

Association Between Serotonin Transport Polymorphisms and Postdischarge Nausea and Vomiting in Women Following Breast Cancer Surgery

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Nausea and vomiting are two of the most common and debilitating side effects following surgery. About half of all patients experience postoperative nausea and vomiting (PONV) during the 24 hours following surgery, or postdischarge nausea and vomiting (PDNV) when they return home following surgery (Cruthirds, Sims, & Louis, 2013). About 80% of patients are considered high-risk, particularly women nonsmokers with a positive history of PONV and who use opioids for relief of pain (Apfel, Korttila, et al., 2004). Opioids given for postoperative pain often are considered the primary cause of PONV (Watcha & White, 1992). Women with breast cancer undergoing mastectomy are particularly high-risk for PONV, with a reported incidence rate of 60%–80% in patients receiving no antiemetic medications (Lee et al., 2008).

PONV and PDNV can lead to aspiration; wound dehiscence; bleeding; hematoma; dehydration; electrolyte imbalance; exhaustion; and delayed mobilization, recovery, and ability to begin oral medications (Jolley, 2001; Miaskowski, 2009). PONV is one of the strongest predictors of prolonged hospital stays and unanticipated admission for outpatients following breast cancer surgery (Marla & Stallard, 2009), accounting for millions of dollars of healthcare costs annually (Apfel, Kranke, & Eberhart, 2004). For some women with breast cancer, PONV and PDNV can be more problematic than pain. In scenario studies, when surgical patients were given limited amounts of money to hypothetically “buy away” potential postoperative complications, nausea and vomiting were chosen before pain (Kerger et al., 2007; Macario, Weinger, Carney, & Kim, 1999). Patients with nausea also reported greater impairment in quality of life and psychological distress (Pirri et al., 2013).

The American Society of Clinical Oncology indicated that the goal for managing treatment-induced nausea and vomiting (from surgery, chemotherapy, or radiation) should be complete antiemetic response (Basch et al.,

Purpose/Objectives: To examine the association of the serotonin transport gene and postdischarge nausea and vomiting (PDNV) in women following breast cancer surgery.

Design: A cross-sectional study.

Setting: A comprehensive cancer center in Pittsburgh, PA.

Sample: 80 post-menopausal women treated surgically for early-stage breast cancer.

Methods: Data were collected using standardized instruments after surgery but before the initiation of chemotherapy. Blood or saliva were used for DNA extraction and analyzed following standardized protocols. Data were analyzed using descriptive statistics and logistic regression.

Main Research Variables: Serotonin transport gene (*SLC6A4*), nausea, vomiting, pain, and anxiety.

Findings: Women who inherited the *L_A/L_A* genotypes were at greater risk for nausea and vomiting when compared to women who carried any other combination of genotypes. Twenty-one percent of women reported nausea and vomiting an average of one month following surgery and prior to initiation of adjuvant therapy. Those women who experienced PDNV reported significantly higher anxiety and pain scores.

Conclusions: Findings of this study suggest that variability in the genotypes of the serotonin transport gene may help to explain the variability in PDNV in women following breast cancer surgery and why 20%–30% of patients do not respond to antiemetic medications.

Implications for Nursing: Nurses need to be aware that women who do not experience postoperative nausea and vomiting following surgery for breast cancer continue to be at risk for PDNV long after they have been discharged from the hospital, and this frequently is accompanied by pain and anxiety.

Key Words: nausea/vomiting; genetics; breast cancer

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2011). However, even when the best available antiemetic medications are applied correctly, that goal has remained elusive (Gan et al., 2007). Documented risk factors for PDNV differ slightly than those for PONV, and include

younger age, history of PONV in the postanesthesia care unit, female gender, and use of opioids for pain (Apfel, Philip, et al., 2012). However, female gender is a better independent predictor than history of PONV (Lee et al., 2008), and nonsmoking has not been found to influence PDNV (Apfel, Philip, et al., 2012). The increased risk for PDNV in female patients is not yet understood, but this increased risk persists throughout life, even following menopause (Apfel, Kranke, et al., 2004). In addition, patients scheduled for breast cancer surgery frequently experience high levels of distress, which also may contribute to PONV and PDNV (Montgomery, Schnur, Erblich, Diefenbach, & Bovbjerg, 2010). The significant impact of post-treatment nausea on quality of life in patients with cancer has been reported both as a single symptom and as a symptom cluster with vomiting and appetite loss. Patients with nausea had significantly higher quality-of-life impairment and psychological distress, as well as greater cancer distress (Pirri et al., 2013). To develop effective strategies for the prevention and management of PONV and PDNV in women following breast cancer, understanding the physiologic basis of these problems is important.

Physiology of Nausea and Vomiting

At the core of the physiology of PONV and PDNV is the vomiting center, a nerve center located in the reticular formation of the brain stem and believed to be the coordinator of the vomiting process (Melton, Klein, & Gan, 2011). After surgery, the vomiting center may be stimulated directly by the vestibular apparatus (e.g., sudden motion) or the cerebral cortex (e.g., anxiety), or indirectly when afferent pathways are stimulated by specific neurotransmitters (dopamine, serotonin, acetylcholine, mu-opioid, and histamine) that activate the chemoreceptor trigger zone (CTZ) (Cruthirds et al., 2013). The CTZ is located in the area postrema, anatomically close to the vomiting center but outside of the blood-brain barrier. Because it rests outside the blood-brain barrier, neurotransmitter receptors located in the CTZ may be activated by medications and toxic agents present in the blood and cerebrospinal fluid (Watcha & White, 1992). Dopamine and serotonin usually are considered the most important neurotransmitters involved in nausea and vomiting (Wickham, 2004). Receptors respond to serotonin released from the gastrointestinal tract because of decreased motility from opioids for postoperative pain, immobility associated with surgery, or blood-borne emetics such as opioids and anesthetic agents (Gan, 2006). Most antiemetic medications act as antagonists and block binding at neurotransmitter-receptor sites, which blocks the transmission of the nausea and vomiting signal. Ondansetron, a serotonin antagonist, often is the first-choice medication for

PONV (Singhal, Kannan, & Gota, 2012); however, the average response rate to this and other antiemetic medications varies between 55%–82% (Apfel, Heidrich, et al., 2012). Variability within the genes of the serotonin pathway may explain, at least in part, the variability in susceptibility to PONV and PDNV, as well as the differences observed in response to antiemetic medications.

Serotonin and Postoperative Nausea and Vomiting

Few studies have examined the variability of genes in the serotonin pathway for association with nausea and vomiting. Rueffert et al. (2009) examined the variability in 19 single nucleotide polymorphisms (SNPs) from serotonin receptor genes, 5-HT_{3A} and 5-HT_{3A}, and postoperative vomiting (POV). When comparing 95 postoperative general surgical patients who experienced POV with 94 control patients who did not experience POV, Rueffert et al. (2009) found three polymorphisms (*HT3A*: c1377A > G; *HT3B*: c5+201_+202delCA; *HT3B*: c6-137C>T) that independently influenced the incidence of POV. Rueffert et al. (2009) also observed a significantly higher risk for POV (odds ratio [OR] = 2.972, *p* = 0.003) in patients with the *HT3A*: c1377A > G polymorphism. The other two polymorphisms were associated with a decreased risk for POV (Rueffert et al., 2009). Laugsand et al. (2011) did not look at PONV, but examined genetic factors associated with nausea and vomiting in patients with cancer receiving opioids. They also found that SNPs within the *HT3B* gene were associated with nausea and vomiting. When genotyping 1,579 patients who were taking opioids for cancer-related pain, Laugsand et al. (2011) found that participants who inherited the G allele of rs1176744 had less intense nausea. These findings are consistent with studies that looked at the association between genes of the serotonin pathway and chemotherapy-induced nausea and vomiting (CINV) (Kaiser et al., 2004; Tremblay et al., 2003). The serotonin transport gene is another gene in this pathway that has been evaluated extensively for other phenotypes, but has not been evaluated for PONV.

Serotonin Transport Gene

Serotonin transport is coded by a single gene, *SLC6A4*, and is a critical element for regulating the serotonin system. The serotonin transport system is responsible for the reuptake of serotonin from neuronal synapses back into the presynaptic neuron (Kosek, Jensen, Lonsdorf, Schalling, & Ingvar, 2009). Several polymorphisms located in the promoter region of the *SLC6A4* influence serotonin transport expression. One is a functional polymorphism known as 5-HTTLPR (serotonin-transporter-linked polymorphic region) characterized by individuals carrying either long (L) or short (S) alleles. The L allele is associated with increased serotonin transport activity,

and the S allele is associated with decreased serotonin transport activity. *SLC6A4* also displays an SNP, rs25531(A) > (G), from the same region that further modulates the effect of the 5-HTTLPR on serotonin expression (Kosek et al., 2009). Although rs25531 is genotyped separately, the two polymorphisms are studied together (Wendland, Martin, Kruse, Lesch, & Murphy, 2006). Individuals with the G allele for rs25531 will have decreased serotonin transport expression, even if they carry the 5-HTTLPR long allele (L_A) (Hu et al., 2006). In-vitro studies indicated that variability in *SLC6A4* can result in a 40-fold effect in serotonin transport (Murphy & Moya, 2011).

Why 20%–30% of women continue to experience PONV or PDNV following breast cancer surgery, even with multiple antiemetic medications, is not clear (Lee et al., 2008). However, understanding genetic variability in the serotonin transport gene may help to explain the variability between PONV and PDNV. To the authors' knowledge, no previous study has addressed the possible influence of *SLC6A4* polymorphisms on the symptoms of nausea and vomiting. Therefore, the purpose of the preliminary study was to explore the association between serotonin transport gene polymorphisms and PDNV in women after breast cancer surgery, but prior to initiation of adjuvant therapy.

Methods

Design

The preliminary study employed a cross-sectional design using samples and data collected from a larger, longitudinal study examining the effect of anastrozole on cognitive function in women with early-stage breast cancer. A second study extended the original investigation and examined potential genetic predictors of cognitive function in the same population. Genetic samples and behavioral assessments from these studies were used for analyzing the serotonin transport gene polymorphisms and PDNV.

Sample

Participants were recruited from the Comprehensive Breast Program at the University of Pittsburgh Cancer Institute after institutional review board approval was secured and informed consent was obtained from every participant. Inclusion criteria included participants diagnosed with stage I, II, or IIIA breast cancer, aged 18–75 years, eligible for hormonal therapy, and able to speak and read English with completion of at least eight years of formal education. Exclusion criteria included evidence

Table 1. Sample Characteristics Comparing Women Who Experienced PDNV With Those Who Did Not

Characteristic	Total (N = 80)		PDNV (n = 17)		No PDNV (n = 63)	
	n		n		n	
Nonsmoker	66		12		54	
Characteristic	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Age (years)	59.63	5.74	58.8	5.7	59.8	5.7
Days postoperative	29.4	15.8	30.64	12.8	29.08	16.6
BPI average pain ^{a,*}	1.91	2.15	3.29	2.5	1.52	1.88
BPI worst pain ^{a,*}	3	3.1	4.71	3.35	2.56	2.93
POMS ^{b,*}	8.78	5.4	11.47	7.7	8.06	4.3

*p = 0.02

^a0–10 scale

^b0–24 scale

BPI—Brief Pain Inventory; PDNV—postdischarge nausea and vomiting; POMS—Profile of Mood States

of distant metastases, prior diagnosis of invasive cancer or neurologic disease, and hospitalization for psychiatric illness in the two years prior. Participants who indicated they were willing to be recontacted were asked via letter to participate in the second study, which included the collection of blood or saliva samples for genomic evaluation. The current study represents the first 80 participants from the larger study who provided samples for evaluation.

Instruments

Assessment occurred after surgery, but before the initiation of systemic adjuvant therapy. Nausea and vomiting were measured by self-report using two items from the **Breast Cancer Prevention Trial (BCPT) Symptom Checklist** (Stanton, Bernaards, & Ganz, 2005). Participants were instructed to report symptoms that bothered them during the four weeks prior on a five-point Likert-type scale, from 0 (not at all) to 4 (extremely). Cronbach alphas for BCPT subscale scores have been reported between 0.43–0.83 for women with breast cancer (Terhorst, Blair-Belanaky, Moore, & Bender, 2011). The scores also related significantly to scores on the SF-36 physical health and mental health subscales (p = 0.05–0.001) (Alfano et al., 2006).

Pain was measured using the severity component of the **Brief Pain Inventory–Short Form (BPI-SF)**, an 11-item numerical scale on which participants were asked to report from 0 (no pain) to 10 (pain as bad as can be imagined) for the 24 hours prior (Cleeland, 2006; Cleeland, Ladinsky, Serlin, & Nguyen, 1988). For the current study, the authors used the participants' worst pain experienced and average pain experienced during the 24 hours prior. The BPI-SF has been found to have good

internal consistency for pain severity (Cronbach alpha = 0.88) (Kapstad, Rokne, & Stavem, 2010).

Anxiety was measured using the tension-anxiety subscale of the short-form version of **Profile of Mood States (POMS-SF)** (McNair, Lorr, & Droppleman, 1992). The tension-anxiety subscale has six items, which are rated on a Likert-type scale ranging from 0 (not at all) to 4 (extremely). The score is the sum of responses for the six items. Internal consistency was 0.92, and test-retest reliability was 0.7 in 1,000 psychiatric outpatients. This scale has demonstrated validity and reliability in women diagnosed with breast cancer (Lerman & Schwartz, 1993), and has reported excellent internal consistency (Cronbach alpha = 0.91) (Montgomery, Schnur, Erbllich, Diefenbach, & Bovbjerg, 2010).

Genotyping for the Serotonin Transporter Polymorphisms

Using Oragene® collection kits, blood and saliva samples were taken from participants and used for DNA extraction using a simple salting-out procedure provided by the manufacturer. The *SLC6A4* promoter region polymorphisms (5-HTTLPR and rs25531) were genotyped using polymerase chain reaction (PCR) with restriction fragment length polymorphism digestion. PCR conditions included initial denaturation (94°C, 4 minutes); 35 cycles consisting of 94°C (30 seconds), 69°C (90 seconds), and 72°C (1 minute); and final extension step (72°C, 10 minutes). The PCR products were electrophoresed through a 3% agarose gel stained with ethidium bromide to genotype the 5-HTTLPR polymorphism. For genotyping the rs25531 polymorphism, the PCR products were digested with 10 units of MspI overnight at 37°C and resolved using 3% agarose gel.

Statistical Analysis

Descriptive statistics were employed to describe the sample and assess for underlying statistical assumptions. Allele frequencies were calculated for all 80 participants. Genotypes were grouped based on predicted

serotonin activity, with participants who carried two *L_A* alleles (high serotonin activity) compared to all others. Hardy-Weinberg equilibrium was assessed using chi-square goodness of fit analysis. Pain and anxiety scores from the two groups were compared with independent samples *t* tests. Contingency tables with the estimations of OR with 95% confidence interval [CI] were computed to compare the prevalence of PDNV between genotypes. Binary logistic regression was used to determine contribution of genotype group to PDNV status. The level of significance for all analyses was set at *p* = 0.05 or less. All data analyses were performed using SPSS®, version 19.01.

Results

The study sample characteristics are displayed in Table 1. The sample consisted of 80 women with early-stage breast cancer. Seventy-eight (98%) were Caucasian, 66 (83%) were nonsmokers, and only eight (10%) reported current use of opioids for pain at baseline testing for the parent study, which occurred an average of 29 days (range = 11–61) following surgery. Seventeen (21%) of the women reported the presence of nausea and vomiting at baseline. Using the BPI, the mean worst pain score was 3.01 (SD = 3.11), and the average pain score was 1.91 (SD = 2.15). The mean anxiety score for the entire group was 8.78 (SD = 5.4); however, women who reported nausea and vomiting reported a higher anxiety score ($\bar{X}$ = 11.47, SD = 7.7) compared to women who did not experience nausea and vomiting.

The genotype frequencies for the *SLC6A4* polymorphisms are presented in Table 2. Twenty-seven (34%) of the women inherited the *L_A/L_A* genotype, all others had at least one G allele from rs25331 or an S allele at HTTLPR. Seventeen women (21%) inherited the S/S alleles for HTTLPR. This distribution is consistent with distributions from other research using Caucasian populations (Murphy & Moya, 2011). Allele distributions for the rs25531 polymorphisms were in Hardy-Weinberg equilibrium (χ^2 = 0.49, *df* = 1, *p* = 0.5).

When comparing women who inherited at least one S or G allele to women who carried the *L_A/L_A* alleles, the authors found the women carrying *L_A/L_A* were at higher risk for nausea and vomiting (unadjusted OR = 2.815, 95% CI [0.616, 12.87], *p* = 0.182). Of the women with an A > G substitution at rs25331, only one woman who carried the G allele experienced nausea and vomiting. But when the same women were compared for reported pain, the group with at least one G allele reported significantly higher worst pain scores (*p* < 0.001). The group that experienced PDNV also reported significantly higher worst pain scores (*t* = -2.602, *df* = 78, *p* = 0.011) than women who did not report PDNV. A significant difference in anxiety also existed, with women who reported

Table 2. Frequency of *SLC6A4* Genotypes and Association With Postdischarge Nausea and Vomiting (PDNV) in Patients With Breast Cancer

Genotype	Total (N = 80)	PDNV (n = 17)	No PDNV (n = 63)
<i>L_A/L_A</i>	27	8	19
<i>L_A/L_G</i>	8	2	6
<i>S_A/L_A</i>	25	3	22
<i>S_A/L_G</i>	3	1	2
<i>S_A/S_A</i>	17	3	14

PDNV reporting greater levels of anxiety ($t = -2.385$, $df = 78$, $p = 0.02$).

Regression analysis results are shown in Table 3. Smoking was not associated with the nausea and vomiting experienced by women in this study. Eight (10%) participants in the current study reported taking opioids for pain one month following surgery, but only two of these women reported nausea or vomiting. The L_A/L_A polymorphism was statistically significant as a predictor of PONV ($p = 0.039$), with the adjusted OR more than four times greater than all other combinations. Only the average pain measure was included in the regression model because the average pain and worst pain measures were closely correlated ($r = 0.896$, $p < 0.001$). The average pain score was a significant predictor of nausea and vomiting ($p = 0.026$).

Discussion

The primary goal for the current study was to determine whether the serotonin transport gene polymorphisms, 5-HTTLPR and rs25331, were associated with nausea and vomiting in women following breast cancer surgery, but prior to adjuvant therapy. The authors found that women who inherited the L_A/L_A genotypes were at greater risk for nausea and vomiting when compared to women who carried any other combination of genotypes for these two polymorphisms, suggesting that decreased serotonin transport gene activity may be protective for PDNV. Other studies have suggested an association of variability in the 5-HTTLPR and rs25331 polymorphisms with emotional, endocrine, and personality characteristics, as well as other diseases, such as migraine and interstitial bowel syndrome (Murphy & Moya, 2011). Researchers also have reported on the association between genes of the serotonin pathway and CINV, with several studies implicating variability in the serotonin receptor gene but not examining its role (Kaiser et al., 2004; Tremblay et al., 2003). Laugsand et al. (2011) also focused on genotypes of the serotonin receptor gene when studying patients who took opioids for cancer-related pain.

Twenty-one percent ($n = 17$) of participants reported nausea and vomiting an average of one month following surgery, but prior to initiation of adjuvant therapy. Most research regarding PONV and PDNV follow patients only a short time after discharge. In most studies, PDNV has been defined as nausea or vomiting that occurs after discharge from the hospital and for the first 48 hours following surgery (Stewart, 2013). PDNV has been found to be more problematic than PONV in nononcology populations, with higher incidence reported (Apfel, Philip, et al., 2012; Wesmiller et al., 2012). Although most research has focused on the symptoms of nausea and vomiting caused by chemotherapy or

Table 3. Binary Logistic Regression for PDNV

Factor ^a	p	Odds Ratio	95% CI
5-HTTLPR	0.039	4.161	[1.075, 16.099]
Anxiety (POMS)	0.383	0.051	[0.94, 1.175]
BPI average	0.026	1.436	[1.044, 1.975]
Opioids for pain	0.852	1.188	[0.194, 7.265]
Smoking status	0.394	1.847	[0.45, 7.575]

^a $df = 1$

BPI—Brief Pain Inventory; CI—confidence interval; PDNV—post-discharge nausea and vomiting; POMS—Profile of Mood States

in advanced cancer (Gupta, Davis, Legrand, Walsh, & Lagman, 2013), the current results support additional examination of nausea and vomiting at the studied time point, as well as at frequent data collection points across the trajectory of the breast cancer experience.

In the current study, women who experienced nausea and vomiting also reported significantly higher levels of anxiety when compared to the women who did not report any nausea or vomiting. Distress has been related to PONV during the preoperative period in women with breast cancer, with results showing that preoperative distress strongly predicted postoperative complications such as nausea and vomiting (Montgomery et al., 2010; Watcha & White, 1992). Evidence also relates anxiety to CINV (Cohen, de Moor, Eisenberg, Ming, & Hu, 2007). Future research is needed to better understand the relationship between anxiety and PDNV.

The women in this study who experienced nausea and vomiting one month after surgery reported significantly higher pain levels compared to the women who did not report PDNV. Wesmiller et al. (2012) did not find that PONV influenced postoperative pain scores 48 hours after surgery in trauma patients. However, Chia et al. (2002) focused on the relationship between pain and PONV in 600 women following gynecologic surgery and found that women who experienced PONV had significantly higher pain scores ($p < 0.05$). They also reported that for participants still experiencing PONV three days postoperatively, pain was the main risk factor (Chia et al., 2002). Ongoing pain after surgery for breast cancer can continue long after the patient believes it should (Toftshagen, 2010), particularly with women who have had axillary nodes removed reporting pain even one year after surgery (Levangie & Drouin, 2009). Persistent clinical postoperative pain has been reported as a predictor for chronic pain following breast cancer surgery (Poleshuck et al., 2006). If PDNV prevents women from achieving effective pain relief in the postoperative period, other problems may develop such as immobility and lymphedema. This

Knowledge Translation

Understanding genetic predictors will lead to personalized medicine, improving the ability to prepare patients at greater risk for the symptoms of nausea and vomiting.

Persistent pain, anxiety, and nausea can continue to be a problem in women a month following breast cancer surgery.

Additional study of these symptoms as a symptom cluster is warranted.

underscores the importance of frequent monitoring and adequate assessment of postoperative pain and PDNV, and for research to elucidate the relationship between nausea and vomiting and pain that occurs following surgery. Additional work in this area may reveal that PDNV, anxiety, and pain are part of a more extensive symptom cluster.

In the current study, two known predictors of PONV, smoking and opioids for pain, were not significant predictors of PDNV. Only two of the women who reported nausea and vomiting were still taking opioids for pain; however, a closer examination of the results revealed that of those women who reported taking opioids for pain 29 days after surgery, six of the eight were in the L_A/L_A group. Researchers have noted that individuals who inherit the L_A/L_A alleles may be more sensitive to pain (Treister et al., 2011). In addition, Kosek et al. (2009) reported that the genotypes coding for low serotonin transport gene expression (carrying at least one S or G allele) were associated with improved analgesic effect from opioids (Kosek et al., 2009).

Smoking was not a predictor for PDNV in the current study, which is consistent with a report from Apfel, Philip, et al. (2012). One theory suggests that smoking prevents PONV because cigarette smoke enhances the enzyme activity of CYP1A2, a member of the CYP450 system involved in the metabolism of many anesthetic agents (Sweeney, 2002). Because these data were collected a month after surgery, the time since surgery and anesthesia may have been sufficient to mitigate the potential influence of cigarette smoking on PDNV.

Limitations

This preliminary study has several limitations. The sample size of 80 women is large enough to generate hypotheses for future research, but not large enough for generalizable findings. The results of the current study support the need for a larger, prospective study of nausea and vomiting in women who are recovering from breast cancer surgery. Because phenotype data were collected as baseline data for the larger study, variability occurred in the timing of the measures. Future research should explore other polymorphisms

within the genes of the serotonin pathway, particularly variability within the serotonin receptor genes and the association of nausea and vomiting following surgery in a larger sample. In addition, more work is needed to understand the relationship between anxiety, pain, and PDNV.

Nursing Implications

The results of the current study provide evidence that women who do not experience PONV while still in the hospital continue to be at risk for PDNV long after they have been discharged. Postdischarge patient education should include how to assess and treat these symptoms when they occur. Prescriptions for antiemetic medications should be provided for patients who are at high risk for PDNV. Patients should be assessed for anxiety and also should be instructed to understand that pain may continue for months after surgery.

Conclusion

The current authors have found that women who were in the L_A/L_A group (two high-expression alleles) were at greater risk for experiencing nausea and vomiting 14–61 days postoperatively, but before adjuvant therapy was administered. Overall, 21% of the women in the current sample experienced PDNV. If nausea and vomiting persist after surgery, women with breast cancer may be at greater risk for these symptoms once systemic adjuvant therapy begins. Additional research is needed to more closely examine the relationship between PONV and CINV. In addition, research is needed to increase understanding of the relationship between variability of *SLC6A4* and nausea and vomiting in women following breast cancer surgery. This research will serve as the basis for the development of strategies to prevent or reduce nausea and vomiting in women with breast cancer and to improve patient outcomes.

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References

- Alfano, C.M., McGregor, B.A., Kuniyuki, A., Reeve, B.B., Bowen, D.J., Baumgartner, K.B., . . . McTiernan, A. (2006). Psychometric properties of a tool for measuring hormone-related symptoms in breast cancer survivors. *Psycho-Oncology*, 15, 985–1000.
- Apfel, C.C., Heidrich, F.M., Jukar-Rao, S., Jalota, L., Hornuss, C., Whelan, R.P., . . . Cakmakaya, O.S. (2012). Evidence-based analysis of risk factors for postoperative nausea and vomiting. *British Journal of Anaesthesia*, 109, 742–753. doi:10.1093/bja/aes276
- Apfel, C.C., Korttila, K., Abdalla, M., Kerger, H., Turan, A., Vedder, I., . . . Roewer, N. (2004). A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *New England Journal of Medicine*, 350, 2441–2451.
- Apfel, C.C., Kranke, P., & Eberhart, L.H. (2004). Comparison of surgical site and patient's history with a simplified risk score for the prediction of postoperative nausea and vomiting. *Anaesthesia*, 59, 1078–1082.
- Apfel, C.C., Philip, B.K., Cakmakaya, O.S., Shilling, A., Shi, Y.Y., Leslie, J.B., . . . Kovac, A. (2012). Who is at risk for postdischarge nausea and vomiting after ambulatory surgery? *Anesthesiology*, 117, 475–486.
- Basch, E., Prestrud, A.A., Hesketh, P.J., Kris, M.G., Feyer, P.C., Somerfield, M.R., . . . Lyman, G.H. (2011). Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology*, 29, 4189–4198. doi:10.1200/JCO.2010.34.4614
- Chia, Y.Y., Kuo, M.C., Liu, K., Sun, G.C., Hsieh, S.W., & Chow, L.H. (2002). Does postoperative pain induce emesis? *Clinical Journal of Pain*, 18, 317–323.
- Cleeland, C.S. (2006). The measurement of pain from metastatic bone disease: Capturing the patient's experience. *Clinical Cancer Research*, 12 (Part 2), 6236s–6242s. doi:10.1158/1078-0432.CCR-06-0988
- Cleeland, C.S., Ladinsky, J.L., Serlin, R.C., & Nguyen, C.T. (1988). Multidimensional measurement of the cancer pain: Comparisons of U.S. and Vietnamese patients. *Journal of Pain and Symptom Management*, 3, 23–27.
- Cohen, L., de Moor, C.A., Eisenberg, P., Ming, E.E., & Hu, H. (2007). Chemotherapy-induced nausea and vomiting: Incidence and impact on patient quality of life at community oncology settings. *Supportive Care in Cancer*, 15, 497–503.
- Cruthirds, D., Sims, P.J., & Louis, P.J. (2013). Review and recommendations for the prevention, management, and treatment of postoperative and postdischarge nausea and vomiting. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*, 115, 601–611.
- Gan, T.J. (2006). Risk factors for postoperative nausea and vomiting. *Anesthesia and Analgesia*, 102, 1884–1898.
- Gan, T.J., Meyer, T.A., Apfel, C.C., Chung, F., Davis, P.J., Habib, A.S., . . . Watcha, M. (2007). Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesthesia and Analgesia*, 105, 1615–1628.
- Gupta, M., Davis, M., Legrand, S., Walsh, D., & Lagman, R. (2013). Nausea and vomiting in advanced cancer: The Cleveland Clinic protocol. *Journal of Support Oncology*, 11, 8–13. doi:10.1016/j.su.ponc.2012.10.002
- Hu, X., Lipsky, R., Zhu, G., Akhtar, L., Taubman, J., Greenberg, B., . . . Goldman, D. (2006). Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *American Journal of Human Genetics*, 78, 815–826. doi:10.1086/503850
- Jolley, S. (2001). Managing post-operative nausea and vomiting. *Nursing Standards*, 15, 47–52.
- Kaiser, R., Tremblay, P.B., Sezer, O., Possinger, K., Roots, I., & Brockmüller, J. (2004). Investigation of the association between 5-HT_{3A} receptor gene polymorphisms and efficiency of antiemetic treatment with 5-HT₃ receptor antagonists. *Pharmacogenetics*, 14, 271–278.
- Kapstad, H., Rokne, B., & Stavem, K. (2010). Psychometric properties of the Brief Pain Inventory among patients with osteoarthritis undergoing total hip replacement surgery. *Health and Quality of Life Outcomes*, 8, 148. doi:10.1186/1477-7525-8-148
- Kerger, H., Turan, A., Kredel, M., Stuckert, U., Alsip, N., Gan, T.J., & Apfel, C.C. (2007). Patients' willingness to pay for antiemetic treatment. *Acta Anaesthesiologica Scandinavica*, 51, 38–43.
- Kosek, E., Jensen, K., Lonsdorf, T., Schalling, M., & Ingvar, M. (2009). Genetic variation in the serotonin transporter gene (5-HTTLPR, rs25531) influences the analgesic response to the short acting opioid remifentanyl in humans. *Molecular Pain*, 5(37), 1–7. doi:10.1186/1744-8069-5-37
- Laugsand, E.A., Fladvad, T., Skorpen, F., Maltoni, M., Kaasa, S., Fayers, P., & Klepstad, P. (2011). Clinical and genetic factors associated with nausea and vomiting in cancer patients receiving opioids. *European Journal of Cancer*, 47, 1682–1691. doi:10.1016/j.ejca.2011.04.014
- Lee, H.J., Kwon, J.Y., Shin, S.W., Kim, C.H., Baek, S.H., Baik, S.W., . . . Kim, K.H. (2008). Preoperatively administered ramosetron oral disintegrating tablets for preventing nausea and vomiting associated with patient-controlled analgesia in breast cancer patients. *European Journal of Anaesthesiology*, 25, 756–762. doi:10.1017/S0265021508004262
- Lerman, C., & Schwartz, M. (1993). Adherence and psychological adjustment among women at high risk for breast cancer. *Breast Cancer Research and Treatment*, 28, 145–155.
- Levangie, P., & Drouin, J. (2009). Magnitude of late effects of breast cancer treatments on shoulder function: A systematic review. *Breast Cancer Research and Treatment*, 116, 1–15. doi:10.1007/s10549-008-0246-4
- Macario, A., Weinger, M., Carney, S., & Kim, A. (1999). Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anaesthesia and Analgesia*, 89, 652–658.
- Marla, S., & Stallard, S. (2009). Systematic review of day surgery for breast cancer. *International Journal of Surgery*, 7, 318–323. doi:10.1016/j.ijsu.2009.04.015
- McNair, D.M., Lorr, M., & Droppleman, L.F. (1992). *EdITS manual for the Profile of Mood States*. San Diego, CA: Educational and Industrial Testing Service.
- Melton, M.S., Klein, S.M., & Gan, T.J. (2011). Management of postdischarge nausea and vomiting after ambulatory surgery. *Current Opinion in Anesthesiology*, 24, 612–619. doi:10.1097/ACO.0b013e32834b9468
- Miaskowski, C. (2009). A review of the incidence, causes, consequences, and management of gastrointestinal effects associated with postoperative opioid administration. *Journal of Perianesthesia Nursing*, 24, 222–228. doi:10.1016/j.jopan.2009.05.095
- Montgomery, G.H., Schnur, J.B., Erblich, J., Diefenbach, M.A., & Bovbjerg, D.H. (2010). Presurgery psychological factors predict pain, nausea, and fatigue one week after breast cancer surgery. *Journal of Pain and Symptom Management*, 39, 1043–1052. doi:10.1016/j.jpain.symman.2009.11.318
- Murphy, D., & Moya, P. (2011). Human serotonin transporter gene (SLC6A4) variants: Their contributions to understanding pharmacogenomic and other functional GxG and GxE differences in health and disease. *Current Opinion in Pharmacology*, 11, 3–10. doi:10.1016/j.coph.2011.02.008
- Pirri, C., Bayliss, E., Trotter, J., Olver, I.N., Katris, P., Drummond, P., & Bennett, R. (2013). Nausea still the poor relation in antiemetic therapy? The impact on cancer patients' quality of life and psychological adjustment of nausea, vomiting, and appetite loss, individually and concurrently as part of a symptom cluster. *Supportive Care in Cancer*, 21, 735–748. doi:10.1007/s00520-012-1574-9
- Poleshuck, E.L., Katz, J., Andrus, C.H., Hogan, L.A., Jung, B.F., Kulick, D.I., & Dworkin, R.H. (2006). Risk factors for chronic pain following breast cancer surgery: A prospective study. *Journal of Pain*, 7, 626–634.
- Rueffert, H., Thieme, V., Wallenborn, J., Lemnitz, N., Bergmann, A., Rudolf, K., . . . Kaisers, U.X. (2009). Do variations in the 5-HT_{3A} and 5-HT_{3B} serotonin receptor genes (HTR3A and HTR3B) influence the occurrence of postoperative vomiting? *Anesthesiology and Analgesia*, 109, 1442–1447. doi:10.1213/ane.0b013e3181b2359b

- Singhal, A.K., Kannan, S., & Gota, V.S. (2012). 5HT₃ antagonists for prophylaxis of postoperative nausea and vomiting in breast surgery: A meta-analysis. *Journal of Postgraduate Medicine*, 58, 22–31.
- Stanton, A.L., Bernards, C.A., & Ganz, P.A. (2005). The BCPT symptom scales: A measure of physical symptoms for women diagnosed with or at risk for breast cancer. *Journal of the National Cancer Institute*, 97, 448–456. doi:10.1093/jnci/dji069
- Stewart, M.W. (2013). Research news: Postdischarge nausea and vomiting. *Journal of Perianesthesia Nursing*, 28, 40–42. doi:10.1016/j.jopan.2012.11.003.
- Sweeney, B.P. (2002). Why does smoking protect against PONV. *British Journal of Anaesthesia*, 89, 810–813.
- Terhorst, L., Blair-Belansky, H., Moore, P.J., & Bender, C. (2011). Evaluation of the psychometric properties of the BCPT Symptom Checklist with a sample of breast cancer patients before and after adjuvant therapy. *Psycho-Oncology*, 20, 961–968. doi:10.1002/pon.1806
- Tofthagen, C. (2010). Patient perceptions associated with chemotherapy-induced peripheral neuropathy [Online exclusive]. *Clinical Journal of Oncology Nursing*, 14, E22–E28. doi:10.1188/10.CJON.E22-E28
- Treister, R., Pud, D., Ebstein, R.P., Laiba, E., Raz, Y., Gershon, E., . . . Eisenberg, E. (2011). Association between polymorphisms in serotonin and dopamine-related genes and endogenous pain modulation. *Journal of Pain*, 12, 875–883. doi:10.1016/j.jpain.2011.02.348
- Tremblay, P.B., Kaiser, R., Sezer, O., Rosler, N., Schelenz, C., Posinger, K., . . . Brockmoller, J. (2003). Variations in the 5-hydroxytryptamine type 3B receptor gene as predictors of the efficacy of antiemetic treatment in cancer patients. *Journal of Clinical Oncology*, 21, 2147–2155.
- Watcha, M.F., & White, P.F. (1992). Postoperative nausea and vomiting. Its etiology, treatment, and prevention. *Anesthesiology*, 77, 162–184.
- Wendland, J.R., Martin, B.J., Kruse, M.R., Lesch, K.P., & Murphy, D.L. (2006). Simultaneous genotyping of four functional loci of human SLC6A4, with a reappraisal of 5-HTTLPR and rs25531. *Molecular Psychiatry*, 11, 224–226.
- Wesmler, S.W., Henker, R.A., Sereika, S.M., Donovan, H.S., Meng, L., Gruen, G.S., . . . Conley, Y.P. (2012). The association of CYP2D6 genotype and postoperative nausea and vomiting in orthopedic trauma patients. *Biological Research for Nursing*, 15, 382–389. doi:10.1177/1099800412449181
- Wickham, R. (2004). Nausea and vomiting. In C. Yarbro, M. Frogge, & M. Goodman (Eds.), *Cancer symptom management* (pp. 187–210). Sudbury, MA: Jones and Bartlett Learning.