

Insight in the prediction of chemotherapy-induced nausea

Joseph A. Roscoe · Gary R. Morrow · Ben Colagiuri ·
Charles E. Heckler · Bryan D. Pudlo · Lauren Colman ·
Karen Hoelzer · Andrew Jacobs

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Abstract

Purpose To identify risk factors for chemotherapy-related nausea.

Methods We examined risk factors for nausea in 1,696 patients from three multicenter studies conducted from 1998 to 2004. All patients were beginning a chemotherapy regimen containing cisplatin, carboplatin, or doxorubicin. Nausea was assessed on a 1–7 scale four times a day for 4 days by diary.

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J. A. Roscoe · G. R. Morrow · C. E. Heckler · B. D. Pudlo
University of Rochester Cancer Center Community
Clinical Oncology Program Research Base,
James P. Wilmot Cancer Center,
University of Rochester School of Medicine and Dentistry,
601 Elmwood Avenue, Box 704, Rochester, NY 14642, USA

B. Colagiuri
Medical Psychology Research Unit, School of Psychology,
University of Sydney,
Sydney, Australia

L. Colman
Northwest Community Clinical Oncology Program,
Tacoma, WA, USA

K. Hoelzer
Central Illinois CCOP, Decatur Memorial Hospital,
Decatur, IL, USA

A. Jacobs
Virginia Mason CCOP,
Seattle, WA, USA

J. A. Roscoe (✉)
University of Rochester,
601 Elmwood Avenue, Box 704, Rochester, NY 14642, USA
e-mail: Joseph_Roscoe@urmc.rochester.edu

Results First, average nausea for breast cancer patients receiving doxorubicin (mean=2.31) was significantly greater than for other patients receiving doxorubicin (mean=1.82), patients receiving cisplatin (mean=1.88), and patients receiving carboplatin (mean=1.45), $P_s < 0.01$. Second, mean nausea decreased steadily with age, $P < 0.0001$. Third, patients rating themselves more susceptible to nausea had significantly more nausea (adjusted mean=2.51) than patients rating themselves less susceptible (adjusted mean=1.92) and were 2.8 times more likely to experience severe nausea, $P_s < 0.0001$. Fourth, expected nausea was a significant predictor of average nausea, $P = 0.034$, but not severe nausea, $P = 0.31$. Last, no evidence that gender is a significant predictor of nausea in 299 patients with gender neutral cancers, $P = 0.35$.

Conclusions Specific patient characteristics, especially younger age and perceived susceptibility to nausea, can help clinicians in the early identification of patients who are more susceptible to treatment-related nausea.

Keywords Chemotherapy · Nausea · Risk factor · Doxorubicin · Expectancy

Background

Chemotherapy-related nausea is a widespread problem that causes extreme discomfort and seriously impairs patients' quality of life (QOL). It negatively affects patients' nutritional habits, abilities to work, and motivation to follow recommended treatment regimens [1, 2]. There is great variation in the frequency and severity of this type of nausea which cannot be explained by the pharmacological properties of the chemotherapeutic agents alone, and numerous risk factors for chemotherapy-induced nausea and vomiting

(CINV) have been identified [3, 4]. The strongest of these are generally assumed to be younger age and female gender [5–10], although others, including a history of low alcohol intake, experience of nausea and emesis during pregnancy, impaired QOL, greater anxiety, previous experience with chemotherapy, and susceptibility to motion sickness, have all shown significant correlations with subsequent CINV [3, 8, 11–14]. Many studies have also reported significant correlations between patients' expectancies for nausea and the subsequent occurrence of nausea [15–21]. Although these expectancies may largely represent a patient's acknowledgment of his/her own propensity to develop nausea based on past experience (e.g., nausea during pregnancy or susceptibility to motion sickness), they are also likely influenced by what the patient is told to expect from the range of information they receive from clinicians, other patients, family, friends, and the world at large.

In the analyses that follow, from a combined sample of three large multicenter studies, we examine risk factors, including nausea expectancies and perceived susceptibility to nausea, as predictors of chemotherapy-induced nausea.

Methods

Patients

The patients were participants in three multicenter clinical trials conducted from January 1998 through June 2004 at 17 geographically diverse member sites of the University of Rochester Cancer Center Community Clinical Oncology Program. All patients were chemotherapy-naïve, 18 or older, and were about to begin a first cancer treatment regimen containing cisplatin, carboplatin, or doxorubicin. Patients receiving concurrent radiotherapy or interferon, or with clinical evidence of bowel obstruction or symptomatic brain metastases, were excluded. All patients received a 5-HT₃ receptor antagonist prior to chemotherapy. Dexamethasone or other corticosteroids were allowed, as were all ancillary treatments as appropriate for control of symptoms caused by the cancer or its treatment. The three studies, described briefly below with demographic and clinical details provided in Table 1, were all randomized clinical trials testing interventions to reduce CINV. The primary results of each study have been published elsewhere [13, 22, 23]. Written informed consent was obtained from each participant prior to data collection.

In study I, 360 patients were enrolled in a study testing the effect of an informational expectancy manipulation on CINV. All patients received ondansetron with dexamethasone on the day of the treatment. Analyses of the 325 (73% female) evaluable patients showed that the expectancy manipulation reduced patients' reported expectations for

the development of nausea but did not reduce occurrence of nausea [22].

In study II, 739 patients were randomly assigned to (1) acupressure bands, (2) an acustimulation band, or (3) a no band control condition as an adjunct to standard antiemetics for the relief of CINV. Of the patients, 700 (92% female) provided evaluable data, and patients in the acupressure condition experienced less nausea on the day of treatment compared to controls, $P < .05$. However, there were no significant differences in delayed nausea or vomiting among the three treatment conditions [23].

In study III, 671 (94% female) patients receiving doxorubicin-based chemotherapy were enrolled in a three-arm study that detected no difference in the ability of a serotonin receptor antagonist vs prochlorperazine (given regularly three times daily or taken only as needed for symptoms) to control the severity of delayed nausea following their first infusion of chemotherapy [13].

Measures

Demographic data and detailed information about diagnosis, chemotherapy agents, and antiemetics were provided by self-report questionnaires or abstracted from medical records by study personnel.

Nausea and emesis were measured in each study by a 4-day patient report diary developed for this purpose by Burish [24] and Carey [25]. Each day was divided into four segments (morning, afternoon, evening, and night), and patients reported the severity of nausea and number of vomiting episodes for the latter three periods on the day of treatment and for all four periods on the three following days (15 total reporting times). Severity of nausea was assessed on a 7-point rating scale, anchored at one end by 1="Not at all nauseated" and at the other end by 7="Extremely nauseated." The description "Moderately nauseated" was centered on the scale below the 4. Patients were given the questionnaires to complete at home.

Expectancies and perceived susceptibility for nausea were measured in studies II and III but not in study I. Nausea expectancies were assessed with the question "What do you think your level of nausea will be at its worst after this treatment?" The possible responses were "very mild or none at all", "mild", "moderate", "severe", "very severe", and "intolerable", which were coded 1–6, respectively. Perceived susceptibility to nausea was assessed with the question, "In general, do you think you are more susceptible to nausea than your friends and family are?" Possible responses were "more" (scored as 3), "about the same" (scored as 2), and "less" (scored as 1). Patients in studies II and III were also asked if they had nausea during pregnancy (coded 1=yes, 0=no or not applicable), and whether or not they were susceptible to motion sickness (coded 1=yes, 0=no).

Table 1 Demographic and treatment details

		Study 1 (N=325) 1/98–9/00	Study 2 (N=700) 11/99–7/01	Study 3 (N=671) 6/01–6/04
Age	Mean (SD)	57.6 (12.7)	52.0 (11.0)	53.0 (11.2)
	Range	28–91	23–84	25–90
Sex	Male	87	56	38
	Female	238	644	633
Ethnicity	White	272	620	591
	Black	22	35	57
	Hispanic	10	11	11
	Other	10	26	10
	Missing data	11	8	2
Education	≥4 years college	101	236	180
	<4 years college	87	206	217
	High school graduate	98	212	223
	Non-high school graduate	39	41	51
	Missing data	–	5	–
Cancer site	Alimentary tract	13 (4.0%)	6 (0.9%)	–
	Breast	144 (44.3%)	592 (84.6%)	602 (89.7%)
	Genitourinary	19 (5.8%)	5 (0.7%)	1 (0.1%)
	Gynecologic	29 (8.9%)	4 (0.6%)	1 (0.1%)
	Head and neck	10 (3.1%)	3 (0.4%)	–
	Hematologic	26 (8.0%)	68 (9.7%)	64 (9.5%)
	Lung	72 (22.2%)	15 (2.1%)	–
	Other or missing	12 (3.7%)	7 (1.0%)	3 (0.4%)
Medications	Adriamycin	171 (52.6%)	665 (95.0%)	All
	Carboplatin	106 (32.6%)	–	–
	Cisplatin	48 (14.8%)	35 (5.0%)	–
	5-HT ₃ receptor antagonist	All	All	All

Statistical analyses

Combined data from all three studies (1,696 total patients) were used to examine the degree of nausea in breast cancer patients compared with other patient groups, the effect of gender on nausea, and the relationship between severe nausea and vomiting. All other analyses used the combined dataset of studies II and III (1,371 total patients) only because study I did not include the necessary questionnaire regarding expectancy and susceptibility to nausea.

The 4-day patient report diary produced three separate measures of CINV: average nausea, severe nausea, and vomiting. Each measure represents a different aspect of CINV. Average nausea was the mean severity of nausea reported at each time point in the 4 days following treatment. Patients were said to have experienced severe nausea if they rated their nausea a 6 or 7 at least once. Vomiting was whether the patient reported vomiting once or more in the 4 days after their infusion. These three measures of CINV comprised the outcome measures throughout the following analyses and are consistent with

measures used in our prior research on chemotherapy-related nausea [18].

To investigate differences in average nausea between breast cancer patients receiving doxorubicin and other patients receiving various chemotherapeutic agents, patients in all three studies were classified into the following groups: breast cancer patients receiving doxorubicin, other patients receiving doxorubicin, patients receiving cisplatin, and patients receiving carboplatin. Analysis of variance controlling for treatment arms from the three studies, followed by pairwise comparisons of least squares means (i.e., group means adjusted for treatment arms in the different studies) using the Tukey–Kramer procedure to control the type I error rate was used to assess differences in average nausea between these groups. The proportion of patients experiencing severe nausea in these groups was similarly compared using logistic regression followed by comparisons of odds ratios.

A subset of the data (N=299 from all three studies) contained patients with tumor sites that are not gender specific. Here, multiple linear regression analysis was used

to assess whether gender affected average nausea after controlling for age, education, tumor site, chemotherapy type, and study arm.

A regression analysis was conducted on the largest homogenous patient group, i.e., female breast cancer patients receiving doxorubicin, to examine the role of age, expectancy, and perceived susceptibility on average nausea ($N=1,178$). Patients from study I were excluded from the analysis because susceptibility and expectancy information was not available. Age was classified into five groups: less than 40, 40–50, 50–60, 60–70, and greater than 70 years of age. For this analysis, the six-point expectancy measure was collapsed into a 1–4 scale because only 22 women responded with a 5 (very severe) or a 6 (intolerable) on the expectancy question. The responses of these 22 patients were included in the fourth group, which was coded as severe. Multiple least squares regression was run with age, perceived susceptibility, and expectancy as independent variables, as well as treatment arm and education (to control for these factors). A similarly structured logistic regression analysis was used to examine the effect of age, expectancy, and perceived susceptibility on occurrence of severe nausea.

Finally, Fisher's exact test was used to determine whether vomiting was related to the occurrence of severe nausea. This was followed by determining the correlation between the occurrence of vomiting and severe nausea so as to estimate the strength of this relationship. All analyses were conducted with SAS version 9.2, and results were considered significant if $p < 0.05$, two-tailed. Given that this was a secondary analysis, adjustment for multiple comparisons was not performed.

Results

There were a total of 1,696 patients in the dataset combined from all three studies. Table 1 shows patient characteristics for each study separately. Overall, 29% of these 1,696 patients reported having severe nausea at some point during the 4-day period, and 18% of the patients had no nausea. Mean nausea for all patients on the 1–7 scale was 2.18.

Average nausea for breast cancer patients receiving doxorubicin was greater than for other patients receiving doxorubicin, patients receiving cisplatin, and patients receiving carboplatin (all $P_s < 0.01$). In addition, nonbreast cancer patients receiving doxorubicin and patients receiving cisplatin reported higher average nausea compared with those receiving carboplatin (both $P_s < 0.01$). Similar patterns were seen for the percentage of patients experiencing severe nausea (all $P_s < 0.03$; see Fig. 1 and Table 2).

For $N=299$ patients having nongender-related cancers (hematological (52.8%), lung (29.1%), other (18.1%)), we ran a regression to ascertain whether gender makes a

difference in average nausea after controlling for tumor site, chemotherapy type, education, and study arm. A gender-by-tumor type interaction term was included in the model to account for any dependencies of the gender effect on tumor type. Gender proved to be nonsignificant ($P=0.35$ for the main gender effect and $P=0.57$ for the gender-by-tumor type interaction).

For female breast cancer patients, regression analysis revealed that perceived susceptibility, age, and expectancy were important risk factors for average nausea (see Table 3). The risk factor with the largest effect according to the F statistic ($F=19.8$, $P < 0.0001$) was susceptibility. Patients who said they were more susceptible to nausea than their friends and family had greater average nausea. The effect of age ($F=17.0$, $P < 0.0001$) was nearly as large, with older patients reporting less nausea. The effect of expectancy was smaller, but still significant ($F=2.9$, $P=0.034$) with patients expecting more severe nausea reporting greater nausea.

In the similarly structured logistic regression equation, examining the influence of age, perceived susceptibility, and expectancy on the report of severe nausea, perceived susceptibility, and age were significant (both $P_s < 0.0001$), but expectancy was not ($P=0.31$; see Table 4). The odds of reporting severe nausea for patients who said they were

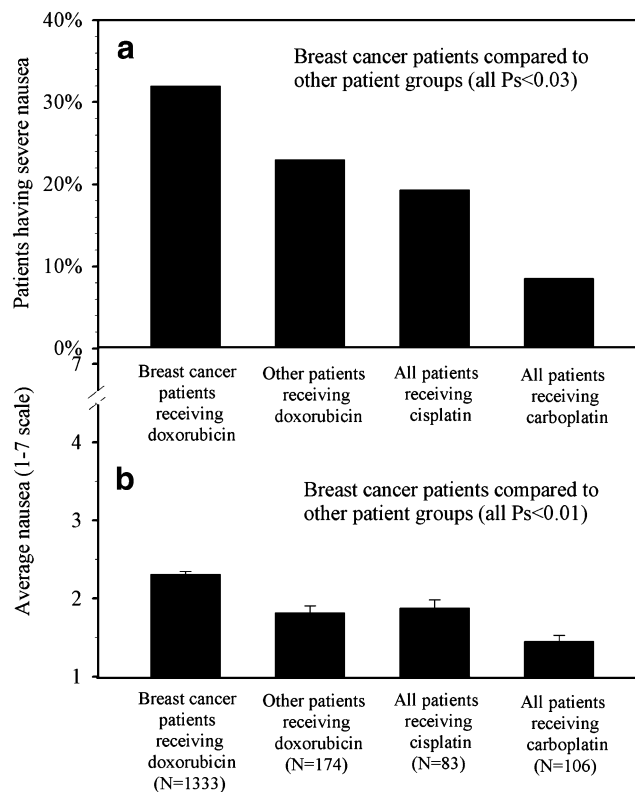


Fig. 1 Observed incidence of severe nausea (proportion) and average nausea (mean + standard error), following first treatment for breast cancer patients receiving doxorubicin-based treatments compared to other patients

Table 2 Effects of treatment group on average nausea and incidence of severe nausea

Treatment group	Average nausea (1–7 scale)			Severe nausea (rating of 6 or 7)			
	Observed mean	Standard error	N	Observed proportion with severe nausea	Odds ratio relative to breast cancer patients receiving doxorubicin		
					Estimate	LCB ^a	UCB ^a
Breast cancer patients receiving doxorubicin	2.31	0.04	1,333	32.0%	NA	NA	NA
Other patients receiving doxorubicin	1.82	0.09	174	23.0%	0.63	0.42	0.91
All patients receiving cisplatin	1.88	0.10	83	19.3%	0.46	0.25	0.82
All patients receiving carboplatin	1.45	0.08	106	8.5%	0.17	0.08	0.37

NA Not applicable

^a Lower and upper 95% confidence bounds

more susceptible to nausea than their friends and family were 2.85 times than those who said they were less susceptible. The effect of age was similar to that reported for average nausea, with a decrease of severe nausea with increasing age. For example, the odds of reporting severe nausea for patients aged 70 or more vs those less than 40 years of age was 0.33.

When age and susceptibility are considered together, the observed average nausea ranged from a mean of 3.34 in the

youngest cohort of patients who classified themselves as more susceptible to nausea to a mean of 1.66 in patients in the oldest cohort who classified themselves as less susceptible to nausea. Observed incidences of severe nausea in these two groups were 71% and 17%, respectively (see Fig. 2).

Fisher's exact test revealed a significant relationship between occurrence of severe nausea and vomiting ($P < 0.001$). In all, 393 patients reported both severe nausea and

Table 3 Risk factors for incidence of average nausea in female breast cancer patients receiving doxorubicin

Risk factor	Least squares mean ^a		
	Estimate	LCB ^b	UCB ^b
Perceived susceptibility ($F=19.8$, $P<0.0001$)			
Less	1.92	1.55	2.28
About the same	2.13	1.76	2.51
More	2.51	2.13	2.89
Age (years; $F=17.0$, $P<0.0001$)			
<40	2.70	2.29	3.11
40–49	2.48	2.11	2.85
50–59	2.12	1.75	2.49
60–69	1.80	1.42	2.17
70+	1.84	1.39	2.28
Expectancy ($F=2.9$, $P=0.034$)			
None or very mild	2.02	1.62	2.41
Mild	2.11	1.74	2.48
Moderate	2.26	1.90	2.63
Severe	2.36	1.95	2.76

Results are from regression analysis after adjustment for education and study arm

^a Least squares means are the means for given factor levels after adjustment for the other factors

^b Lower and upper 95% confidence bounds

Table 4 Risk factors for incidence of severe nausea in female breast cancer patients receiving doxorubicin

Risk factor	Odds ratio ^a		
	Estimate	LCB ^b	UCB ^b
Perceived susceptibility (chi-square=36.66, $P<0.0001$)			
More vs less	2.85	4.00	2.03
More vs about the same	1.87	2.64	1.32
Age (years; chi-square=47.26, $P<0.0001$)			
70+ vs <40	0.33	0.65	0.17
70+ vs 40–49	0.56	1.03	0.30
70+ vs 50–59	1.07	1.97	0.58
70+ vs 60–69	1.45	2.87	0.74
Expectancy (chi-square=3.6, $P=0.31$)			
Severe vs none or very mild	1.35	2.29	0.79
Severe vs mild	1.25	1.99	0.79
Severe vs moderate	0.98	1.47	0.65

Results are from logistic regression analysis after adjustment for education and study arm

^a Odds of severe nausea for the reference group divided by the odds of severe nausea for the other groups. Values less than 1.0 indicate a lower propensity to report severe nausea. For example, the odds of experiencing severe nausea for patients 70 years old or more are 0.33 times the odds of severe nausea for young patients less than 40 years old

^b Upper and lower 95% confidence bounds

Any severe nausea and average nausea in 1184 breast cancer patients following first treatment by age cohort and perceived susceptibility of nausea compared to friends and family members

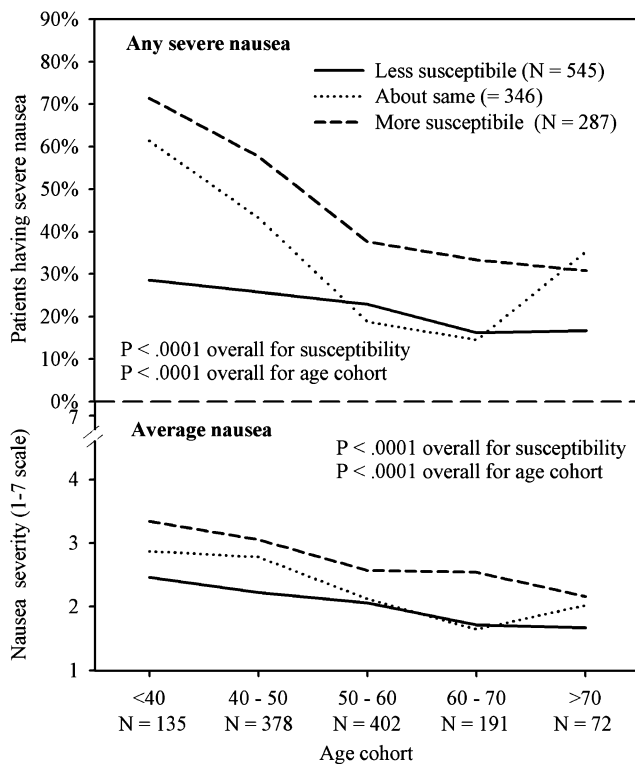


Fig. 2 Observed incidence of severe nausea (proportion) and average nausea (mean) in 1,178 breast cancer patients following first treatment by age cohort and perceived susceptibility of nausea compared to friends and family members

vomiting, 434 patients reported vomiting but not severe nausea, 97 patients reported severe nausea with no vomiting, and 768 patients did not report severe nausea or vomiting. The tetrachoric correlation between occurrence of severe nausea and occurrence of vomiting was large, 0.63.

Discussion

Our analyses regarding predictors of chemotherapy-related nausea from the combined sample of 1,696 patients following their first treatment yielded six findings of interest: (1) strong evidence that breast cancer patients experience significantly greater nausea than other patients, (2) confirmation of prior reports that younger patients experience greater nausea than older patients, (3) a new finding that perceived susceptibility to nausea is a significant predictor of actual nausea, (4) evidence that expectancy is a predictor of nausea, (5) the incidence of any severe nausea and any vomiting have a strong relationship, and (6) contrary to many prior reports, gender is not a

significant predictor of nausea. Each of these findings is discussed below.

In the present analyses, we compared average nausea and incidence of severe nausea in breast cancer patients receiving doxorubicin to three other groups of patients. One of these groups was comprised of other patients receiving doxorubicin, typically those with hematologic cancers, and they would likely have received a lower dose of doxorubicin than the breast cancer patients. A second group was comprised of patients receiving cisplatin. The third group of patients received carboplatin. Our analyses showed that breast cancer patients receiving doxorubicin had significantly greater average nausea and a higher incidence of severe nausea than patients in the other three groups. Thirty-two percent of the breast cancer patients experienced severe nausea compared to less than 20% of patients receiving cisplatin and less than 10% of patients receiving carboplatin. Virtually, all of the breast cancer patients in our study received not only doxorubicin but also cyclophosphamide, and it is possible that it is this particular combination of drugs that caused the high level of nausea observed in these patients rather than the doxorubicin alone.

Our finding that age is a significant predictor of nausea is not surprising; it has been reported many times previously [3, 5, 6, 8–10, 26]. In the present analyses, because of our large sample size, we were able to divide age into five categories (<40, 40–49, 50–59, 60–69, ≥ 70) rather than the dichotomous category of younger or older than 50 years that is often reported in the literature [6, 27]. Mean nausea decreased with age category, with patients in the oldest category having average nausea that was one point less on the 7-point scale than patients in the youngest age category. Incidence of severe nausea ranged from over 50% of patients in the youngest cohort to less than half that in each of the two oldest cohorts. These analyses were done only in female breast cancer patients receiving doxorubicin-based treatments as a method of controlling for cancer and type of treatment; therefore, we are not sure if this will generalize to men and other cancer treatments.

The simple question of whether patients believed that they were more susceptible to nausea than their friends or family was a substantial determinant of average nausea in our sample. We examined the predictive role of susceptibility only in female breast cancer patients receiving doxorubicin-based treatments, our largest homogenous patient group. Taking into account age, expectancy, and education, patients rating themselves more susceptible to nausea had significantly greater average nausea than patients rating themselves less susceptible. They were also nearly three times as likely to experience severe nausea. Patients who rated their nausea susceptibility about the same as friends and family members fell close to midpoint between the other two patient groups in both average nausea and incidence of severe nausea.

In a similar vein and in the same patient sample, nausea expectancy was a significant predictor of average nausea, even after controlling for age and perceived susceptibility. Individuals expecting nausea, whether because they consider themselves to be very susceptible to nausea or for any other reason, may be more likely to interpret vague or ambiguous sensations as nauseating than an individual not expecting the symptom [28]. The idea that perceptions are influenced by expectations in this way is a well-established principle in the study of cognition [29].

We report on one analysis regarding vomiting, that is, the relationship between severe nausea and vomiting. Far more, patients reported vomiting (827) than severe nausea (490) and fewer than half (48%) of those reporting at least one incidence of emesis also reported having severe nausea. On the other hand, of the 490 patients reporting severe nausea, 80% reported at least one episode of emesis. These findings suggest that the occurrence of vomiting is a strong contributing factor to the report of severe nausea, but that the two symptoms are clearly different because over half of the patients reporting emesis do not report having severe nausea.

We did not find a significant relationship between gender and nausea. We conducted these analyses on 299 (male=155) patients with gender neutral cancers, i.e., excluding patients with breast, genitourinary, or gynecological cancers. Regression analysis controlling for age, education, chemotherapy type, and study arm showed that gender did not significantly predict average nausea or incidence of severe nausea in these 299 patients. Our findings are contrary to much of the current literature regarding the relationship between gender and nausea in cancer patients, and we speculate that this contradiction is due to our using a sample of patients with only gender neutral cancers in our analyses. Considering our previously discussed finding that breast cancer patients receiving doxorubicin have significantly more nausea than other patients, we speculate that prior reports showing an effect of gender on nausea that included breast cancer patients in their analyses are in error because they did not adequately control for the significantly higher level of nausea in breast cancer patients receiving doxorubicin. Further research on the effect of gender on nausea will be needed to determine if this hypothesis is correct.

Conclusion

Our findings confirm that age is a major risk factor for the development of chemotherapy-related nausea, with younger patients having significantly more nausea than older patients. They also provide strong evidence that breast cancer patients have more nausea than patients in other

diagnostic groups. We also found that a simple question regarding susceptibility to nausea was a strong predictor of subsequent nausea and suggest this assessment be added to the antiemetic treatment guidelines as a risk factor. Studies examining the benefit to patient QOL from modifying antiemetic regimens based upon risk factors are warranted.

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