January 2008 and December 2011. The exclusion criteria in the study protocol were having received cancer chemotherapy, radiation therapy or surgery within 2 weeks before or 1 week after administration of opioid analgesics and experiencing continuous nausea or vomiting due to organic or functional complications at the start of opioid administration. Patients with whom no communication was possible were excluded from participation. Oxycodone is currently most used as an opioid analgesic for moderate to severe cancer-related pain in Japan, so patients given oxycodone for the first time were included.[9]

This study was performed with the approval of the Ethics Review Boards of Kyoto Prefectural University of Medicine.

Statistical analysis

Extraction of variables. According to previous studies,[1–8] the predictors evaluated were factors potentially affecting nausea or vomiting. They were demographic factors (gender, age), initial daily dose of oxycodone, concomitant medication (dopamine D_2 blockers, steroids, benzodiazepines, nonsteroidal anti-inflammatory drugs, histamine H_2-receptor antagonist, proton pump inhibitor, magnesium oxide, stimulant laxatives), and type of cancer (lung, digestive organ, liver, hematologic, breast, gynecologic, urologic, head and neck, and others). Concomitant medication including dopamine D_2 blockers (prophylactic medication) for at least 3 days after starting oral oxycodone was extracted. The incidence of opioid-induced nausea or vomiting that appeared within the 3 days after starting oral oxycodone was investigated from the medical records. The occurrence of nausea or vomiting was recorded by interviewing the patients in daily clinical practice by the treating physician and/or primary nurse. For nausea, the following scoring for response was used: 0 = absence of nausea; 1 = presence of nausea within 3 days but continued to take oxycodone; and 2 = presence of nausea within 3 days and oxycodone was discontinued due to nausea. For vomiting, at least 1 vomiting episode during the 3 days was regarded as vomiting-positive. As for predictors, binary scales were used for gender (female = 0; male = 1), and miscellaneous (no = 0; yes = 1).

Statistical–analytical approach. The actual procedure used was multivariate logistic regression analysis. For nausea, ordered logistic regression analysis was used because the severity of nausea was evaluated by a graded scale. Variables were screened by examining for multicollinearity (correlation coefficient $r > 0.7$), which occurs when correlations exist among the variables and results in the use of an inappropriate model. Univariate analysis between outcome and each of candidate independent variable was performed first. A

TABLE 1. PATIENT CHARACTERISTICS AND FACTORS THAT MAY POTENTIALLY IMPACT NAUSEA OR VOMITING ($N = 280$)

	n *(%)*	Mean ± SD *(range)*	p *(nausea)*	p *(vomiting)*
Demographic factors				
Gender (male)	172 (61.4)		0.038[a]	0.014[a]
Age, years		64.8 ± 12.9 (16–92)	0.838	0.711
Initial daily dose of oxycodone, mg		11.7 ± 4.2 (5–30)	0.115	0.006[a]
Concomitant medication				
Dopamine D_2 blockers	224 (80)		0.817	0.426
Prochlorperazine maleate	212 (75.7)		0.904	0.706
Metoclopramide	12 (4.29)		0.020[a]	0.309
Steroids	45 (16.1)		0.090	0.786
Benzodiazepines	122 (43.6)		0.590	0.385
NSAIDs	198 (70.7)		0.390	0.309
H_2RAs	68 (24.3)		0.698	0.422
PPIs	93 (33.2)		0.475	0.825
Magnesium oxide	189 (67.5)		0.704	0.633
Stimulant laxatives	52 (18.6)		0.283	0.007[a]
Type of cancer				
Lung	56 (20.0)		0.046[a]	0.933
Digestive organ	69 (24.6)		0.015[a]	0.228
Gastric	16 (5.7)		0.916	0.803
Colon	16 (5.7)		0.269	0.634
Pancreas	19 (6.8)		0.121	0.257
Esophageal	18 (6.4)		0.149	0.283
Liver	13 (4.6)		0.227	0.938
Hematologic	21 (7.5)		0.468	0.555
Myeloma	11 (3.9)		0.773	0.239
Lymphoma	10 (3.6)		0.464	0.675
Breast	9 (3.2)		0.272	0.518
Gynecologic	13 (4.6)		0.659	0.385
Urologic	24 (8.6)		0.190	0.141
Head and neck	52 (18.6)		0.700	0.485
Others	23 (8.2)			

[a] $p < 0.05$.
Binary scales were female = 0 and male = 1 for gender, and absent = 0 and present = 1 for others.
NSAIDs, monsteroidal anti-inflammatory drugs; H_2RA, histamine H_2-receptor antagonist; PPI, proton pump inhibitor.

TABLE 2. CATEGORIZATION OF NAUSEA AND VOMITING ($N=280$)

Response (Y)	*Number of patients*
Y=nausea	
0	191
1	65
2	24
Y=vomiting	
0	239
1	41

For nausea, the following scoring for response was used: 0=absence of nausea; 1=presence of nausea within 3 days after start of oral oxycodone but oxycodone was continued; 2=presence of nausea within 3 days and oxycodone was discontinued due to nausea.

For vomiting, at least 1 vomiting episode during the 3 days was regarded as vomiting-positive (no=0; yes=1).

multivariate logistic regression model was constructed using forward stepwise selection among several candidate variables with a variable entry criterion of 0.25 and a variable retention criterion of 0.1 (JMP® version 10; SAS Institute, Cary, NC). All statistical analyses were performed at a two-sided significance level of 0.05.

Results

Table 1 shows the clinical characteristics of the patients, various factors that could be related to the occurrence of opioid-induced nausea or vomiting and results of univariate analysis. Table 2 shows the categorization of nausea and vomiting. For nausea, gender, urologic cancer, digestive organ cancer, hepatocellular carcinoma, hematologic malignancy, lung cancer, initial daily dose of oxycodone, steroid use, age, and use of dopamine D_2 blockers were identified by forward selection. This was followed by multivariate ordered logistic regression analysis using these variables. This analysis identified gender (in male; odds ratio [OR]=0.429], lung cancer (OR=2.049), and use of steroid (OR=0.417) as significant factors for the occurrence of opioid-induced nausea. Use of dopamine D_2 blockers (prophylactic medication) to prevent opioid-induced nausea was not a significant factor. For vomiting, gender, urologic cancer, digestive organ cancer, proton pump inhibitor therapy, steroid use, and use of dopamine D_2 blockers were identified by forward selection. Multivariate logistic regression analysis identified gender (in male; OR=0.4) and use of dopamine D_2 blockers (OR=2.778) as significant factors. Accuracy means the ratio of patients whose expected value is equal to observed value (Table 3).

Discussion

The multivariate logistic regression analysis used in this study demonstrated that gender, lung cancer, and steroid use were closely associated with the occurrence of opioid-induced nausea. Gender and use of dopamine D_2 blockers were closely associated with vomiting. The analysis showed that female gender was a predictive factor for the occurrence of opioid-induced nausea or vomiting. This finding is in agreement with the results of other studies.[10–12] Clinicians need to be alert to the greater risk of opioid-induced nausea or vomiting among women.

As far as we can tell from a literature search, this is the first study to identify close association between lung cancer and opioid-induced nausea. Patients with advanced lung cancer frequently develop metastases to bone and brain, which sometimes cause hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[13–15] Hypercalcemia should be anticipated in patients with bone metastases. Patients may experience nausea/vomiting as a consequence of hypercalcemia and so on or other electrolyte

TABLE 3. RESULTS OF LOGISTIC REGRESSION ANALYSIS FOR VARIABLES EXTRACTED BY FORWARD SELECTION ($N=280$)

						CI of odds ratio	
Variable	*EV*	*SE*	χ^2 *value*	p	*Odds ratio*	*Lower 95%*	*Lower 95%*
Y=nausea (accuracy=193/280)							
Gender (male)	−0.847	0.284	8.92	0.0028[a]	0.429	0.246	0.747
Urologic	0.642	0.474	1.84	0.1754	1.901	0.751	4.813
Digestive organ	−0.726	0.377	3.71	0.054	0.484	0.231	1.013
HCC	−1.092	0.802	1.85	0.1733	0.336	0.070	1.615
Hematologic	−0.778	0.569	1.87	0.1718	0.459	0.150	1.402
Lung	0.717	0.362	3.93	0.0476[a]	2.049	1.008	4.166
Initial dose of oxycodone/day	0.053	0.030	3.16	0.0756	1.055	0.995	1.119
Steroids	−0.874	0.414	4.47	0.0345[a]	0.417	0.185	0.938
Age	0.003	0.010	0.1	0.7538	1.003	0.983	1.024
Dopamine D_2 blockers	−0.030	0.316	0.01	0.9239	0.970	0.522	1.802
Y=vomiting (accuracy=240/280)							
Gender (male)	−0.917	0.358	6.56	0.0105[a]	0.400	0.198	0.806
Urologic	0.892	0.549	2.63	0.1046	2.439	0.831	7.160
Digestive organ	−0.539	0.457	1.39	0.2382	0.584	0.238	1.428
PPI	−0.677	0.418	2.63	0.1049	0.508	0.224	1.152
Steroids	−0.820	0.647	1.61	0.2051	0.441	0.124	1.566
Dopamine D_2 blockers	1.022	0.514	3.96	0.0466[a]	2.778	1.015	7.604

[a]$p<0.05$.

EV, estimated value; SE, standard error; CI, confidence interval; HCC, hepatocellular carcinoma; PPI, proton pump inhibitor.

disturbances, such as hyponatremia, hypokalemia, or metabolic alkalosis, which occur secondary to paraneoplastic syndromes.[16–18] Brain metastasis also causes nausea. Patients with lung cancer may, therefore, tend to not respond well to antiemetic therapy. We intend to further investigate differences in responses to antiemetics in patients with different diseases.

Use of dopamine D_2 blockers (prophylactic medication) to prevent opioid-induced nausea was ineffective, and vomiting occurred even if dopamine D_2 blockers were prescribed. The present results showed that the use of steroids was effective as prophylaxis. A previous study clarified the effectiveness of steroids for prevention of opioid-induced nausea.[19,20] Treatment with steroids often results in increased appetite, reduced nausea and improved well-being in patients with advanced metastatic cancer.[21] It might also be better to use steroid as prophylactic medication for prevention of opioid-induced nausea for patients with risk factors. Previous studies suggested other types of antiemetic drugs such as mirtazapine, 5-HT_3 receptor blockers, and antihistaminic might be effective for prevention of opioid-induced nausea.[22–25] In our study, steroids were used not only to prevent opioid-induced nausea or vomiting, but also to improve well-being (betamethasone 1–4 mg/d). Further studies will be needed in this issue.

In conclusion, female gender was found to be predictive factors for the occurrence of nausea given oral opioid analgesics for relief of cancer pain for the first time. Lung cancer might be closely associated with opioid-induced nausea. The use of steroids might be effective as prophylaxis for nausea. Female gender was also a predictive factor for the occurrence of vomiting. Use of dopamine D_2 blockers (prophylactic medication) to prevent opioid-induced nausea was not a significant factor, and vomiting occurred even if dopamine D_2 blockers were given.

This study has several limitations. First, the retrospective nature of the investigation may have decreased the reliability of the data collected. Second, this study was performed at a single institute and involved a relatively small number of patients, so the results should be confirmed in a further multicenter study.

In conclusion, our study demonstrated that gender, lung cancer, and steroid use were closely associated with the occurrence of opioid-induced nausea. Gender and use of dopamine D_2 blockers were closely associated with vomiting. These findings should be considered preliminary and in need of further refinement and study. However, statistical identification of factors associated with opioid-induced nausea or vomiting should contribute to establish optimal treatment of cancer pain.

Author Disclosure Statement

No competing financial interests exist.

References

1. Wirz S, Wittmann M, Schenk M, Schroeck A, Schaefer N, Mueller M, Standop J, Kloecker N, Nadstawek J: Gastrointestinal symptoms under opioid therapy: A prospective comparison of oral sustained-release hydromorphone, transdermal fentanyl, and transdermal buprenorphine. Eur J Pain 2009;13:737–743.
2. Porreca F, Ossipov MH: Nausea and vomiting side effects with opioid analgesics during treatment of chronic pain: mechanisms, implications, and management options. Pain Med 2009;10:654–662.
3. Laugsand EA, Kaasa S, Klepstad P: Management of opioid-induced nausea and vomiting in cancer patients: Systematic review and evidence-based recommendations. Palliat Med 2011;25:442–453.
4. Ishihara M, Iihara H, Okayasu S, Yasuda K, Matsuura K, Suzui M, Itoh Y: Pharmaceutical interventions facilitate premedication and prevent opioid-induced constipation and emesis in cancer patients. Support Care Cancer 2010;18: 1531–1538.
5. Ishihara M, Ikesue H, Matsunaga H, Suemaru K, Kitaichi K, Suetsugu K, Oishi R, Sendo T, Araki H, Itoh Y; Japanese Study Group for the Relief of Opioid-induced Gastrointestinal Dysfunction: A multi-institutional study analyzing effect of prophylactic medication for prevention of opioid-induced gastrointestinal dysfunction. Clin J Pain 2012;28: 373–381.
6. Aparasu R, McCoy RA, Weber C, Mair D, Parasuraman TV: Opioid-induced emesis among hospitalized nonsurgical patients: Effect on pain and quality of life. J Pain Symptom Manage 1999;18:280–288.
7. Porreca F, Ossipov MH: Nausea and vomiting side effects with opioid analgesics during treatment of chronic pain: mechanisms, implications, and management options. Pain Med 2009;10:654–662.
8. Glare P, Miller J, Nikolova T, Tickoo R. Treating nausea and vomiting in palliative care: a review. Clin Interv Aging. 2011; 6:243–59.
9. Koizumi W, Toma H, Watanabe K, Katayama K, Kawahara M, Matsui K, Takiuchi H, Yoshino K, Araki N, Kodama K, Kimura H, Kono I, Hasegawa H, Hatanaka K, Hiraga K, Takeda F: Efficacy and tolerability of cancer pain management with controlled-release oxycodone tablets in opioid-naive cancer pain patients, starting with 5 mg tablets. Jpn J Clin Oncol 2004;34:608–614.
10. Cepeda MS, Farrar JT, Baumgarten M, Boston R, Carr DB, Strom BL: Side effects of opioids during short-term administration: Effect of age, gender, and race. Clin Pharmacol Ther 2003;74:102–112.
11. Zun LS, Downey LV, Gossman W, Rosenbaumdagger J, Sussman G: Gender differences in narcotic-induced emesis in the ED. Am J Emerg Med 2002;20:151–154.
12. Zacny JP, Drum M: Psychopharmacological effects of oxycodone in healthy volunteers: Roles of alcohol-drinking status and sex. Drug Alcohol Depend 2010;107:209–214.
13. Langer C, Hirsh V: Skeletal morbidity in lung cancer patients with bone metastases: Demonstrating the need for early diagnosis and treatment with bisphosphonates. Lung Cancer 2010;67:4–11.
14. Kawabe T, Phi JH, Yamamoto M, Kim DG, Barfod BE, Urakawa Y: Treatment of brain metastasis from lung cancer. Prog Neurol Surg 2012;25:148–155.
15. Vantyghem MC, Balavoine AS, Wémeau JL, Douillard C: Hyponatremia and antidiuresis syndrome. Ann Endocrinol (Paris) 2011;72:500–512.
16. Yeung SC, Habra MA, Thosani SN: Lung cancer-induced paraneoplastic syndromes. Curr Opin Pulm Med 2011;17: 260–268.
17. Pelosof LC, Gerber DE: Paraneoplastic syndromes: An approach to diagnosis and treatment. Mayo Clin Proc 2010; 85:838–854.
18. van Meerbeeck JP, Fennell DA, De Ruysscher DK: Small-cell lung cancer. Lancet 2011;378:1741–1755

19. Allen TK, Jones CA, Habib AS: Dexamethasone for the prophylaxis of postoperative nausea and vomiting associated with neuraxial morphine administration: A systematic review and meta-analysis. Anesth Analg 2012;114:813–822.
20. Song JW, Park EY, Lee JG, Park YS, Kang BC, Shim YH: The effect of combining dexamethasone with ondansetron for nausea and vomiting associated with fentanyl-based intravenous patient-controlled analgesia. Anaesthesia 2011; 66:263–267.
21. Lundström S, Fürst CJ, Friedrichsen M, Strang P: The existential impact of starting corticosteroid treatment as symptom control in advanced metastatic cancer. Palliat Med 2009;23:165–170.
22. Peixoto AJ, Celich MF, Zardo L, Peixoto Filho AJ: Ondansetron or droperidol for prophylaxis of nausea and vomiting after intrathecal morphine. Eur J Anaesthesiol 2006;23:670–675.
23. Lu CW, Jean WH, Wu CC, Shieh JS, Lin TY: Antiemetic efficacy of metoclopramide and diphenhydramine added to patient-controlled morphine analgesia: a randomised controlled trial. Eur J Anaesthesiol 2010;27:1052–1057.
24. Chang FL, Ho ST, Sheen MJ: Efficacy of mirtazapine in preventing intrathecal morphine-induced nausea and vomiting after orthopaedic surgery. Anaesthesia 2010;65:1206–1211.
25. George RB, Allen TK, Habib AS: Serotonin receptor antagonists for the prevention and treatment of pruritus, nausea, and vomiting in women undergoing cesarean delivery with intrathecal morphine: A systematic review and meta-analysis. Anesth Analg 2009;109:174–182.

Address correspondence to:
Yuko Kanbayashi, PhD
Department of Hospital Pharmacy
Kyoto Prefectural University of Medicine
Kawaramachi Hirokoji
Kamigyo-ku, Kyoto 602-8566
Japan

E-mail: ykokanba@koto.kpu-m.ac.jp