Summary of Anticipatory Nausea and Chemotherapy-Related Nausea and Vomiting**

	Cycle 1 (n=991)	Cycle 2 (n=888)	Cycle 3 (n=769)
Mean score for pre-chemotherapy nausea (VAS 0-100mm)	1.74 (7.11)	2.47 (10.09)	3.60 (11.52)
Pre-chemotherapy nausea ( $\geq 5$ mm)	80 (8.3%)	91 (10.1%)	110 (13.8%)
Significant pre-chemotherapy nausea ( $\geq 25$ mm)	19 (2.0%)	24 (2.7%)	38 (4.8%)
Acute nausea ( $\geq 5$ mm)	380 (38.3%)	333 (37.5%)	308 (40.1%)
Significant acute nausea ( $\geq 25$ mm)	179 (18.1%)	157 (17.7%)	149 (19.4%)
Delayed nausea ( $\geq 5$ mm)	387 (39.1%)	346 (39.0%)	302 (39.3%)

Significant delayed nausea ( $\geq 25$ mm)	193 (19.5%)	162 (18.2%)	148 (19.2%)
Acute emesis	243 (24.5%)	173 (19.5%)	144 (18.7%)
Delayed emesis	292 (29.5%)	210 (23.6%)	166 (21.6%)

**Table 2. Crude Logistic Regression Models of the Impact of Anticipatory Nausea on Acute and Delayed Nausea, and Acute and Delayed Emesis (Odds Ratio [95% CI])**

Pre-chemotherapy nausea (0 to 100 mm)	Acute nausea ( $\geq 5$ mm)	Significant Acute Nausea ( $\geq 25$ mm)
Cycle 1	1.03 (1.01, 1.05)**	1.04 (1.02, 1.06)***
Cycle 2	1.13 (1.08, 1.19)***	1.04 (1.03, 1.06)***
Cycle 3	1.12 (1.08, 1.17)***	1.05 (1.04, 1.07)***
	Delayed Nausea ( $\geq 5$ mm)	Significant Delayed Nausea ( $\geq 25$ mm)
Cycle 1	1.05 (1.02, 1.08)***	1.02 (1.01, 1.04)*
Cycle 2	1.09 (1.05, 1.13)***	1.04 (1.02, 1.05)***
Cycle 3	1.09 (1.06, 1.12)***	1.05 (1.03, 1.06)***
	Acute Emesis	Delayed Emesis
Cycle 1	1.02 (1.00, 1.04)*	1.04 (1.02, 1.06)***

Cycle 2	1.03 (1.01, 1.04)***	1.02 (1.01, 1.04)**
Cycle 3	1.03 (1.02, 1.04)***	1.03 (1.01, 1.04)***

\* $P < 0.05$

\*\* $P < 0.01$

\*\*\* $P < 0.001$

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**Table 3. Multivariate Regression on Anticipatory Nausea (Odds Ratio [95% CI])**

	Pre-chemo Nausea ( $\geq 5$ mm)	Significant Pre-chemo Nausea ( $\geq 25$ mm)
<b>Cycle 1</b>		
Female	1.91 (0.90, 4.05)	0.84 (0.18, 4.03)
Emetogenicity of chemotherapy (cycle 1)		
Female anthracycline plus cyclophosphamide	0.87 (0.47, 1.63)	1.19 (0.33, 4.29)
Highly emetogenic chemotherapy	0.87 (0.42, 1.82)	0.43 (0.08, 2.31)
Moderately emetogenic chemotherapy	Ref	Ref
Metastatic disease	2.79 (1.55, 5.01)**	5.44 (1.67, 17.71)**
History of nausea / vomiting	1.69 (0.99, 2.90)	2.83 (0.97, 8.21)
Age	0.997 (0.975, 1.020)	1.028 (0.977, 1.082)
Alcohol intake (drinks per week)	0.989 (0.932, 1.050)	0.792 (0.598, 1.050)
Anxiety over last 24 hours (0-100 mm VAS)	1.010 (1.002, 1.017)*	1.023 (1.007, 1.040)**

Expectation for nausea (0-100 mm VAS)	1.005 (0.997, 1.013)	1.010 (0.994, 1.026)
<b>Cycle 2</b>		
Female	0.63 (0.30, 1.31)	0.93 (0.25, 3.47)
Emetogenicity of chemotherapy (cycle 2)		
Female anthracycline plus cyclophosphamide	0.86 (0.43, 1.73)	0.54 (0.17, 1.77)
Highly emetogenic chemotherapy	1.23 (0.59, 2.54)	0.84 (0.21, 3.38)
Moderately emetogenic chemotherapy	Ref	Ref
Metastatic disease	1.02 (0.54, 1.92)	1.02 (0.34, 3.06)
History of nausea / vomiting	0.79 (0.41, 1.53)	1.57 (0.53, 4.61)
Age	0.996 (0.973, 1.020)	0.993 (0.951, 1.037)
Alcohol intake (drinks per week)	0.970 (0.909, 1.035)	0.839 (0.674, 1.044)
Anxiety over last 24 hours (0-100 mm VAS)	1.031 (1.022, 1.041)***	1.026 (1.014, 1.039)***
Expectation for nausea (0-100 mm VAS)	0.995 (0.986,	0.992 (0.977, 1.008)

	1.003)	
Overall CINV (cycle 1)	3.72 (1.80, 7.65)***	4.09 (0.89, 18.86)
Pre-chemotherapy nausea (cycle 1, 0-100 mm VAS)	1.028 (1.001, 1.056)*	1.031 (0.999, 1.064)
<b>Cycle 3</b>		
Female	0.66 (0.31, 1.40)	1.36 (0.42, 4.44)
Emetogenicity of chemotherapy (cycle 3)		
Female anthracycline plus cyclophosphamide	1.42 (0.70, 2.87)	1.39 (0.46, 4.15)
Highly emetogenic chemotherapy	1.34 (0.62, 2.88)	2.83 (0.90, 8.96)
Moderately emetogenic chemotherapy	Ref	Ref
Metastatic disease	0.91 (0.48, 1.74)	1.00 (0.36, 2.75)
History of nausea / vomiting	0.62 (0.33, 1.16)	0.66 (0.26, 1.67)
Age	1.020 (0.996, 1.044)	1.005 (0.969, 1.043)
Alcohol intake (drinks per week)	0.985 (0.929, 1.046)	0.988 (0.892, 1.094)



Anxiety over last 24 hours (0-100 mm VAS)	1.025 (1.016, 1.035)***	1.028 (1.016, 1.041)***
Expectation for nausea (0-100 mm VAS)	1.001 (0.993, 1.008)	0.999 (0.988, 1.011)
Overall CINV (cycle 2)	3.30 (1.71, 6.38)***	3.89 (1.10, 13.83)*
Pre-chemotherapy nausea (cycle 2, 0-100 mm VAS)	1.049 (1.023, 1.077)***	1.027 (1.008, 1.047)**

\* $P < 0.05$ .

\*\* $P < 0.01$ .

\*\*\* $P < 0.001$ .

**Table 4. Multivariate regression analysis on chemotherapy-related nausea and vomiting predictors (Odds ratio (95% CI))**

	Significant acute nausea ( $\geq 25$ mm)	Significant delayed nausea ( $\geq 25$ mm)	Acute emesis	Delayed emesis	Overall CINV
<b>Cycle 1</b>					
Female	0.96 (0.48, 1.90)	1.04 (0.57, 1.89)	1.25 (0.75, 2.09)	0.98 (0.63, 1.54)	1.40 (0.92, 2.12)
Emetogenicity of chemotherapy (cycle 1)					
Female anthracycline plus cyclophosphamide	2.77 (1.60, 4.82)***	1.98 (1.21, 3.22)**	1.95 (1.26, 3.00)**	1.40 (0.94, 2.10)	1.46 (0.99, 2.15)
Highly emetogenic chemotherapy	1.97 (1.01, 3.83)*	1.05 (0.58, 1.91)	1.42 (0.86, 2.34)	1.04 (0.67, 1.62)	1.10 (0.73, 1.68)
Moderately emetogenic chemotherapy	Ref	Ref	Ref	Ref	Ref
Metastatic disease	1.22 (0.72, 2.06)	1.68 (1.05, 2.68)*	1.27 (0.84, 1.92)	1.60 (1.10, 2.32)*	1.59 (1.11, 2.27)*
History of nausea / vomiting	1.52 (1.01, 2.29)*	1.57 (1.06, 2.32)*	1.13 (0.78, 1.63)	1.16 (0.81, 1.66)	1.09 (0.75, 1.58)
Age	0.959 (0.943, 0.975)**	0.983 (0.968, 1.000)*	0.983 (0.969, 0.997)*	0.996 (0.983, 1.010)	0.992 (0.979, 1.006)
Alcohol intake (drinks per week)	0.973 (0.929, 1.020)	0.968 (0.925, 1.011)	0.980 (0.943, 1.019)	0.973 (0.939, 1.009)	1.036 (1.000, 1.071)*
Anxiety over last 24 hours (0-100 mm VAS)	1.009 (1.003, 1.015)**	1.008 (1.003, 1.014)**	1.003 (0.998, 1.009)	1.005 (1.000, 1.010)	1.011 (1.006, 1.016)***
Expectation for nausea (0-100 mm VAS)	1.012 (1.006, 1.018)***	1.011 (1.005, 1.016)***	1.002 (0.997, 1.008)	1.004 (0.999, 1.009)	1.005 (1.000, 1.010)
Pre-chemotherapy nausea (cycle 1, 0-100 mm VAS)	1.026 (1.005, 1.048)*	1.012 (0.992, 1.033) <sup>2</sup>	1.014 (0.994, 1.034)	1.029 (1.007, 1.052)**	1.060 (1.013, 1.052)*

<b>Cycle 2</b>					
Female	1.13 (0.54, 2.35)	0.86 (0.42, 1.77)	1.91 (0.95, 3.84)	1.43 (0.82, 2.48)	0.85 (0.51, 1.41)
Emetogenicity of chemotherapy (cycle 2)					
Female anthracycline plus cyclophosphamide	2.07 (1.17, 3.68)*	2.53 (1.43, 4.49)**	2.14 (1.26, 3.63)**	1.31 (0.84, 2.04)	1.60 (1.01, 2.51)*
Highly emetogenic chemotherapy	1.98 (0.97, 4.05) <sup>1</sup>	1.14 (0.55, 2.37)	1.58 (0.80, 3.09)	0.85 (0.47, 1.51)	1.19 (0.71, 1.99)
Moderately emetogenic chemotherapy	Ref	Ref	Ref	Ref	Ref
Metastatic disease	0.71 (0.39, 1.30)	0.89 (0.50, 1.57)	1.51 (0.89, 2.55)	1.06 (0.68, 1.67)	0.94 (0.61, 1.45)
History of nausea / vomiting	1.33 (0.84, 2.11)	1.06 (0.67, 1.67)	1.33 (0.87, 2.05)	0.94 (0.63, 1.42)	1.95 (1.24, 3.07)**
Age	0.969 (0.950, 0.986)**	0.971 (0.954, 0.990)**	0.966 (0.948, 0.982)***	0.987 (0.971, 1.003)	0.973 (0.957, 0.989)**
Alcohol intake (drinks per week)	0.969 (0.919, 1.019)	0.947 (0.897, 1.000)	0.999 (0.953, 1.046)	0.955 (0.913, 1.000)	0.981 (0.943, 1.021)
Anxiety over last 24 hours (0-100 mm VAS)	1.024 (1.016, 1.033)***	1.026 (1.018, 1.036)***	1.012 (1.005, 1.020)**	1.010 (1.003, 1.017)**	1.021 (1.010, 1.031*)**
Expectation for nausea (0-100 mm VAS)	1.005 (0.998, 1.011)	1.003 (0.996, 1.009) <sup>2</sup>	1.003 (0.996, 1.009)	1.002 (0.997, 1.008)	1.001 (0.995, 1.007)
Pre-chemotherapy nausea (cycle 1, 0-100 mm VAS)	1.035 (1.007, 1.062)*	1.023 (0.997, 1.049) <sup>2</sup>	1.019 (0.995, 1.044)	1.023 (0.999, 1.048)	1.048 (0.996, 1.103)
Pre-chemotherapy nausea (cycle 2, 0-100 mm VAS)	1.035 (1.013, 1.055)**	1.024 (1.005, 1.044)*	1.021 (1.004, 1.039)**	1.011 (0.995, 1.027)	1.157 (1.047, 1.279)**
Overall CINV (cycle 1)	/	/	/	/	6.46 (4.54, 9.20)***

<b>Cycle 3</b>					
Female	0.81 (0.38, 1.76)	1.42 (0.70, 2.87)	1.37 (0.65, 2.89)	1.06 (0.58, 1.93)	1.14 (0.62, 2.08)
Emetogenicity of chemotherapy (cycle 3)					
Female anthracycline plus cyclophosphamide	1.73 (0.96, 3.12) <sup>1</sup>	1.36 (0.78, 2.35)	2.62 (1.46, 4.69)**	0.91 (0.56, 1.50)	0.91 (0.54, 1.54)
Highly emetogenic chemotherapy	0.97 (0.42, 2.24)	1.11 (0.53, 2.32)	1.16 (0.53, 2.53)	0.76 (0.39, 1.48)	1.49 (0.76, 2.90)
Moderately emetogenic chemotherapy	Ref	Ref	Ref	Ref	Ref
Metastatic disease	0.67 (0.35, 1.29)	1.16 (0.65, 2.06)	1.46 (0.82, 2.60)	1.11 (0.67, 1.83)	0.98 (0.59, 1.63)
History of nausea / vomiting	1.85 (1.15, 2.97)*	1.17 (0.73, 1.87)	1.68 (1.07, 2.63)*	1.13 (0.73, 1.76)	0.85 (0.52, 1.41)
Age	0.967 (0.947, 0.986)**	0.969 (0.950, 0.988)**	0.993 (0.973, 1.012)	0.982 (0.965, 1.000)*	0.994 (0.975, 1.013)
Alcohol intake (drinks per week)	0.982 (0.931, 1.036)	1.010 (0.962, 1.060)	1.029 (0.981, 1.079)	1.001 (0.956, 1.048)	1.065 (1.015, 1.119)**
Anxiety over last 24 hours (0-100 mm VAS)	1.022 (1.014, 1.031)***	1.019 (1.011, 1.028)***	1.015 (1.007, 1.024)***	1.009 (1.001, 1.017)*	1.013 (1.001, 1.024)*
Expectation for nausea (0-100 mm VAS)	1.002 (0.995, 1.009)	1.002 (0.996, 1.009)	1.004 (0.997, 1.010)	1.007 (1.001, 1.013)*	1.009 (1.003, 1.016)**
Pre-chemotherapy nausea (cycle 1, 0-100 mm VAS)	1.025 (0.994, 1.058)	1.002 (0.969, 1.038) <sup>2</sup>	1.000 (0.970, 1.029)	1.012 (0.983, 1.042)	1.989 (0.955, 1.024)
Pre-chemotherapy nausea (cycle 2, 0-100 mm VAS)	1.049 (1.020, 1.079)**	1.029 (1.007, 1.052)**	1.017 (0.999, 1.035)	1.007 (0.990, 1.024)	1.037 (0.981, 1.095)

Pre-chemotherapy nausea (cycle 3, 0-100 mm VAS)	1.041 (1.022, 1.059)***	1.030 (1.015, 1.047)***	1.015 (1.000, 1.030)*	1.020 (1.005, 1.036)**	1.095 (1.029, 1.164)**
Overall CINV (cycle 3)	/	/	/	/	14.17 (9.28, 21.63)***

<sup>1</sup>Significant for acute nausea ( $\geq 5$ mm) only.

<sup>2</sup>Significant for delayed nausea ( $\geq 5$ mm) only.

\* $P < 0.05$

\*\* $P < 0.01$

\*\*\* $P < 0.001$