Retrospective Study

Chronic Smoking is Not Associated with Increased Postoperative Opioid Use in Patients with Lung Cancer or Esophageal Cancer

Tak Kyu Oh, MD[1], Jae Hyun Jeon, MD[2], Jong Mog Lee, MD[2], Moon Soo Kim, MD[2], Jee Hee Kim, MD, PhD[3], Se Jun Lee, MS[3], and Woosik Eom, MD, PhD[3]

From: [1]Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Gumi-ro, Bundang-gu, Seongnam, Korea; [2]Department of Thoracic Surgery, National Cancer Center, Ilsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do, Republic of Korea; [3]Business School, Business Statistical Analysis and Risk Management, University of Manchester, Manchester, UK

Address Correspondence:
Tak Kyu Oh, MD
Department of Anesthesiology and Pain Medicine
Seoul National University Bundang Hospital, 166, Gumi-ro, Bundang-gu, Seongnam 463-707, Korea
E-mail: airohtak@hotmail.com

Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 03-23-2017
Revised manuscript received: 08-01-2017
Accepted for publication: 08-07-2017

Free full manuscript: www.painphysicianjournal.com

Background: Chronic smokers show differences in pain sensitivity compared to healthy non-smokers. Yet, no study to date has examined whether smoker status has an effect on postoperative pain.

Objective: We aim to examine a possible correlation between preoperative smoking and postoperative opioid dose based on the hypothesis that smokers would use higher doses of opioids to manage increased postoperative pain.

Study Design: A retrospective observational cohort study.

Setting: The National Cancer Center in Korea.

Methods: We examined medical record data for patients who had undergone curative resection for either lung or esophageal cancer (lobectomy or bilobectomy for lung cancer or an Ivor Lewis operation for esophageal cancer) between January 1, 2006 and December 31, 2010. We examined the correlation between the total preoperative average number of packs per day multiplied by years of cigarette smoking (pack-years) and morphine equivalent daily doses administered to patients after surgery, considering each type of cancer both individually and together. Partial correlation and regression analyses were performed to determine the causality of a possible relationship between pack-years of cigarette smoking and postoperative opioid dose.

Results: A total of 1,129 patients (871 patients with lung cancer and 258 patients with esophageal cancer) were included in the final analysis. There was no significant correlation between total pack-years of cigarette smoking and postoperative opioid dose for lung cancer, esophageal cancer, or both cancer types combined (r = 0.042, -0.012, and 0.037, respectively). In the analysis of both cancer types combined, video-assisted thoracic surgery (VATS) was associated with an 11.1% decrease in opioid dose (β = -0.111, P = 0.003) and epidural analgesia was associated with a 7.2% increase in opioid dose (β = 0.072, P = 0.042).

Limitations: The retrospective design of this study is a limitation.

Conclusion: Our study did not observe a correlation between preoperative smoking and postoperative opioid dose in patients with lung or esophageal cancer.

Key words: Smoking, postoperative pain, opioid, lung cancer, esophageal cancer, analgesia

Pain Physician 2018; 21:E49-E55

Smokers have an increased risk of developing lung cancer and esophageal cancer (1,2). Accordingly, there are a high proportion of smokers among patients diagnosed with and receiving treatment for lung and esophageal cancers. In these cases, chronic smoker status needs to be considered during perioperative care. Moreover, patients who receive radical treatment, such as thoracotomy, experience severe postoperative pain, and insufficient pain control can lead to the development of chronic

pain (3,4). Thus, appropriate pain control and an understanding of the potential relationship between pain control and chronic smoking is important in these patients.

A Cochrane Review meta-analysis published in 2016 reported that perioperative administration (intranasal or transdermal) of nicotine had a weak analgesic effect on postoperative pain (5). This effect is controversially thought to be mediated by the action of nicotine on nicotinic acetylcholine receptors (nAchRs) (6). Conversely, chronic smokers show altered pain perception compared to non-smokers, and are known to be more tolerant to electrical pain stimulation (7). These observations are potentially explained by the desensitization of nAchRs, pain pathway neuroplasticity, altered opioid signaling, and/or cross-tolerance. Thus, it has been proposed that chronic smoking may be associated with increased postoperative opioid use (6); however, this observation has been a matter of debate.

To test the hypothesis that chronic smokers show differences in pain perception compared to healthy non-smokers, we investigated the severity of postoperative pain in chronic smokers by measuring postoperative opioid use. Specifically, we examined whether there was any correlation between total pack-years of smoking and postoperative opioid dose.

Methods

This was a retrospective observational cohort study based on electronic medical record data from the National Cancer Center in Korea. This study was approved as a secondary study to 2 previous studies examining opioid use and the recurrence of lung and esophageal cancer by the Institutional Review Board of the National Cancer Center (NCC2015-0297, NCC2015-0298). We collected the medical record data of patients who had undergone curative resection for either lung or esophageal cancer (lobectomy or bilobectomy for lung cancer or an Ivor Lewis operation for esophageal cancer) between January 1, 2006 and December 31, 2010. The exclusion criteria were as follows. For lung cancer, patients who died of postoperative complications within the first postoperative month and patients who underwent intraoperative conversion to pneumonecomy or sublobar resection were excluded. For esophageal cancer, patients who died of postoperative complications within 3 months post-surgery and stage N2 and M1 patients (i.e., patients with heavy disease burden) were excluded. Otherwise, patients with incomplete electronic medical records, patients with less than 5 years of postoperative follow-up, patients who developed another primary cancer within 5 years, and patients with preoperative opioid use were excluded. All patients abstained from smoking for at least 2 – 3 weeks prior to surgery, and surgery was delayed in all cases if patients smoked within one to 2 days prior to surgery.

Demographic data included gender, body weight (kg), height (cm), smoking experience, preoperative forced expiratory volume (FEV1), Charlson Comorbidity Index score, American Society of Anesthesiologists (ASA) class, operation type, epidural analgesia, length of hospital stay, stage, tumor, node, and total acetaminophen consumption. The postoperative pathological cancer stage was determined in terms of the tumor, node, and stage classification, with reference to the seventh American Joint Committee on Cancer guideline (8). Total smoking amount was calculated as the average number of packs per day multiplied by years of smoking (pack-years). Opioid dose was the total amount of opioid analgesics used intra and postoperatively for a total of 7 days (postoperative days [PODs] 0 – 6) in patients with lung cancer and for a total of 10 days (PODs 0 – 9) in patients with esophageal cancer, accounting for the mean hospitalization period for each cancer type (12.691 days and 21.00 days, respectively). Standard conversion ratios were used to calculate the postoperative oral morphine equivalent daily dose (MEDD) for each patient (Appendix 1) (9).

The main outcome of the study was a correlation between total preoperative pack-years of cigarette smoking and postoperative MEDD in patients with lung or esophageal cancer, considering each cancer type individually and together.

Statistical Analysis

SPSS Version 23.0 (IBM Corporation, Armonk, NY) was used for statistical analysis. Data shown represent the mean ± standard deviation unless otherwise noted. We performed a frequency analysis, partial correlation analysis, and regression analysis. The frequency analysis used patient (demographic) as the dependent variable. The partial correlation analysis tested the relationship between pack-year of cigarette smoking and total opioid dose, controlling for confounding factors. The regression analysis confirmed the findings of the partial correlation analysis.

Results

Among patients who underwent surgery between January 1, 2006 and December 31, 2010, 1,129 patients

Table 1. *Demographic data for lung cancer patients.*

Variable	Category	N	%	Mean	SD
Gender	Male	628	72.1		
	Female	243	27.9		
Age				62.49	9.393
Body weight (kg)				62.97	11.158
Height (cm)				163.09	9.095
Experience Smoking	Yes	597	68.5		
	No	274	31.5		
Total Pack-Year of Cigarette Smoking				14805.58	7380.557
Preoperative FEV1 (L)				2.36	.622
Preoperative FEV1 (percent)				93.75	20.045
Charlson Comorbidity Index Score				2.38	.616
ASA Class	I	223	25.6		
	II	613	70.4		
	III	35	4.0		
Operation Type I	Lobectomy	739	84.8		
	Bilobectomy	71	8.2		
	Sleeve lobectomy	61	7.0		
Operation Type II	VATS	335	38.5		
	Open	535	61.4		
	Robot	1	0.1		
Epidural Analgesia	Yes	631	72.4		
	No	240	27.6		
Length of Hospital Stay				12.691	6.938
Stage	Ia	186	21.4		
	Ib	225	25.8		
	IIa	148	17.0		
	IIb	95	10.9		
	IIIa	217	24.9		
Tumor	Ia	152	17.5		
	Ib	102	11.7		
	IIa	357	41.0		
	IIb	99	11.4		
	III	151	17.3		
	IV	10	1.1		
Node	0	537	61.7		
	I	187	21.5		
	II	146	16.8		
Total Opioid Dose (Oral) (POD 0–POD 6), MEDD				1563.10	816.476
Acetaminophen Consumption				5742.55	6264.081

FEV1 = forced expiratory volume; ASA = Americal Society of Anesthesiologists; VATS = video-assisted thoracic surgery; MEDD = morphine equivalent daily dose; POD = postoperative day

(871 patients with lung cancer and 258 patients with esophageal cancer) were included in the final analysis. Tables 1 and 2 show the demographic data for patients

Table 2. *Demographic data for esophageal cancer patients.*

Variable	Category	N	%	Mean	SD
Gender	Male	247	95.7		
	Female	11	4.3		
Age				85.12	7.887
Body weight (kg)				61.50	15.159
Height (cm)				163.30	12.202
Experience Smoking	Yes	222	86.0		
	No	36	14.0		
Total Pack-Year of Cigarette Smoking				12979.93	6232.904
Pre-operative FEV1 (L)				2.51	.581
Pre-operative FEV1 (percent)				96.14	18.186
Charlson Comorbidity Index Score				2.38	.657
ASA Class	I	67	26.0		
	II	175	67.8		
	III	16	6.2		
Operation Type I	Thoraco-abdominal approach	186	72.1		
	Cervico-thoracic-abdominal approach	72	27.9		
Operation Type II	VATS	9	3.5		
	Open	249	96.5		
Epidural Analgesia	Yes	196	76.0		
	No	62	24.0		
Length of Hospital Stay				21.00	15.966
Stage	Ia	8	3.5		
	Ib	74	28.7		
	IIa	14	5.4		
	IIb	79	30.6		
	IIIa	74	28.7		
	IIIc	8	3.1		
Tumor	I	100	38.8		
	II	48	18.6		
	III	101	39.1		
	IVa	9	3.5		
Node	0	126	48.8		
	I	132	51.2		
Total Opioid Dose (Oral) (POD 0–POD 9), MEDD				1788.36	692.110
Acetaminophen Consumption				2740.91	2441.062

FEV = forced expiratory volume; ASA = Americal Society of Anesthesiologists; VATS = video-assisted thoracic surgery; MEDD = morphine equivalent daily dose; POD = postoperative day

with lung cancer and patients with esophageal cancer, respectively. In patients with lung cancer, the mean preoperative smoking volume was 14805.58 ± 7390.56 pack-years and the mean total opioid dose up to POD 6 was a MEDD of 1563.10 ± 816.476 mg. In patients with esophageal cancer, the mean preoperative smoking volume was 12979.93 ± 6232.90 pack-years and the mean total opioid dose up to POD 9 was a MEDD of 1788.36 ± 692.110 mg.

Table 3 shows the results of the partial correlation analysis examining the correlation between total pack-years of cigarette smoking and total opioid dose. The model was adjusted for video-assisted thoracic surgery (VATS), epidural analgesia, stage, tumor, and node. No significant correlation was identified for lung cancer, esophageal cancer, or both types of cancer combined (r = 0.042, -0.012, and 0.037, respectively) (Table 3). These non-significant correlations are shown graphically in Figs. 1, 2, and 3.

Tables 4, 5, and 6 summarize factors significantly affecting total opioid dose in the multiple regression analysis for lung cancer, esophageal cancer, and both cancers combined. For lung cancer, VATS was associated with a 9.2% decrease in opioid dose (β = -0.092, *P* = 0.033; Table 4), while epidural analgesia was associated with a 20% increase in opioid dose (β = 0.201, *P* < 0.0001; Table 4). For esophageal cancer, epidural analgesia was similarly associated with a 31.6% increase in opioid dose (β = 0.316, *P* < 0.0001; Table 5). In the analysis of both cancers combined, VATS was associated with an 11.1% decrease in opioid dose (β = -0.111, *P* = 0.003) and epidural analgesia was associated with a 7.2% increase in opioid dose (β = 0.072, *P* = 0.042; Table 6).

Discussion

The present study did not identify a significant correlational or causal relationship between preoperative smoking volume and postoperative opioid dose in patients with lung or esophageal cancer. Our finding indicates that chronic exposure to nicotine had no apparent effect on postoperative pain intensity in this study. These results are particularly meaningful given that we

Table 3. *Partial correlation analysis between total pack-year of cigarette smoking and total opioid dose after controlled confounding variables (operation types I and II, epidural analgesia, stage, tumor, node).*

	Total Pack-Year of Cigarette Smoking	Total Opioid Dose (Oral)
Total Pack-Year of Cigarette Smoking	1	
Total Opioid Dose (POD 0–POD 6), (Lung Cancer)	.042	1
Total Opioid Dose (POD 0–POD 9), (Esophageal Cancer)	-0.012	1
Total Opioid Dose Lung Cancer and Esophageal Cancer	0.037	1

POD = postoperative day

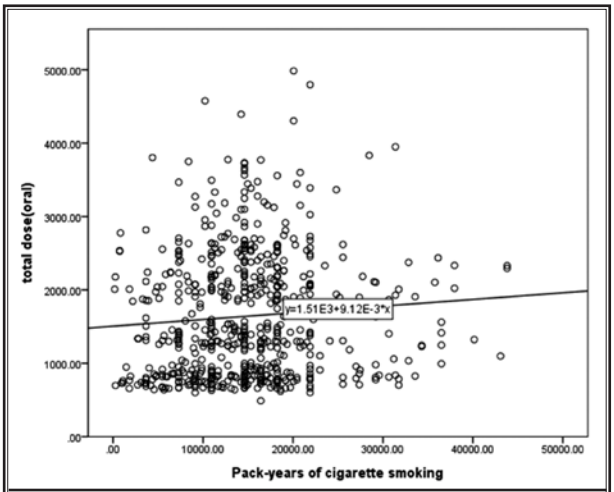

Fig. 1. *Correlation between total pack-years of cigarette smoking and total opioid dose in lung cancer patients.*

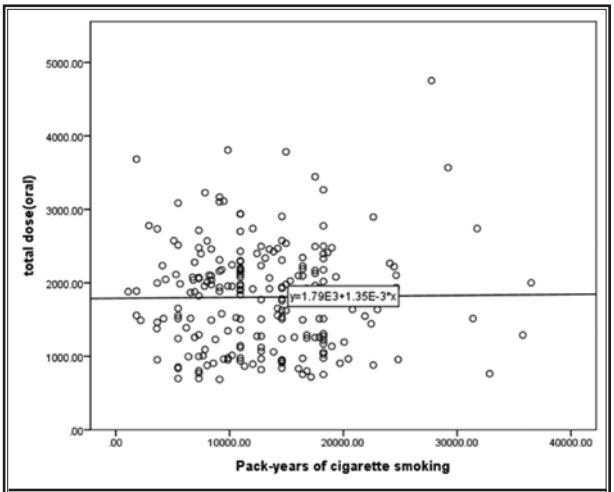

Fig. 2. *Correlation between total pack-years of cigarette smoking and total opioid dose in esophageal cancer patients.*

calculated total smoking volume rather than smoking status and analyzed its relationship with opioid dose over a relatively long postoperative period (7 – 10 days). The reliability of our results is supported by the fact that we accounted for several potentially confounding factors in our regression model, including operation technique (VATS or open), epidural analgesia, stage, tumor, and node.

Our findings are contradictory to those of a previous study that indicated that chronic smoking might cause intolerance to pain (6). The previous study showed that nicotine-tolerant rats developed greater mechanical hyperalgesia than did nicotine-naïve rats, which is explained by increased spinal dynorphin levels (10) as well as increased production of cytokines centrally and peripherally (11). However, in our retrospective cohort study, increased hyperalgesia was not observed post-operation in chronic smokers, who were nicotine-tolerant patients. Considering the severe pain intensity associated with thoracotomy in lung cancer surgery or esophageal

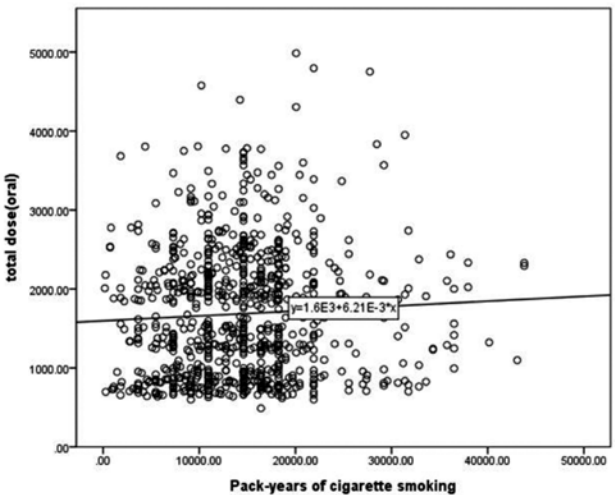

Fig. 3. *Correlation between total pack-years of cigarette smoking and total opioid dose in both lung and esophageal cancer patients.*

Table 4. *Multiple regression analysis (lung cancer).*

	Total Opioid Dose (POD 0–POD 6), Lung Cancer								
Variable	**B**	**SD**	**Beta**	**t**	***P***	**VIF**	**DW**	**R^2**	**F**
Pack-Years of Cigarette Smoking	0.005	0.005	0.041	1.015	0.311	1.031	1.108	0.085	7.733** (0.000)
VATS	169.610	79.449	-.092	-2.135	0.033*	1.177			
Robot	688.123	820.208	-0.033	-0.839	0.402	1.008			
Epidural Analgesia	393.523	80.083	0.201	4.914	0.000**	1.070			
Stage	-6.736	65.015	-0.012	-0.104	0.918	8.103			
Tumor	18.029	48.127	0.029	0.375	0.708	3.836			
Node	118.206	92.379	0.105	1.280	0.201	4.293			

VATS = video-assisted thoracic surgery; POD = postoperative day
*$P < 0.05$, **$P < 0.01$

Table 5. *Multiple regression analysis (esophageal cancer).*

	Total Opioid Dose (POD 0–POD 9), Esophageal Cancer								
Variable	**B**	**SD**	**Beta**	**t**	***P***	**VIF**	**DW**	**R^2**	**F**
Pack-Years of Cigarette Smoking	-0.001	0.007	-0.011	-0.177	0.860	1.024	1.880	0.114	4.607** (0.000)
Operation Type	45.581	234.634	0.013	0.194	0.846	1.039			
Epidural Analgesia	520.890	106.545	0.316	4.889	0.000	1.014			
Stage	40.166	89.751	0.078	0.448	0.655	7.387			
Tumor	-95.653	98.293	-0.127	-0.973	0.332	4.150			
Node	163.724	154.044	.116	1.063	.289	2.871			

Operation type = thoraco-abdominal approach vs. cervico-thoraco-abdominal approach.
*$P < 0.05$, **$P < 0.01$

Table 6. *Multiple regression analysis (lung cancer and esophageal cancer)*

Variable	Total Opioid Dose, Lung Cancer, and Esophageal Cancer								
	B	SD	Beta	t	*P*	VIF	DW	R^2	F
Pack-Years of Cigarette Smoking	0.004	0.004	0.039	1.122	0.262	1.030	1.220	0.048	5.863** (0.000)
VATS	215.253	71.990	-0.111	-2.990	0.003*	1.166			
Robot	888.682	801.953	-0.038	-1.108	0.268	1.007			
Epidural Analgesia	135.127	66.210	0.072	2.041	0.042*	1.044			
Stage	54.313	37.412	0.098	1.452	0.147	3.838			
Tumor	-36.112	28.092	-0.060	-1.285	0.199	1.855			
Node	57.107	63.005	0.048	0.906	0.365	2.431			

VATS = video-assisted thoracic surgery
*$P < 0.05$, **$P < 0.01$

cancer surgery, our concern for increased intolerance to pain in chronic smokers was not a significant problem in clinical settings. However, future studies are needed to determine the accurate relationship between chronic smoking and anti-noception in postoperative pain.

As mentioned above, the exact effects of chronic smoking on pain processing and perception remain unclear. In one previous study, ischemic pain due to a tourniquet was more severe in female chronic smokers compared to female non-smokers; the authors proposed that chronic smoking modulated pain perception by altering function of the neuroendocrine system (12). Typically, the stress response (sympathetic and hypothalamic-pituitary-adrenal activation) reduces pain perception. Chronic smoking exposure leads to the down-regulation of this hormone axis, resulting in insufficient baroreceptor function and a decrease in beta-endorphin levels (13,14). Thus, chronic smokers were predicted to show less hypothalamic-pituitary-adrenal activation in response to pain and other stressors and to show weaker endogenous analgesic activity than non-smokers. In contrast, we did not identify a significant effect of smoking on postoperative pain.

An important consideration in this study is the possibility that smokers were experiencing withdrawal symptoms, which may have affected pain perception. Previous studies have reported that patients show a reduced pain threshold in cases of sudden smoking withdrawal (15,16). Unfortunately, it was not possible to obtain a complete record of our patients' most recent smoking habits given the design of our study; however, all patients were strongly encouraged to abstain from smoking after their cancer diagnosis, and surgery was delayed for patients who smoked during the 1 to 2 days of hospitalization prior to surgery. Although the primary aim of this approach was to prevent pulmonary complications, it is possible that withdrawal symptoms caused an increase in postoperative opioid dose that obscured a relationship between smoking and postoperative pain. Thus, future studies should examine the relationship between chronic smoking and postoperative opioid use when the effects of acute smoking deprivation (i.e., withdrawal symptoms) are eliminated.

Another important finding in this study was that when both cancer groups were combined, VATS was associated with a significant decrease in opioid dose while epidural analgesia was associated with a significant increase in opioid dose. Although this was not the main outcome of the study, it is still an interesting result. Consistent with our finding, a prospective controlled trial reported that patients who underwent VATS had lower pain intensity scores compared to patients who underwent open thoracotomy (17). Conversely, our results contrast with the fact that epidural analgesia is recognized as the gold standard of analgesia for thoracotomy pain (18). Our finding may have been subject to bias as a retrospective study, as patients scheduled for open thoracotomy were more likely to receive epidural analgesia than those scheduled for VATS. Additionally, a possible reason a larger positive effect of epidural analgesia on opioid dose in patients with esophageal cancer compared to those with lung cancer is that a dual epidural catheterization technique is required in the Ivor-Lewis operation to provide sufficient analgesia from the neck to the lower abdomen, yet procedures in our study only used a single catheter (19). Therefore, future studies should reexamine our findings accounting for these factors.

The present study had several limitations. First, pain should have been measured using a numeric rating scale rather than total opioid dose, but this was not possible given a retrospective design. Second, it was

impossible to avoid use of the standard conversion ratio to calculate total opioid dose. This conversion ratio is controversial when used for long-acting opioids such as those used to manage postoperative pain (20,21). Third, we were not able to account for a possible association between smoking volume and postoperative non-steroidal anti-inflammatory or acetaminophen use. Despite these limitations, our study is valuable as the first cohort study to analyze the correlation between preoperative smoking volume and postoperative opioid dose in a large sample. A well-designed prospective study should be conducted to confirm our findings in the future.

Appendix 1. *Equianalgesic opioid conversion table.*

Opioid	Administration route	Dose equivalent to 10 mg of oral morphine (mg)
Morphine	Oral	10
Morphine	Intravenous	3.3
Morphine	Epidural	0.33
Hydromorphone	Oral	2
Fentanyl	Intravenous	0.03
Oxycodone	Oral	7
Codeine	Oral	80
Tramadol	Oral	40

References

1. Castellsagué X, Muñoz N, De Stefani E, Victora CG, Castelletto R, Rolón PA, Quintana MJ. Independent and joint effects of tobacco smoking and alcohol drinking on the risk of esophageal cancer in men and women. *Int J Cancer* 1999; 82:657-664.
2. Peto R, Darby S, Deo H, Silcocks P, Whitley E, Doll R. Smoking, smoking cessation, and lung cancer in the UK since 1950: Combination of national statistics with two case-control studies. *BMJ* 2000; 321:323-329.
3. Kajiyama S, Miyoshi H, Kato T, Kawamoto M. [Evaluation of postoperative pain intensity related to post-thoracotomy pain syndrome occurring after video-assisted thoracic surgery lobectomy for lung cancer]. *Masui* 2014; 63:391-395.
4. Kol E, Erdogan A, Karsli B. Nature and intensity of the pain following thoracotomy. *Int J Nurs Pract* 2012; 18:84-90.
5. Matthews AM, Fu R, Dana T, Chou R. Intranasal or transdermal nicotine for the treatment of postoperative pain. *Cochrane Database Syst Rev* 2016; 1:CD009634.
6. Shi Y, Weingarten TN, Mantilla CB, Hooten WM, Warner DO. Smoking and pain: Pathophysiology and clinical implications. *Anesthesiology* 2010; 113:977-992.
7. Silverstein B. Cigarette smoking, nicotine addiction, and relaxation. *J Pers Soc Psychol* 1982; 42:946-950.
8. Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. *AJCC Cancer Staging Manual. 7th ed.* Springer, New York, 2010.
9. Benzon H, Rathmell JP, Wu CL, Turk DC, Argoff CE. *Raj's Practical Management of Pain.* Elsevier Health Sciences, Philadelphia, 2008.
10. Lough C, Young T, Parker R, Wittenauer S, Vincler M. Increased spinal dynorphin contributes to chronic nicotine-induced mechanical hypersensitivity in the rat. *Neurosci Lett* 2007; 422:54-58.
11. Brett K, Parker R, Wittenauer S, Hayashida K, Young T, Vincler M. Impact of chronic nicotine on sciatic nerve injury in the rat. *J Neuroimmunol* 2007; 186:37-44.
12. Girdler SS, Maixner W, Naftel HA, Stewart PW, Moretz RL, Light KC. Cigarette smoking, stress-induced analgesia and pain perception in men and women. *Pain* 2005; 114:372-385.
13. Arosio E, De Marchi S, Rigoni A, Prior M, Lechi A. Effects of smoking on cardiopulmonary baroreceptor activation and peripheral vascular resistance. *Eur J Clin Invest* 2006; 36:320-325.
14. Mancia G, Groppelli A, Di Rienzo M, Castiglioni P, Parati G. Smoking impairs baroreflex sensitivity in humans. *Am J Physiol* 1997; 273:H1555-H1560.
15. Anderson KL, Pinkerton KE, Uyeminami D, Simons CT, Carstens MI, Carstens E. Antinociception induced by chronic exposure of rats to cigarette smoke. *Neurosci Lett* 2004; 366:86-91.
16. Schmidt BL, Tambeli CH, Gear RW, Levine JD. Nicotine withdrawal hyperalgesia and opioid-mediated analgesia depend on nicotine receptors in nucleus accumbens. *Neuroscience* 2001; 106:129-136.
17. Palade E, Guenter J, Kirschbaum A, Wiesemann S, Passlick B. [Postoperative pain in the acute phase after surgery: VATS lobectomy vs. open lung resection - results of a prospective randomised trial]. *Zentralbl Chir* 2014; 139:S59-S66.
18. Ng A, Swanevelder J. Pain relief after thoracotomy: Is epidural analgesia the optimal technique? *Br J Anaesth* 2007; 98:159-162.
19. Brown MJ, Kor DJ, Allen MS, Kinney MO, Shen KR, Deschamps C, Nichols FC, Mauck WD, Mantilla CB. Dual-epidural catheter technique and perioperative outcomes after Ivor-Lewis esophagectomy. *Reg Anesth Pain Med* 2013; 38:3-8.
20. O'Bryant CL, Linnebur SA, Yamashita TE, Kutner JS. Inconsistencies in opioid equianalgesic ratios: Clinical and research implications. *J Pain Palliat Care Pharmacother* 2008; 22:282-290.
21. Patanwala AE, Duby J, Waters D, Erstad BL. Opioid conversions in acute care. *Ann Pharmacother* 2007; 41:255-266.