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Psychological predictors of chemotherapy-induced nausea in women with breast cancer: Expectancies and perceived susceptibility

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Abstract

Objective: Chemotherapy-induced nausea is challenging to predict and treat. Research indicates that pretreatment psychological variables including patients' perceptions of their susceptibility to nausea, expectancies of treatment-related nausea and nausea history (i.e., motion sickness, morning sickness and baseline levels of nausea) may aid in predicting nausea severity during chemotherapy. However, this research is dated and limited in quantity. We investigated whether psychological variables could improve prediction of nausea severity to inform interventions targeting chemotherapy-induced nausea.

Methods: In this secondary analysis, a subgroup of women receiving chemotherapy (for the first time) for breast cancer completed pretreatment measures: perceived nausea susceptibility, nausea expectancies, nausea history and baseline nausea. They rated subsequent nausea severity across 4-days, during treatment and posttreatment in a self-report diary. Structural Equation Modelling was used to explore associations.

Results: Across the women ($N = 481$), perceived nausea susceptibility predicted subsequent nausea severity ($\beta = 0.16$), but nausea expectancies did not ($\beta = 0.05$). Nausea history variables demonstrated small-moderate associations with perceived susceptibility ($\beta = 0.21$–0.32) and negligible-small associations with nausea expectancies ($\beta = 0.07$–0.14).

Conclusion: Perceived nausea susceptibility appears to capture patients' nausea history, to a degree, and is related to nausea severity during treatment. This is an important variable to include in pretreatment prediction of patients at risk of severe nausea.

KEYWORDS
chemotherapy, expect, nausea, nocebo, path analysis, susceptibility

1 | INTRODUCTION

Advances in antiemetic medications have reduced emesis (vomiting) for patients undergoing chemotherapy (Hesketh et al., 2003; Roila et al., 2010); however, this success has not extended to the control of chemotherapy-induced nausea (CIN). Up to 75% of patients report CIN at some stage of treatment (Colagiuri & Zachariae, 2010). It is within the top 10 most distressing and debilitating side effects reported by patients (Russo et al., 2014) and can endure for years following primary treatment completion (Chan et al., 2015; Olver et al., 2014). CIN commonly affects quality of life (Aldaz et al., 2018; Lorusso et al., 2016) by interfering with daily functioning (Molassiotis et al., 2008; Singh et al., 2018). These complications can reduce the amount of chemotherapeutic agent(s) tolerated, potentially leading to poor treatment adherence, lower doses of chemotherapy and even discontinuation, compromising survival (Molassiotis et al., 2012; Morrow et al., 2002; Navari & Aapro, 2016).

Experiencing minimal or no nausea on the first day of chemotherapy appears to lead to lower reports of CIN in subsequent cycles (Kottschade et al., 2016), suggesting that the ideal time for intervention may be prior to treatment commencement. Establishing pretreatment risk factors for CIN, especially severe CIN, could help identify at-risk patients in need of additional support and inform intervention strategies aimed at nausea prevention.

There has been a wealth of research on physical and pharmacological predictors of CIN (Roila et al., 2016), including being female, aged below 50 years and receiving chemotherapy with high emetic potential. Psychological variables have received less attention (Warr, 2014). However, there is some indication patients' pre-chemotherapy response expectancies for nausea (nausea expectancies) and perceived general susceptibility to nausea (nausea susceptibility) play a role in the experience of CIN (Colagiuri & Zachariae, 2010; Devlin et al., 2017; Morrow, 1985; Roscoe et al., 2010; Sohl et al., 2009).

Response expectancies refer to individuals' anticipations for the degree to which they will *automatically* respond to stimuli (Kirsch, 1985); for example, an individual anticipating that they will experience severe nausea during chemotherapy. Expectancies have been shown to directly affect subsequent experiences and are believed to underlie nocebo effects (Kirsch, 1985; Montgomery & Bovbjerg, 2004; Petrie & Rief, 2019). Response expectancies for nausea before treatment commencement consistently predict CIN during treatment a small to moderate degree; three meta-analyses revealed that patients reporting stronger expectancies of CIN before treatment were approximately twice as likely to experience nausea throughout chemotherapy (Colagiuri & Zachariae, 2010; Devlin et al., 2017; Sohl et al., 2009). Patients' reports of their susceptibility to experiencing nausea have received less attention; it is not clear whether this variable represents a different construct to response expectancies or whether it plays an independent role in predicting the severity of CIN (Morrow, 1985; Roscoe et al., 2010).

In an early study, Morrow (1985) compared patients (scheduled for chemotherapy) who reported that they are susceptible to motion sickness to those rating themselves as not susceptible (matched for age, sex, scheduled chemotherapy type and dosage, and antiemetic medication). Patients who reported they were susceptible to motion sickness rated their frequency, severity and duration of CIN significantly higher than those who did not feel they were susceptible. They were also more likely to have other nausea-related side effects (including chills and detached sensations; Olver et al., 2014) resulting from their tretment. More recently, Roscoe et al. (2010) combined the results of three multisite studies ($N = 1178$) of women with breast cancer who were chemotherapy-naïve. The authors found that patients who rated themselves more susceptible to nausea (in comparison to family and friends) were almost three times more likely to experience severe posttreatment nausea than those who rated themselves as less susceptible.

Although it is possible that nausea susceptibility informs patients' nausea expectancies, this has not been formally tested. However, in the aforementioned study (Roscoe et al., 2010), when nausea expectancies, nausea susceptibility and age were simultaneously analysed, only nausea susceptibility and age remained significant predictors of CIN severity. The findings outlined thus far suggest that nausea expectancies and nausea susceptibility are separate constructs which may both be prominent psychological predictors of subsequent CIN severity in clinical settings. If so, patients at risk of CIN may benefit from simple psychological interventions prior to chemotherapy to lower their perceived susceptibility to CIN, as have been explored for reducing expectancies (Shelke et al., 2008). It is also important to determine how patients form judgements about their expectancies of, and susceptibility to nausea in the first place, particularly those who have not previously experienced chemotherapy.

Historical nausea experiences, such as previous motion sickness and morning sickness, and the amount of nausea experienced before beginning chemotherapy (pretreament), have been theorised to predict nausea expectancies (Hickok et al., 2005; Hofman et al., 2004; Montgomery & Bovbjerg, 2003). However, the evidence is mixed (Colagiuri & Zachariae, 2010; Meissner et al., 2019; Molassiotis et al., 2013; Molassiotis et al., 2014; Montgomery & Bovbjerg, 2003). Further, relationships between such historical nausea experiences and perceived nausea susceptibility have not yet been investigated.

We sought to confirm and explore the interrelations between the aforementioned variables, using structural equation modelling. Based on previous findings (Hickok et al., 2005; Hofman et al., 2004; Montgomery & Bovbjerg, 2003; Roscoe et al., 2010), we hypothesised that (1) both nausea expectancies and nausea susceptibility would predict CIN severity but that nausea susceptibility and CIN severity would demonstrate a stronger association and (2) both nausea expectancies and nausea susceptibility would be influenced by nausea history, namely baseline (pretreatment) nausea and previous history of nausea, measured separately as motion sickness and morning sickness.

2 | METHODS

2.1 | Study design and participants

This study is a secondary analysis of a subset of patients from a previously completed trial (Peoples et al., 2017; Roscoe et al., 2012). As

described briefly below and in full detail previously (Roscoe et al., 2012), the parent study from which this dataset was drawn was a randomised, double-blind, placebo-controlled phase III clinical trial examining the efficacy of different antiemetic regimens for the prevention of delayed nausea in cancer patients during the first cycle of chemotherapy. All patients were provided with the anti-emetics, dexamethasone, prochlorperazine, palonosetron, granisetron and aprepitant, in varying orders, as per the larger study. Because all patients received the medications over the course of the 4 days (in varying combinations), the different regimens were not controlled for in statistical analyses.

The original trial had 944 chemotherapy-naïve patients, with any cancer diagnosis, at least 18 years of age, who provided evaluable data from 15 private-practice oncology groups affiliated with the University of Rochester Cancer Center NCI's Community Oncology Research Program (URCC NCORP) between May 2007 and September 2010. Patients were scheduled to receive their first treatment with a chemotherapy regimen containing any of the five following chemotherapy agents: doxorubicin, epirubicin, cisplatin, carboplatin or oxaliplatin. For our secondary analysis, we included a subsample of 481 female cancer patients who had a diagnosis of breast cancer and had previously been pregnant (to evaluate the influence of past nausea during pregnancy).

The institutional review boards of the University of Rochester (approval number RSRB00012306) and of each participating site approved the protocol for the original study in accordance with an assurance filed with and approved by the US Department of Health and Human Services, and subjects were provided written informed consent. This trial was registered with ClinicalTrials.gov, number NCT00475085.

2.2 | Data collection

Collected data included typical demographic information as well as specific information related to nausea, participants' history of nausea during pregnancy (yes, no), susceptibility to motion sickness (yes, no), perception of being more susceptible to nausea than family and friends (no, about the same, yes) and response expectancies of CIN compared to other patients receiving the same treatment (less, about the same, more). Baseline (pretreatment) level of nausea at its worst was assessed on an 11-point scale anchored by '0' (symptom is not present) to '10' (as bad as you can imagine it could be).

CIN severity (i.e., nausea severity posttreatment) was assessed by a self-report diary (Roscoe et al., 2010), completed by patients over a 4-day period surrounding their first treatment cycle. Each day was divided into four segments (morning, afternoon, evening and night), and subjects reported the severity of nausea for each period on the day of chemotherapy cycle 1 and on the three following days. Nausea severity was rated on a 7-point measure from 1 = no nausea to 7 = extremely nauseated. In line with previous research (Roscoe et al., 2004; Roscoe et al., 2010), CIN severity was calculated as the number of times a patient selected a score of 6 or 7 across all 16 sessions.

2.3 | Statistical analyses

To investigate associations between the proposed variables, we performed recursive path analysis using IBM SPSS AMOS Graphic 24. Path analysis is a form of structural equation modelling which extends regression analyses, allowing estimation of complex interrelations between multiple variables. Goodness of fit was calculated using chi-square analysis whereby a nonsignificant p-value and an estimate that is close to the degrees of freedom suggest a good fit. We also measured goodness of fit with the Comparative Fit Index (CFI) and Tucker Lewis Index (TLI), with scores greater than 90 suggesting a good fit; the Root Mean Square Error of Approximation (RMSEA); and the Standardised Root Mean Square Residual (SRMR), whereby values below 0.08 suggest a good fit. Standardised Beta coefficients (β) of 0.10, 0.30 and 0.50 represent small, medium and large effect sizes (Cohen, 1988).

3 | RESULTS

3.1 | Data screening

Based on the small amount of missing data ($n = 5$, 0.01%), and the large sample size, missing data were estimated using regression imputation. Univariate normality was checked with skewness and kurtosis values, and multivariate normality was assessed using Mardia's Tests of Multivariate Normality (Table 1). Critical values indicated significant skew for all variables; however, only one variable (CIN severity) was slightly greater than a problematic value of 3 (Byrne, 2010). Significant kurtosis was also indicated for baseline nausea, nausea susceptibility, nausea expectancies and CIN severity. Only one variable (CIN severity) fell into a problematic range of 8–20 (Byrne, 2010; West et al., 1995; Yuan et al., 2005), but because the sample size was above 200 and bootstrapping was used, risks were minimised (Tabachnick & Fidell, 2013,

TABLE 1 Test of univariate and multivariate normality for endogenous variables

Variable	Min	Max	Skew	Critical ratio	Kurtosis	Critical ratio
Baseline nausea	0	10	2.86	25.63	7.98	35.72
Perceived nausea susceptibility	0	2	0.47	4.25	−1.32	−5.90
Response expectancies for nausea	0	2	0.00	0.01	−0.11	−0.48
CIN severity	0	13	3.29	29.49	12.51	56.00
Multivariate normality					19.57	21.91

Abbreviation: CIN = chemotherapy-induced nausea, severity of nausea resulting from chemotherapy (outcome variable).

p 80). The Mardia's Test of Multivariate Normality score (19.5) was greater than 5; thus, nonnormal. Nonnormality has minimal impact on model parameters (in SEM); however, *p*-values and standard errors are often affected (Nevitt & Hancock, 2001). Therefore, we obtained and referred to bootstrapped *p*-values and confidence intervals, resampled 2000 times, which do not rely on the assumption of normality (Zhu, 1997).

3.2 | Demographics

The final sample included 481 women with breast cancer, all were treated with chemotherapy and had a history of being pregnant (Table 2). Patients' ages ranged from 29 to 80 years, with an average age of 54.5 (SD = 10.2). Most of the women were white, married and worked in a professional industry.

TABLE 2 Patient characteristics ($N = 481$)

	N (%)
Race	
White	436 (90.6)
African American	41 (8.5)
Asian	3 (0.6)
Native American	1 (0.02)
Marital status	
Married	338 (70.3)
Divorced or separated	71 (14.8)
Single	37 (7.7)
Widowed	35 (7.3)
Occupation	
Professional	161 (33.4)
Clerical	78 (16.2)
Other	61 (12.7)
Homemaker	56 (11.6)
Labour/trade	55 (11.4)
Service	53 (11.0)
Technical	14 (2.9)
Student	3 (0.6)

3.3 | Univariate analyses of variables

Means, standard deviations and univariate correlations (Table 3) were observed as preliminary assessments of the variables of interest. Frequencies and mean scores indicated one third of patients reported a history of motion sickness and more than half had experienced morning sickness during pregnancy. The women reported low levels of baseline (pretreatment) nausea and reported similar average levels of nausea susceptibility and nausea expectancies. At posttreatment, the women experienced CIN at low levels of severity. Correlation analyses revealed a history of motion, and morning sickness were related to each other, but only a history of motion sickness was significantly associated with baseline nausea. All three nausea history variables showed significant associations with both nausea susceptibility and nausea expectancies. Baseline nausea, nausea susceptibility and nausea expectancies were also significantly associated with CIN severity.

3.4 | Path model

Chi-squared analysis revealed that the model (Figure 1) was an excellent fit to the data, $\chi^2(3) = 5.78$, $p = 0.12$. Because chi-squared analyses are sensitive to a lack of multivariate normality (Schermelleh-Engel et al., 2003; Vandenberg, 2006), we also explored other fit indices. The CFI (0.99), TLI (0.95), RMSEA (0.04) and SRMR (0.02) also suggested that the model was an excellent fit to the data.

Estimates revealed that most direct paths (associations) were significant, except between history of morning sickness and nausea expectancies and between nausea expectancies and CIN severity (Figure 1 and Table 4). Standardised coefficients (β) revealed that history of motion sickness was associated with nausea susceptibility, to a moderate degree. Baseline nausea and a history of morning sickness were also associated with nausea susceptibility, to a small degree. History of motion sickness and baseline nausea was also significantly associated with nausea

TABLE 3 Correlations, means and standard deviations for all variables in path analysis

	1	2	3	4	5	6			*n* (%) yes
1. History of motion sickness	-								154 (32.4)
2. History of nausea during pregnancy	0.15 (0.001)	-							284 (59.7)
							M	SD	Range
3. Baseline nausea	0.12 (0.01)	0.04 (0.45)	-				0.8	2.0	0–10
4. Perceived nausea susceptibility	0.38 (<0.001)	0.25 (<0.001)	0.25 (<0.001)	-			0.8	0.8	0–2
5. Response expectancies of nausea	0.28 (<0.001)	0.17 (<0.001)	0.23 (<0.001)	0.41 (<0.001)	-		0.9	0.6	0–2
6. CIN severity	0.04 (0.36)	0.08 (0.08)	0.14 (0.002)	0.18 (<0.001)	0.11 (0.01)	-	0.8	1.9	0–13

Abbreviation: CIN = chemotherapy-induced nausea, severity of nausea resulting from chemotherapy (outcome variable).

FIGURE 1 Path model

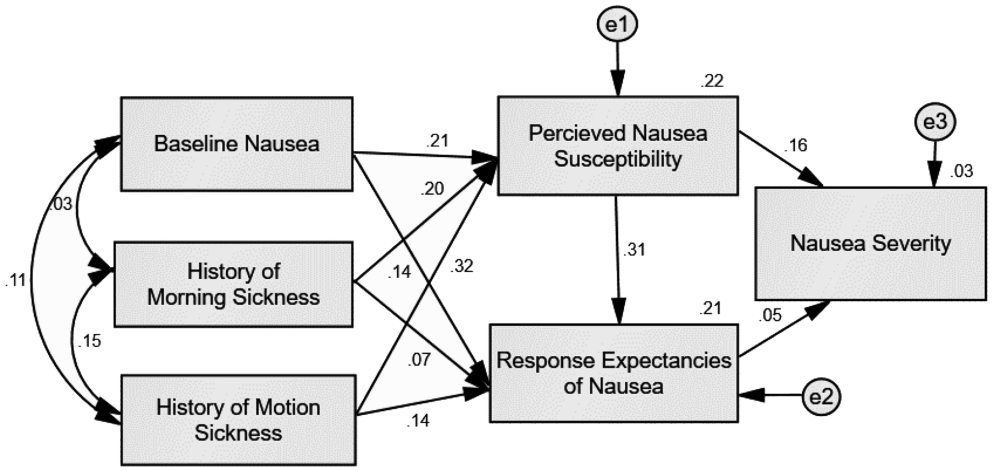

TABLE 4 Direct effects within the path model

Path	β	Bootstrapped CIs	p
History of motion sickness → perceived nausea susceptibility	0.32	0.25, 0.38	0.001
History of nausea during pregnancy → perceived nausea susceptibility	0.20	0.13, 0.26	0.001
Baseline nausea → perceived nausea susceptibility	0.21	0.14, 0.29	0.001
History of motion sickness → response expectancies for nausea	0.14	0.07, 0.21	0.002
History of nausea during pregnancy → response expectancies for nausea	0.07	−0.00, 0.13	0.12
Baseline nausea → response expectancies for nausea	0.14	0.07, 0.20	0.002
Perceived nausea susceptibility → response expectancies for nausea	0.31	0.23, 0.39	0.001
Perceived nausea susceptibility → CIN severity	0.16	0.07, 0.24	0.004
Response expectancies for nausea → CIN severity	0.05	−0.04, 0.14	0.34

Abbreviations: CIN = chemotherapy-induced nausea, severity of nausea resulting from chemotherapy (outcome variable); β = standardised regression coefficients (beta) represented by 0.10 for small, 0.30 for moderate and 0.50 for large effects (Cohen, 1988).

expectancies, to a small degree. The exogenous variables demonstrated stronger and more consistent associations with nausea susceptibility than they did with nausea expectancies.

Nausea susceptibility had a moderate influence on nausea expectancies and a small influence on CIN severity. Total effects (multiplication of both indirect and direct effects) of nausea susceptibility on CIN severity were also significant ($\beta = 0.17$, $p = 0.001$), in isolation and when taking nausea expectancies into account. Nausea expectancies were not independently associated with CIN severity.

Table 5 displays the indirect effects in the model. Because AMOS is unable to separate individual indirect effects, a plugin was utilised (Gaskin & Lim, 2018). However, bootstrapped CIs and p-values were not available through this program, therefore, we displayed inferential statistics for these indirect paths, where required (denoted in Table 5 with superscript a). Analyses revealed small significant indirect effects between history variables (motion sickness, morning sickness and baseline nausea) with nausea expectancies, via nausea susceptibility. Thus, nausea susceptibility partially mediates associations between history of nausea and nausea expectancies. The indirect paths from history variables and from nausea susceptibility to CIN severity, through nausea expectancies, were not significant.

4 | DISCUSSION

We investigated interrelationships between psychological variables that have been theorised, and shown, to predict CIN severity and their potential antecedents. Results indicated that the model was an excellent fit to the data. Thus, we were able to consider the associations in more depth.

The previous history variables showed nonsignificant or small associations with nausea expectancies. Baseline nausea and a history of motion sickness each only explained a small amount of variance in nausea expectancies (both $\beta = 0.14$), and a history of morning sickness did not explain a significant amount ($\beta = 0.07$). Furthermore, no previous history variables predicted CIN severity indirectly,

TABLE 5 Indirect effects within the path model

Path: nausea history variables to response expectancies for nausea	β	Bootstrapped CIs	p
History of motion sickness → perceived nausea susceptibility → response expectancies for nausea	0.10	0.07, 0.14	0.001
History of nausea during pregnancy → perceived nausea susceptibility → response expectancies for nausea	0.06	0.04, 0.09	0.001
Baseline nausea → perceived nausea susceptibility → response expectancies for nausea	0.06	0.04, 0.10	0.001
Path: nausea history variables to CIN severity			
History of motion sickness:			
→ perceived nausea susceptibility → CIN severity	0.05	0.10, 0.34[a]	0.002
→ response expectancies for nausea → CIN severity	0.01	−0.01, 0.10[a]	0.24
→ perceived nausea susceptibility + response expectancies for nausea → CIN severity	0.06	0.03, 0.10	0.001
History of nausea during pregnancy:			
→ perceived nausea susceptibility → CIN severity	0.03	0.05, 0.21[a]	0.002
→ response expectancies for nausea → CIN severity	0.01	−0.01, 0.06[a]	0.26
→ perceived nausea susceptibility + response expectancies for nausea → CIN severity	0.04	0.02, 0.06	0.001
Baseline nausea:			
→ perceived nausea susceptibility → CIN severity	0.03	0.01, 0.06[a]	0.002
→ response expectancies for nausea → CIN severity	0.01	−0.00, 0.02[a]	0.29
→ perceived nausea susceptibility + response expectancies for nausea → CIN severity	0.04	0.02, 0.08	0.001
Perceived susceptibility → response expectancies for nausea → CIN severity	0.02	−0.01, 0.05	0.31

Abbreviations: CIN = chemotherapy-induced nausea, severity of nausea resulting from chemotherapy (outcome variable); β = standardised regression coefficients (beta) represented by 0.10 for small, 0.30 for moderate, and 0.50 for large effects (Cohen, 1988).
[a]Bootstrapping was not available for this path, therefore inferential statistics were calculated.

through associations with patients' reported nausea expectancies. Thus, it does not appear that patients are reporting expectancies for CIN which are based on their previous nausea experiences. This can help explain inconsistent findings in the literature for the impact of patients' nausea history on response expectancies (Colagiuri & Zachariae, 2010; Meissner et al., 2019; Molassiotis et al., 2013; Molassiotis et al., 2014; Montgomery & Bovbjerg, 2003). Although this appears promising, because it suggests nausea expectancies might be less fixed and therefore more open to modification, it may be irrelevant because the current model also indicated that nausea expectancies were not related to the severity of CIN nausea.

Consistent with Roscoe et al. (2010) large study, we found that nausea expectancies were related to subsequent CIN severity in univariate correlations, but not in the multivariate model. This is an important finding, which has implications for the efficacy of expectancy-based interventions. For example, in an information-based intervention with 358 patients, Shelke et al. (2008) provided either standard information about nausea or information designed to reduce nausea expectancies. They found that although the intervention was effective at reducing patients' expectancies of nausea, this did not translate to a difference to their subsequent nausea severity.

Nausea history variables were associated with patients' perceptions of their susceptibility to nausea before treatment, a small to moderate degree ($\beta = 0.21$–0.32). All three previous history variables were also indirectly associated with CIN severity, through nausea susceptibility (Morrow, 1985; Roscoe et al., 2010). Thus, the individual nausea history variables (baseline nausea, history of motion sickness and history of morning sickness) demonstrated similar patterns of associations with all variables in this model, suggesting that combining them into a general 'previous history of nausea' measure is acceptable in research. In fact, measuring nausea susceptibility might be an efficient way to combine history of nausea into a single item that captures some degree of a patients' (perceived) nausea history. However, there is still much variance in susceptibility to nausea currently unexplained and requiring further investigation.

Perceived susceptibility explained a significant but small amount of variance in CIN severity ($\beta = 0.16$). However, small to moderate effect sizes for psychological variables are common in clinical contexts (Colagiuri & Zachariae, 2010; Devlin et al., 2017; Sohl et al., 2009),

because there are multiple variables that contribute to the severity of nausea experienced following chemotherapy, including the direct emetic potential of the chemotherapy regimen, gender, age (below 50 years), pain and anxiety (Kamen et al., 2014; Molassiotis et al., 2013). Thus, the impact of patients' perceptions of their own susceptibility to nausea, for patients who are chemotherapy-naïve, is an important finding and warrants future research. Perceived susceptibility demonstrated a moderate association with response expectancies but did not indirectly predict CIN severity by influencing patients' nausea expectancies. Again, patients' nausea expectancies did not appear to play an important role in the model.

Importantly, based on previous research, and the current model, it appears that nausea expectancies and nausea susceptibility share some variance; however, only nausea susceptibility captures previous history variables and predicts CIN severity. Such differences could be based on the wording of the questions. When patients who have not had any direct experience with chemotherapy are asked how 'susceptible' they are to nausea, they may draw on pre-existing cognitive frameworks, known as schemas (Piaget, 1954), which utilise previous nausea experiences to make judgements. On the other hand, those asked about how much nausea they think they *will* experience (i.e., response expectancies) might make future-facing predictions and thus draw on previous history to less of a degree. Thus, consideration of the wording of items surrounding expectancies and susceptibility appears to be vital when designing research.

Taken together, it is important to include measurement of patients' perceived susceptibility to nausea to any pretreatment screening measures. Intervention techniques that have traditionally targeted patients' expectancies (Shelke et al., 2008) could be expanded to include nausea susceptibility. Additionally, although previous reviews indicate that cognitive and behavioural therapies have minimal effect on CIN following chemotherapy (Cobeanu & David, 2018; Redd et al., 2001), these reviews combine a number of different therapies, mainly progressive muscle relaxation. Based on the current results, more specific cognitive-based therapies focused on schemas, such as cognitive restructuring or schema-based therapies, may be better suited to this patient group (Daniels, 2015). These could involve informing patients about differences between chemotherapy and other nausea-inducing experiences, reframing cognitions such as 'I always get nauseous', or focusing on past situations where patients have not experienced nausea (e.g., medications or form of travel that do not induce nausea). Future research into the efficacy of such interventions is warranted.

5 | LIMITATIONS

There are limitations to the current study that need to be considered. Path analyses allow modelling of theory, based on data. Although endogenous variables are recursive (the arrow can only go in one direction), we cannot know about causality or the direction of a relationship based on this type of analysis.

Furthermore, data screening revealed that the outcome variable, CIN severity, was not normally distributed and demonstrated kurtosis. Research shows that interpretations of maximum likelihood can be problematic with nonnormal data; chi-square values can be overestimated (a higher chi-square value indicates a poorer fit), meaning models can be rejected that are in fact accurate representations. However, as the model was found to be a good fit in the current study, this was not a problem. Also, standard errors can be distorted with nonnormal data. Using an asymptotic distribution free estimation (Browne, 1984) was not appropriate for our sample, as this estimation often provides inaccurate estimates and standard errors with samples below 1000 (Montfort et al., 2009; West et al., 1995). Instead, we chose to use bootstrapping, which does not depend on inferential calculations.

Because this was a secondary analysis of an investigation of different treatment schedule for nausea, all patients received anti-emetics. The treatment may have confounded the results because the number of patients experiencing severe nausea was low in this sample. However, this is in line with research into prediction of CIN (Meissner et al., 2019; Molassiotis et al., 2013) and clinical trials for CIN (Navari & Aapro, 2016), where for ethical reasons some degree of anti-emetics and/or "rescue" medications are given (they are not withheld for research purposes). Further exploration in patient groups who experience high levels of nausea would strengthen understanding of pretreatment influences on nausea severity.

Nonetheless, the sample size was adequate and allowed for a diagnostically and demographically homogenous group. For example, all participants were women being treated with chemotherapy (cycle 1) for breast cancer, for the first time (chemotherapy-naïve). This reduced the number of potential confounding variables, which could have interfered with the findings. Furthermore, all of the patients had previously been pregnant, which allowed for a more comprehensive investigation of the impact of morning sickness, separate from motion sickness and current nausea levels. Future research into whether demographic differences impact patients perceived susceptibility and response expectancies would provide a more nuanced understanding of these psychological predictors.

Taken together, based on this preliminary investigation, patients' perceived nausea susceptibility and response expectancies for nausea are separate constructs. Patients' perceived nausea susceptibility is an additional important variable to measure before treatment as it captures patients' previous experiences and helps predict the severity of subsequent nausea experiences.

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CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception, design, data acquisition, data analysis, drafting and/or revision of the manuscript. All authors have approved publication of the manuscript.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

Aldaz, B. E., Treharne, G. J., Knight, R. G., Conner, T. S., & Perez, D. (2018). 'It gets into your head as well as your body': The experiences of patients with cancer during oncology treatment with curative intent. *Journal of Health Psychology*, *23*, 3–16. https://doi.org/10.1177/1359105316671185

Browne, M. W. (1984). Asymptotically distribution-free methods for the analysis of covariance structures. *British Journal of Mathematical and Statistical Psychology*, *37*, 62–83. https://doi.org/10.1111/j.2044-8317.1984.tb00789.x

Byrne, B. M. (2010). *Structural Equation Modeling With AMOS: Basic Concepts, Applications, and Programming*. New York: Routledge.

Chan, A., Kim, H.-K., Hsieh, R. K., Yu, S., de Lima Lopex, G. J., Su, W. C., Baños, A., Bhatia, S., Burke, T. A., & Keefe, D. M. (2015). Incidence and predictors of anticipatory nausea and vomiting in Asia Pacific clinical practice—A longitudinal analysis. *Supportive Care in Cancer*, *23*, 283–291. https://doi.org/10.1007/s00520-014-2375-0

Cobeanu, O., & David, D. (2018). Alleviation of side effects and distress in breast Cancer patients by cognitive-behavioral interventions: A systematic review and meta-analysis. *Journal of Clinical Psychology in Medical Settings*, *25*, 335–355. https://doi.org/10.1007/s10880-017-9526-7

Cohen, J. (1988). Statistical Power Analyses for the Behavioral Sciences (2nd ed). *New Jersey: Lawrence Erlbaum Associates.*, *23*, 283–291. https://doi.org/10.1007/s00520-014-2375-0

Colagiuri, B., & Zachariae, R. (2010). Patient expectancy and post-chemotherapy nausea: A meta-analysis. *Annals of Behavioral Medicine*, *40*, 3–14. https://doi.org/10.1007/s12160-010-9186-4

Daniels, S. (2015). Cognitive behavior therapy for patients with Cancer. *Journal of the Advanced Practitioner in Oncology*, *6*, 54–56.

Devlin, E. J., Denson, L. A., & Whitford, H. S. (2017). Cancer treatment side effects: A meta-analysis of the relationship between response expectancies and experience. *Journal of Pain and Symptom Management*, *54*, 245–258.e2. https://doi.org/10.1016/j.jpainsymman.2017.03.017

Gaskin, J., & Lim, J. (2018). IndirectEffects, AMOS Plugin. In: StatWiki Gs (ed).

Hesketh, P. J., Grunberg, S. M., Gralla, R. J., Warr, D. G., Roila, F., de Wit, R., Chawla, S. P., Carides, A. D., Ianus, J., Elmer, M. E., Evans, J. K., Beck, K., Reines, S., & Horgan, K. J. (2003). The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: A multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—The Aprepitant protocol 052 study group. *Journal of Clinical Oncology*, *21*, 4112–4119. https://doi.org/10.1200/JCO.2003.01.095

Hickok, J. T., Roscoe, J. A., Morrow, G. R., Mustian, K., Okunieff, P., & Bole, C. W. (2005). Frequency, severity, clinical course, and correlates of fatigue in 372 patients during 5 weeks of radiotherapy for cancer. *Cancer*, *104*, 1772–1778. https://doi.org/10.1002/cncr.21364

Hofman, M., Morrow, G. R., Roscoe, J. A., Hickok, J. T., Mustian, K. M., Moore, D. F., Wade, J. L., & Fitch, T. R. (2004). Cancer patients' expectations of experiencing treatment-related side effects. *Cancer*, *101*, 851–857. https://doi.org/10.1002/cncr.20423

Kamen, C., Tejani, M. A., Chandwani, K., Janelsins, M., Peoples, A. R., Roscoe, J. A., & Morrow, G. R. (2014). Anticipatory nausea and vomiting due to chemotherapy. *European Journal of Pharmacology*, *722*, 172–179. https://doi.org/10.1016/j.ejphar.2013.09.071

Kirsch, I. (1985). Response expectancy as a determinant of experience and behavior. *American Psychologist*, *40*, 1189–1202. https://doi.org/10.1037/0003-066X.40.11.1189

Kottschade, L., Novotny, P., Lyss, A., Mazurczak, M., Loprinzi, C., & Barton, D. (2016). Chemotherapy-induced nausea and vomiting: incidence and characteristics of persistent symptoms and future directions NCCTG N08C3 (Alliance). *Supportive Care in Cancer*, *24*, 2661–2667. https://doi.org/10.1007/s00520-016-3080-y

Lorusso, D., Bria, E., Costantini, A., Di Maio, M., Rosti, G., & Mancuso, A. (2016). Patients' perception of chemotherapy side effects: Expectations, doctor–patient communication and impact on quality of life—An Italian survey. *European Journal of Cancer Care*, *26*, e12618. https://doi.org/10.1111/ecc.12618

Meissner, K., Talsky, N., Olliges, E., Jacob, C., Stotzer, C. S., Salat, C., Braun, M., & Flondor, R. (2019). Individual factors contributing to nausea in first-time chemotherapy patients: A prospective cohort study. *Frontiers in Pharmacology*, *10*, 410. https://doi.org/10.3389/fphar.2019.00410

Molassiotis, A., Aapro, M., Dicato, M., Gascon, P., Novoa, S. A., Isambert, N., Burke, T. A., Gu, A., & Roila, F. (2014). Evaluation of risk factors predicting chemotherapy-related nausea and vomiting: Results from a European prospective observational study. *Journal of Pain and Symptom Management*, *47*, 839–848.e4. https://doi.org/10.1016/j.jpainsymman.2013.06.012

Molassiotis, A., Farrell, C., Bourne, K., Brearley, S. G., & Pilling, M. (2012). An exploratory study to clarify the cluster of symptoms predictive of chemotherapy-related nausea using random forest modeling. *Journal of Pain and Symptom Management*, *44*, 692–703. https://doi.org/10.1016/j.jpainsymman.2011.11.003

Molassiotis, A., Stamataki, Z., & Kontopantelis, E. (2013). Development and preliminary validation of a risk prediction model for chemotherapy-related nausea and vomiting. *Supportive Care in Cancer*, *21*, 2759–2767. https://doi.org/10.1007/s00520-013-1843-2

Molassiotis, A., Stricker, C., Eaby, B., Velders, L., & Coventry, P. (2008). Understanding the concept of chemotherapy-related nausea: The patient experience. *European Journal of Cancer Care*, *17*, 444–453. https://doi.org/10.1111/j.1365-2354.2007.00872.x

Montfort, K. V., Mooijaart, A., & Meijerink, F. (2009). Estimating structural equation models with non-normal variables by using transformations. *Statistica Neerlandica*, *63*, 213–226. https://doi.org/10.1111/j.1467-9574.2009.00420.x

Montgomery, G. H., & Bovbjerg, D. H. (2003). Expectations of chemotherapy-related nausea: Emotional and experiential predictors. *Annals of Behavioral Medicine*, *25*, 48–54. https://doi.org/10.1207/S15324796ABM2501_07

Montgomery, G. H., & Bovbjerg, D. H. (2004). Presurgery distress and specific response expectancies predict postsurgery outcomes in surgery patients confronting breast cancer. *Health Psychology*, *23*, 381–387. https://doi.org/10.1037/0278-6133.23.4.381

Morrow, G. R. (1985). The effect of a susceptibility to motion sickness on the side effects of cancer chemotherapy. *Cancer*, *55*, 2766–2770. https://doi.org/10.1002/1097-0142(19850615)55:12<2766::aid-cncr2820551207>3.0.co;2-7

Morrow, G. R., Roscoe, J. A., Hickok, J. T., Andrews, P. R., & Matteson, S. (2002). Nausea and emesis: Evidence for a biobehavioral perspective. *Supportive Care in Cancer*, *10*, 96–105. https://doi.org/10.1007/s005200100294

Navari, R. M., & Aapro, M. (2016). Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting. *New England Journal of Medicine*, *374*, 1356–1367. https://doi.org/10.1056/NEJMra1515442

Nevitt, J., & Hancock, G. R. (2001). Performance of bootstrapping approaches to model test statistics and parameter standard error estimation in structural equation modeling. *Structural Equation Modeling: A Multidisciplinary Journal*, *8*, 353–377. https://doi.org/10.1207/S15328007SEM0803_2

Olver, I. N., Eliott, J. A., & Koczwara, B. (2014). A qualitative study investigating chemotherapy-induced nausea as a symptom cluster. *Supportive Care in Cancer*, *22*, 2749–2756. https://doi.org/10.1007/s00520-014-2276-2

Peoples, A. R., Roscoe, J. A., Block, R. C., Heckler, C. E., Ryan, J. L., Mustian, K. M., Janelsins, M. C., Peppone, L. J., Moore, D. F. Jr., Coles, C., Hoelzer, K. L., Morrow, G. R., & Dozier, A. M. (2017). Nausea and disturbed sleep as predictors of cancer-related fatigue in breast cancer patients: A multicenter NCORP study. *Supportive Care in Cancer*, *25*, 1271–1278. https://doi.org/10.1007/s00520-016-3520-8

Petrie, K. J., & Rief, W. (2019). Psychobiological mechanisms of placebo and nocebo effects: Pathways to improve treatments and reduce side effects. *Annual Review of Psychology*, *70*, 599–625. https://doi.org/10.1146/annurev-psych-010418-102907

Piaget, J. (1954). *The Construction of Reality in the Child*. New York: Basic Books. https://doi.org/10.1037/11168-000

Redd, W. H., Montgomery, G. H., & DuHamel, K. N. (2001). Behavioral intervention for cancer treatment side effects. *Journal of the National Cancer Institute*, *93*, 810–823. https://doi.org/10.1093/jnci/93.11.810

Roila, F., Herrstedt, J., Aapro, M., Gralla, R. J., Einhorn, L. H., Ballatori, E., … Warr, D. (2010). Guideline update for MASCC and ESMO in the prevention of chemotherapy-and radiotherapy-induced nausea and vomiting: Results of the Perugia consensus conference. *Annals of Oncology*, *21*, v232–v243. https://doi.org/10.1093/annonc/mdq194

Roila, F., Molassiotis, A., Herrstedt, J., Aapro, M., Gralla, R. J., Bruera, E., Clark-Snow, R. A., Dupuis, L. L., Einhorn, L. H., Feyer, P., Hesketh, P. J., Jordan, K., Olver, I., Rapoport, B. L., Roscoe, J., Ruhlmann, C. H., Walsh, D., Warr, D., & van der Wetering, M. (2016). 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Annals of Oncology*, *27*, v119–v133. https://doi.org/10.1093/annonc/mdw270

Roscoe, J. A., Bushunow, P., Morrow, G. R., Hickok, J. T., Kuebler, P. J., Jacobs, A., & Banerjee, T. K. (2004). Patient expectation is a strong predictor of severe nausea after chemotherapy: A University of Rochester Community Clinical Oncology Program study of patients with breast carcinoma. *Cancer*, *101*, 2701–2708. https://doi.org/10.1002/cncr.20718

Roscoe, J. A., Heckler, C. E., Morrow, G. R., Mohile, S. G., Dakhil, S. R., Wade, J. L., & Kuebler, J. P. (2012). Prevention of delayed nausea: A University of Rochester Cancer Center Community Clinical Oncology Program study of patients receiving chemotherapy. *Journal of Clinical Oncology*, *30*, 3389–3395. https://doi.org/10.1200/JCO.2011.39.8123

Roscoe, J. A., Morrow, G. R., Colagiuri, B., Heckler, C. E., Pudlo, B. D., Colman, L., Hoelzer, K., & Jacobs, A. (2010). Insight in the prediction of chemotherapy-induced nausea. *Supportive Care in Cancer*, *18*, 869–876. https://doi.org/10.1007/s00520-009-0723-2

Russo, S., Cinausero, M., Gerratana, L., Bozza, C., Iacono, D., Driol, P., Deroma, L., Sottile, R., Fasola, G., & Puglisi, F. (2014). Factors affecting patient's perception of anticancer treatments side-effects: An observational study. *Expert Opinion on Drug Safety*, *13*, 139–150. https://doi.org/10.1517/14740338.2013.830710

Schermelleh-Engel, K., Moosbrugger, H., & Müller, H. (2003). Evaluating the fit of structural equation models: Tests of significance and descriptive goodness-of-fit measures. *Methods of Psychological Research*, *8*, 23–74.

Shelke, A. R., Roscoe, J. A., Morrow, G. R., Colman, L. K., Banerjee, T. K., & Kirshner, J. J. (2008). Effect of a nausea expectancy manipulation on chemotherapy-induced nausea: A university of Rochester cancer center community clinical oncology program study. *Journal of Pain and Symptom Management*, *35*, 381–387. https://doi.org/10.1016/j.jpainsymman.2007.05.008

Singh, K. P., Kober, K. M., Dhruva, A. A., Flowers, E., Paul, S. M., Hammer, M. J., Cartwright, F., Wright, F., Conley, Y. P., Levine, J. D., & Miaskowski, C. (2018). Risk factors associated with chemotherapy-induced nausea in the week before the next cycle and impact of nausea on quality of life outcomes. *Journal of Pain and Symptom Management*, *56*, 352–362. https://doi.org/10.1016/j.jpainsymman.2018.05.019

Sohl, S. J., Schnur, J. B., & Montgomery, G. H. (2009). A meta-analysis of the relationship between response expectancies and cancer treatment-related side effects. *Journal of Pain and Symptom Management*, *38*, 775–784. https://doi.org/10.1016/j.jpainsymman.2009.01.008

Tabachnick, B. G., & Fidell, L. S. (2013). *Using Multivariate Statistics*. Boston: Pearson.

Vandenberg, R. J. (2006). Introduction: Statistical and methodological myths and urban legends: Where, pray tell, did they get this idea? *Organizational Research Methods*, *9*, 194–201. https://doi.org/10.1177/1094428105285506

Warr, D. (2014). Prognostic factors for chemotherapy induced nausea and vomiting. *European Journal of Pharmacology*, *722*, 192–196. https://doi.org/10.1016/j.ejphar.2013.10.015

West, S. G., Finch, J. F., & Curran, P. J. (1995). *Structural Equations with Non-Normal Variables: Problems and Remedies*. Newbury Park, CA: Sage.

Yuan, K.-H., Bentler, P. M., & Zhang, W. (2005). The effect of skewness and kurtosis on mean and covariance structure analysis: The univariate case and its multivariate implication. *Sociological Methods & Research*, *34*(2), 240–258. https://doi.org/10.1177/0049124105280200

Zhu, W. (1997). Making bootstrap statistical inferences: A tutorial. *Research Quarterly for Exercise and Sport*, *68*, 44–55. https://doi.org/10.1080/02701367.1997.10608865

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