Published OnlineFirst July 22, 2020; DOI: 10.1158/1055-9965.EPI-20-0206

Chronic Opioid Use and Risk of Cancer in Patients with Chronic Noncancer Pain: A Nationwide Historical Cohort Study

Tak Kyu Oh and In-Ae Song

ABSTRACT

Background: To investigate whether chronic opioid therapy is associated with a higher risk of cancer among noncancer patients with chronic pain.

Methods: A population-based historical cohort study of the South Korean adult population was conducted using data from the National Health Insurance Service. We included patients registered with a diagnostic code of M00–M99 (musculoskeletal system and connective tissue diseases) according to the International Classification of Diseases, 10th revision, in 2010. Patients prescribed a continuous supply of any opioid drug for ≥90 days were defined as chronic opioid users.

Results: A total of 351,701 patients were analyzed. Among them, 25,153 (7.2%) were chronic opioid users. Using a multivariate time-dependent Cox regression model, the risk of cancer in chronic opioid users was 1.20-fold higher than that in controls [HR, 1.20; 95% confidence interval (CI), 1.15–1.25; $P < 0.001$]. On subgroup analysis according to opioid potency, the cancer risk in chronic weak and strong opioid users was 1.18-fold (HR, 1.18; 95% CI, 1.13–1.23; $P < 0.001$) and 1.32-fold (HR, 1.32; 95% CI, 1.10–1.59; $P = 0.003$) higher than that in controls, respectively.

Conclusions: Chronic opioid therapy was associated with an increased risk of cancer among noncancer patients with chronic pain. This association was more evident in chronic strong opioid users. However, as unmeasured and potential confounders may have affected the results, the relationship between chronic opioid use and cancer risk should be evaluated with caution.

Impact: Chronic opioid therapy was associated with an increased risk of cancer among noncancer patients.

Introduction

Cancer is one of the most common causes of death worldwide (1). Between 2006 and 2016, there were 17.2 million new cancer cases per year, with 8.9 million new deaths from cancer and an increase in the global cancer incidence by 28% (2). The incidence of cancer is expected to increase in the future; thus, its prevention should be emphasized to reduce the global burden (3).

Opioids are the most commonly prescribed analgesics (4), and their use has continued to increase in many countries such as the United States (5), United Kingdom (6), Taiwan (7), France (8), China (9), and Croatia (10). In 2010, it was estimated that there were 15.5 million opioid-dependent people worldwide (11). The number of cases of opioid overdose increased with the increase in the number of opioid-dependent people, leading to an increase in the number of deaths due to drug overdose (12). Thus, the epidemic of opioid dependence arising from opioid use is currently becoming a matter of public health concern in many countries, including the United States (11, 13, 14).

One of the major adverse effects of long-term opioid therapy is immunosuppression (15). It is caused by the suppression of mitogen-induced T- and B-lymphocyte proliferation, natural killer-cell activity, cytokine production, and antibody formation (16). Previous studies have reported that long-term and high-dose opioid therapy is related to poorer outcomes in patients with cancer, as their immune system is already impaired (17–20). However, noncancer patients are known to receive chronic opioid therapy for chronic pain (21), which has been reported to be associated with an increase in the all-cause mortality rate (22). As the immunosuppressive effect of long-term opioid therapy is closely related to an increased risk of cancer (15), chronic opioid therapy among noncancer patients with chronic pain may increase their risk of cancer. Most previous studies have focused only on the effect of chronic opioid use in patients with cancer (23, 24), and the relationship between chronic opioid use and cancer risk in noncancer patients remains controversial.

Therefore, this study aimed to investigate whether chronic opioid therapy is associated with a higher risk of cancer in noncancer patients with chronic pain from musculoskeletal and connective tissue diseases. In addition, we assessed whether this association may differ according to the potency of the opioid agent or the type of cancer.

Materials and Methods

Data source

The "historical cohort database" of the National Health Insurance Service (NHIS) was used to obtain data for this study, which includes health and medical surveys of the Korean population. The database comprised a stratified random sample of approximately 1 million people registered with the NHIS since 2002, and was designed to be representative of the national population in terms of demographic and socioeconomic variables. To maintain the demographic and socioeconomic integrity of the cohort, people were added to the cohort each year to replace individuals who had died or emigrated in the preceding year, using stratified extraction methods to ensure that the cohort remained representative of the national population in terms of demographic and socioeconomic information (25). For instance, if a

Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, Republic of Korea (South).

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: In-Ae Song, Seoul National University Bundang Hospital, Seongnam 13620, Republic of Korea (South). Phone: 823-1787-7499; E-mail: songoficu@outlook.kr

Cancer Epidemiol Biomarkers Prev 2020;29:1962–7

doi: 10.1158/1055-9965.EPI-20-0206

Published OnlineFirst July 22, 2020; DOI: 10.1158/1055-9965.EPI-20-0206

65-year-old individual who lived in the capital city at the lowest income level died in the preceding year, the cohort was supplemented with a new 65-year-old individual who lived in the capital city at the lowest income level in the following year, using a stratified extraction method. Through this process, the cohort remained balanced at 1 million individuals until 2015.

Ethical statement

The protocol of this study was approved by the Institutional Review Board of Seoul National University Bundang Hospital [Seongnam, Gyeonggi-do, Republic of Korea (South), no. X-1808-489-904] and the Health Insurance Review and Assessment Service (NHIS-2018-2-256).

Study population

We included all adult patients (age ≥18 years) registered with a diagnostic code of M00–M99 (diseases of the musculoskeletal system and connective tissue) according to the International Classification of Diseases, 10th revision (ICD-10), in 2010. We then excluded individuals who died in 2010 and those who had emigrated between 2011 and 2015, as opioid prescription information was no longer available after emigration. In addition, individuals with a history of cancer in 2010 were excluded, as our study focused on new cancer diagnoses between 2011 and 2015.

Long-term opioid prescription as an exposure variable

Chronic opioid users were defined as people who had been prescribed a continuous supply of any opioid for ≥90 days (26). The classification of chronic opioid use in the 2010 cohort was based on opioid prescription data between October 1, 2009, and March 31, 2011. Regarding the variability in opioid potency (27), codeine, dihydrocodeine, hydrocodone, and tramadol were categorized as weak opioids, whereas all others (e.g., fentanyl, morphine, oxycodone, hydromorphone, and methadone) were categorized as strong opioids. Individuals who received prescriptions for both weak and strong opioids for a continuous period of ≥90 days were classified as chronic strong opioid users. Individuals who did not receive long-term opioid prescriptions in 2010 were classified as controls.

Study endpoint

The primary endpoint of this study was the development of new cancer cases between January 1, 2011, and December 31, 2015.

Development of cancer as the dependent variable

In this study, the development of cancer was defined as newly registered diagnoses of any malignancy (C00–C96) between 2011 and 2015 in the 2010 NHIS cohort in South Korea. In detail, the cancers were categorized as follows: gastric cancer (C16), esophageal cancer (C15), colorectal cancer (C18–C20), gall bladder and biliary tract cancer (C23–C24), head and neck cancer (C00–C14), brain cancer (C71), liver cancer (C22), pancreatic cancer (C25), lung cancer (C34), bone and articular cartilage cancer (C40–C41), neoplasms of the breast and genital organs (C50–C63), urinary tract cancer (C64–C68), thyroid cancer (C73), and lymphoma or leukemia (C81–C96). The time to cancer diagnosis was calculated from January 1, 2011, to the date of cancer diagnosis, as registered officially in the NHIS database. In South Korea, all patients diagnosed with cancer of any C-code should be registered in the NHIS database to receive special financial coverage; the NHIS covers 95% of the total cost of cancer treatment. Therefore, all patients in South Korea who received a diagnosis of cancer were registered in the NHIS database.

Confounding variables

Data on the following variables as confounders were collected in this study: (i) demographic information (age and sex); (ii) socioeconomic information [income level in deciles and place of residence in 2010 (Seoul, metropolitan cities, or others)]; (iii) Charlson comorbidity index, which was calculated using the registered ICD-10 diagnostic codes between 2009 and 2010 in the NHIS database (Supplementary Table S1); (iv) surgical history in 2010; and (v) chronic use of other

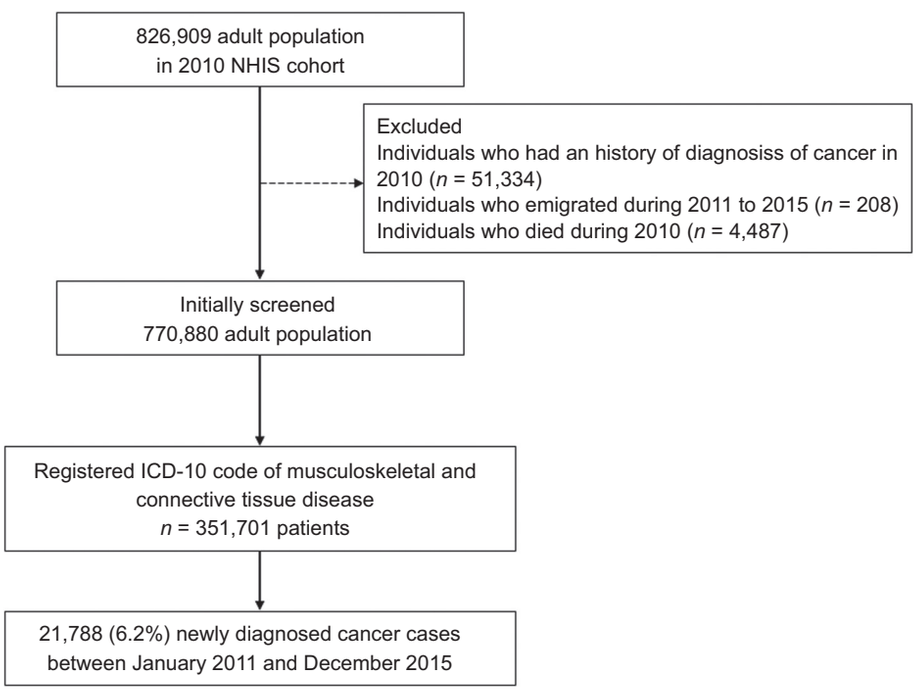

Figure 1.
Flow chart of patient selection in this study.

Published OnlineFirst July 22, 2020; DOI: 10.1158/1055-9965.EPI-20-0206

analgesics for ≥90 days (NSAIDs, paracetamol, gabapentin, and pregabalin). Data on obesity and physical activity, as well as lifestyle-related risk factors for cancer, such as smoking and alcohol consumption, were not included in this study because they were not included in the NHIS database.

Statistical analysis

The baseline characteristics of the chronic opioid users and controls were compared using the *t* test for continuous variables and the χ^2 test for categorical variables. The results of the tests are presented as means with SDs for continuous variables and numbers with percentages for categorical variables. First, as our study focused on time-dependent exposure to chronic opioid therapy in the 2010 cohort between 2011 and 2015, we investigated the proportion of chronic opioid users who discontinued opioid therapy or commenced it during the evaluation period, that is, 2011 to 2015. Exposure to chronic opioid therapy among both the chronic opioid users and controls in 2010 varied throughout the evaluation period (Supplementary Table S2).

Therefore, we investigated the association between exposure to chronic opioid therapy and the development of new cancers using a time-dependent Cox regression model. In this model, exposure to chronic opioid therapy was considered a time-dependent variable, and all other covariates were included in the time-dependent Cox regression model for multivariate adjustment. In particular, age, sex, income level, residence, Charlson comorbidity index, all underlying diseases, surgery in 2010, and the use of other chronic analgesics were included.

During the first subgroup analysis, the chronic opioid users were categorized into two groups (chronic strong opioid users and chronic weak opioid users), and the association of chronic strong and weak opioid use with the development of cancer was assessed using a time-dependent Cox regression model. We then developed 14 time-dependent Cox regression models to investigate whether chronic opioid use was associated with specific cancer development. Diagnoses of 14 specific cancer types were used as endpoints in these models. The results of the Cox regression models are presented as HRs with 95% confidence intervals (CI). All multivariate models of the entire cohort

Table 1. The comparison of the demographic and clinical characteristics between the chronic opioid users and the control group.

Variable	Chronic opioid user (n = 25,153)	Control group (n = 326,548)	*P*
Age, year	61.0 (13.0)	48.3 (16.4)	<0.001
Sex, male	9,568 (38.0)	139,936 (42.9)	<0.001
Income level (deciles distribution ratio)			<0.001
1st (lowest income level)	1,775 (7.1)	26,162 (8.0)	
2nd	1,170 (4.7)	20,247 (6.2)	
3rd	1,347 (5.4)	24,337 (7.5)	
4th	1,420 (5.6)	27,233 (8.3)	
5th	1,492 (5.9)	27,927 (8.6)	
6th	3,040 (12.1)	47,563 (14.6)	
7th	2,457 (9.8)	34,453 (10.6)	
8th	2,909 (11.6)	36,581 (11.2)	
9th	3,797 (15.1)	40,554 (12.4)	
10th (highest income level)	5,746 (22.8)	41,491 (12.7)	
Residence			
Capital city (Seoul)	7,688 (30.6)	58,723 (18.0)	
Metropolitan city	4,448 (17.7)	84,750 (26.0)	
Others	13,017 (51.8)	183,075 (56.1)	
Charlson comorbidity index	2.8 (2.1)	1.5 (1.7)	<0.001
Congestive heart failure	2,182 (8.7)	8,766 (2.7)	<0.001
Chronic pulmonary disease	10,654 (42.4)	107,172 (32.8)	<0.001
Cerebrovascular disease	5,408 (21.5)	23,434 (7.2)	<0.001
Dementia	266 (1.1)	1,053 (0.3)	<0.001
DM with chronic complication	4,491 (17.9)	16,202 (5.0)	<0.001
DM without chronic complication	8,779 (34.9)	42,276 (12.9)	<0.001
Hemi- or paraplegia	527 (2.1)	2,745 (0.8)	<0.001
Myocardial infarction	1,373 (5.5)	2,754 (0.8)	<0.001
Mild liver disease	7,548 (30.0)	68,845 (21.1)	<0.001
Severe liver disease	309 (1.2)	2,897 (0.9)	<0.001
Peptic ulcer disease	10,964 (43.6)	104,314 (31.9)	<0.001
Peripheral vascular disease	5,574 (22.2)	39,372 (12.1)	<0.001
Renal disease	691 (2.7)	2,684 (0.8)	<0.001
Rheumatic disease	2,871 (11.4)	17,346 (5.3)	<0.001
Surgery at 2010	5,896 (23.4)	58,719 (18.0)	<0.001
Other chronic analgesic use			
Paracetamol	81 (0.3)	285 (0.1)	<0.001
Gabapentin	511 (2.0)	1,925 (0.6)	<0.001
Pregabalin	263 (1.0)	697 (0.2)	<0.001
NSAIDs	40 (0.2)	126 (0.0)	<0.001

Abbreviation: DM, diabetes mellitus.

Published OnlineFirst July 22, 2020; DOI: 10.1158/1055-9965.EPI-20-0206

were confirmed to contain no multicollinearity (variance inflation factor < 2.0).

All statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing). $P < 0.05$ was considered statistically significant.

Results

The 2010 NHIS cohort comprised 826,909 individuals. We excluded 4,487 individuals who died in 2010, 208 who emigrated between 2011 and 2015, and 51,334 who had a history of cancer in 2010. Thus, 770,880 individuals were initially screened. Among them, 351,701 were registered with a diagnosis of musculoskeletal and connective tissue disease (ICD-10 codes M00–M99) in 2010. Among them, 25,153 (7.2%) were chronic opioid users, whereas 326,548 (92.8%) were controls. Among the chronic opioid users, 24,415 (6.9%) and 712 (0.2%) were chronic weak and strong opioid users, respectively. There were 21,788 (6.2%) cases of newly diagnosed cancer between January 2011 and December 2015 (**Fig. 1**). The median duration from January 1 to the date of diagnosis of cancer was 2.3 (interquartile range, 1.1–3.6) years. The results of comparison of the demographic and clinical characteristics between the chronic opioid users and the control group are shown in **Table 1**.

Development of cancer

The results of the multivariate time-dependent Cox regression analysis for the development of cancer are presented in **Table 2**. The risk of cancer in chronic opioid users was 1.20-fold higher than that

Table 2. Multivariate time-dependent Cox regression analysis for the development of cancer.

Variable	Multivariate model HR (95% CI)	*P*
Chronic opioid users (vs. control group): model 1	1.20 (1.15–1.25)	<0.001
Sensitivity analysis: model 2		
Control group	1	
Chronic weak opioid users	1.18 (1.13–1.23)	<0.001
Chronic strong opioid users	1.32 (1.10–1.59)	0.003
Other variables in model 1		
Age, year	1.04 (1.04–1.04)	<0.001
Sex, male	1.70 (1.65–1.75)	<0.001
Income level (deciles distribution ratio)		
1st (lowest income level)	1	
2nd	1.01 (0.94–1.08)	0.859
3rd	1.07 (1.00–1.15)	0.050
4th	0.99 (0.93–1.06)	0.819
5th	1.05 (0.98–1.12)	0.208
6th	1.07 (1.01–1.13)	0.027
7th	0.97 (0.91–1.04)	0.370
8th	1.00 (0.94–1.06)	0.913
9th	1.02 (0.96–1.08)	0.592
10th (highest income level)	1.03 (0.97–1.09)	0.314
Residence		
Capital city (Seoul)	1	
Metropolitan city	1.03 (0.99–1.08)	0.120
Other area	1.00 (0.96–1.03)	0.796
Charlson comorbidity index in 2010	1.11 (1.10–1.12)	<0.001
Congestive heart failure	0.99 (0.94–1.05)	0.847
Chronic pulmonary disease	1.12 (1.08–1.15)	<0.001
Cerebrovascular disease	1.01 (0.97–1.05)	0.847
Dementia	1.03 (0.89–1.19)	0.677
DM with chronic complication	1.12 (1.07–1.18)	<0.001
DM without chronic complication	1.15 (1.11–1.19)	<0.001
Hemi- or paraplegia	0.96 (0.86–1.07)	0.469
Myocardial infarction	1.02 (0.93–1.11)	0.706
Mild liver disease	1.28 (1.24–1.32)	<0.001
Severe liver disease	1.41 (1.27–1.57)	<0.001
Peptic ulcer disease	1.13 (1.10–1.16)	<0.001
Peripheral vascular disease	1.02 (0.99–1.06)	0.256
Renal disease	1.11 (1.00–1.22)	0.042
Rheumatic disease	1.08 (1.03–1.14)	0.003
Surgery at 2010	1.06 (1.03–1.09)	0.001
Other chronic analgesic use		
Paracetamol	1.07 (0.78–1.46)	0.686
Gabapentin	1.15 (1.03–1.28)	0.014
Pregabalin	1.04 (0.87–1.25)	0.653
NSAIDs	1.32 (0.88–1.99)	0.182

Abbreviation: DM, diabetes mellitus.

Published OnlineFirst July 22, 2020; DOI: 10.1158/1055-9965.EPI-20-0206

Table 3. Multivariate time-dependent Cox regression analysis for development of cancer in detail during 2011–2015.

Type of cancer	Multivariable model HR (95% CI)	*P*
Gastric cancer (C16; $n = 1{,}748$)	0.89 (0.76–1.05)	0.177
Esophageal cancer (C15; $n = 107$)	0.79 (0.40–1.54)	0.480
Colorectal cancer (C18–20; $n = 2{,}621$)	1.02 (0.90–1.15)	0.751
Gall bladder and biliary tract cancer (C23–24; $n = 451$)	1.01 (0.75–1.37)	0.939
Head and neck cancer (C00–C14; $n = 128$)	0.70 (0.38–1.30)	0.260
Brain cancer (C71; $n = 102$)	0.81 (0.39–1.71)	0.587
Liver cancer (C22; $n = 3{,}525$)	1.35 (1.22–1.50)	<0.001
Pancreatic cancer (C25; $n = 1{,}189$)	1.04 (0.86–1.24)	0.703
Lung cancer (C34; $n = 2{,}047$)	1.19 (1.04–1.36)	0.009
Bone and articular cartilage cancer (C40–C41; $n = 53$)	0.92 (0.35–2.38)	0.860
Neoplasms of breast and genital organs (C50–C63; $n = 5{,}696$)	1.36 (1.26–1.47)	<0.001
Urinary tract cancer (C64–68; $n = 974$)	1.18 (0.98–1.43)	0.082
Thyroid cancer (C73; $n = 1{,}297$)	1.48 (1.24–1.78)	<0.001
Lymphoma or leukemia (C81–C96; $n = 591$)	1.23 (0.96–1.58)	0.107

among controls (HR, 1.20; 95% CI, 1.15–1.25; $P < 0.001$; model 1). In the subgroup analysis according to opioid potency, the cancer risk in chronic weak and strong opioid users was 1.18-fold (HR, 1.18; 95% CI, 1.13–1.23; $P < 0.001$; model 2) and 1.32-fold (HR, 1.32; 95% CI, 1.10–1.59; $P = 0.003$; model 2) higher than that among controls, respectively.

Details of the results regarding the development of cancer during 2011–2015 are shown in **Table 3**. Using multivariate time-dependent Cox regression models, we found that chronic opioid users had HRs of 1.35 (95% CI, 1.22–1.50; $P < 0.001$) for liver cancer, 1.19 (95% CI, 1.04–1.36; $P = 0.009$) for lung cancer, 1.36 (95% CI, 1.26–1.47; $P < 0.001$) for neoplasms of the breast and genital organs, and 1.48 (95% CI, 1.24–1.78; $P < 0.009$) for thyroid cancer, compared with controls.

Discussion

This population-based historical cohort study, based on a national historical cohort in South Korea, showed that chronic opioid therapy was associated with a higher risk of cancer in noncancer patients with chronic pain. This association was more evident among chronic strong opioid users and for liver cancer, lung cancer, cancer of the breast and genital organs, and thyroid cancer. Our results suggest that there might be a potential relationship between long-term opioid exposure and cancer risk, and further studies are needed to confirm these findings.

Opioids bind directly to opioid receptors, and their overexpression is known to influence tumor growth and cancer progression (28, 29). From this perspective, opioid therapy has been reported to suppress immune function, particularly natural killer cells, which spontaneously recognize and kill tumor cells (30). Furthermore, opioids may also increase the concentration of VEGF, consequently increasing the rate of angiogenesis and cell migration (31). In this regard, our results suggest that there is a potential association between long-term opioid exposure and a higher risk of cancer.

Two cohort studies have reported conflicting results regarding the association between chronic opioid therapy and the risk of cancer (23, 24). Boudreau and colleagues reported that chronic opioid use was associated with a second breast cancer event in primary breast cancer survivors (23), whereas Cronin-Fenton and colleagues reported that postdiagnosis opioid prescription was not significantly associated with breast cancer recurrence after surgery (24). Our study differs from these previous studies in that we included a general population with no history of cancer. Furthermore, we set the primary endpoint as the new development of all malignancies with C-codes as per the ICD-10 system. In South Korea, all patients with cancer need to have their ICD-10 codes registered in the NHIS database to obtain financial coverage of 95% of their cancer treatment costs. Therefore, it is likely that there was no missing data regarding cancer in the South Korea registry between 2011 and 2015.

The subgroup analysis according to opioid dosage was also noteworthy. As reported in previous studies (32, 33), we classified tramadol as a weak opioid in this study, because oral tramadol is commonly prescribed in outpatient clinics in South Korea for patients with chronic noncancer pain (34). Because long-term weak opioid therapy also causes opioid dependence or addiction similar to strong opioid therapy (35), the former should also be prescribed carefully. The results of our study suggest that both chronic weak and strong opioid therapy are associated with an increased risk of cancer.

This study has several limitations. First, some important physiologic variables, such as body mass index, were not included in the multivariate models because they are not recorded in the NHIS database. Because obesity is associated with both the risk of cancer (36) and the development of chronic pain (37), this was an important limitation of this study. Second, physical activity and lifestyle-related risk factors for cancer, such as smoking history and alcohol consumption, were not considered as they too are not included in the NHIS database. Furthermore, this study defined comorbidities using the ICD-10 codes registered in the NHIS database. The diseases specified in the ICD-10 codes may have differed from the actual underlying diseases. In addition, data on the exact opioid doses used by patients were not included in the analysis; thus, the effect of opioid dose among chronic users could not be evaluated. In addition, as we used opioid prescription information in the NHIS database, we could not evaluate actual adherence or compliance among those classified as chronic opioid users. Furthermore, multivariate adjustments are known to only control for the known confounding variables. However, there may have been residual or unmeasured confounding variables, which could have affected the results of this study. Finally, we assessed chronic opioid use from 2010; therefore, usage before 2010 was not considered in this study. Accordingly, it is uncertain whether chronic opioid use can cause cancer in such a short duration with a short latency period. For example, if an individual was diagnosed with cancer in 2011, the

latency period between initial exposure to chronic opioid therapy and development of cancer might be too short. In this case, a reverse causal relationship between chronic opioid therapy and cancer risk may be possible.

In conclusion, this population-based historical cohort study showed that chronic opioid therapy was associated with an increased risk of cancer among noncancer patients with chronic pain. This association was more evident in chronic strong opioid users and for liver cancer, lung cancer, neoplasms of the breast and genital organs, and thyroid cancer. However, as unmeasured and potential confounders may have affected the results of this study, the relationship between chronic opioid use and cancer risk should be evaluated carefully. A future prospective cohort study is needed to confirm our findings.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol 2018;4:1553–68.
3. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol 2017;3:524–48.
4. Lyden J, Binswanger IA. The United States opioid epidemic. Semin Perinatol 2019;43:123–31.
5. Shah A, Hayes CJ, Martin BC. Characteristics of initial prescription episodes and likelihood of long-term opioid use—United States, 2006–2015. MMWR Morb Mortal Wkly Rep 2017;66:265.
6. Cooper AJM, Willis J, Fuller J, Benecke H, Leighton-Scott J, Andersohn F, et al. Prevalence and incidence trends for diagnosed prescription opioid use disorders in the United Kingdom. Pain Ther 2017;6:73–84.
7. Kang KH, Kuo LF, Cheng IC, Chang CS, Tsay WI. Trends in major opioid analgesic consumption in Taiwan, 2002–2014. J Formos Med Assoc 2017;116:529–35.
8. Chenaf C, Kabore JL, Delorme J, Pereira B, Mulliez A, Zenut M, et al. Prescription opioid analgesic use in France: trends and impact on morbidity-mortality. Eur J Pain 2019;23:124–34.
9. Fang W, Liu T, Gu Z, Li Q, Luo C. Consumption trend and prescription pattern of opioid analgesics in China from 2006 to 2015. Eur J Hosp Pharm 2018;26:140–5.
10. Krnic D, Anic-Matic A, Dosenovic S, Draganic P, Zezelic S, Puljak L. National consumption of opioid and nonopioid analgesics in Croatia: 2007–2013. Ther Clin Risk Manag 2015;11:1305–14.
11. Degenhardt L, Charlson F, Mathers B, Hall WD, Flaxman AD, Johns N, et al. The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study. Addiction 2014;109:1320–33.
12. Soffin EM, Lee BH, Kumar KK, Wu CL. The prescription opioid crisis: role of the anaesthesiologist in reducing opioid use and misuse. Br J Anaesth 2019;122:e198–208.
13. King NB, Fraser V, Boikos C, Richardson R, Harper S. Determinants of increased opioid-related mortality in the United States and Canada, 1990–2013: a systematic review. Am J Public Health 2014;104:e32–42.
14. Rudd RA, Seth P, David F, Scholl L. Increases in drug and opioid-involved overdose deaths - United States, 2010–2015. MMWR Morb Mortal Wkly Rep 2016;65:1445–52.
15. Sacerdote P. Opioid-induced immunosuppression. Curr Opin Support Palliat Care 2008;2:14–8.
16. Liang X, Liu R, Chen C, Ji F, Li T. Opioid system modulates the immune function: a review. Transl Perioper Pain Med 2016;1:5–13.
17. Oh TK, Do SH, Yoon YS, Song IA. Association between opioid use and survival time in patients with unresectable pancreatic cancer: 10 years of clinical experience. Pancreas 2018;47:837–42.
18. Oh TK, Jeon JH, Lee JM, Kim MS, Kim JH, Cho H, et al. Investigation of opioid use and long-term oncologic outcomes for non-small cell lung cancer patients treated with surgery. PLoS One 2017;12:e0181672.
19. Oh TK, Jeon JH, Lee JM, Kim MS, Kim JH, Lim H, et al. Association of high-dose postoperative opioids with recurrence risk in esophageal squamous cell carcinoma: reinterpreting ERAS protocols for long-term oncologic surgery outcomes. Dis Esophagus 2017;30:1–8.
20. Zylla D, Kuskowski MA, Gupta K, Gupta P. Association of opioid requirement and cancer pain with survival in advanced non-small cell lung cancer. Br J Anaesth 2014;113:i109–i16.
21. Cheung CW, Qiu Q, Choi SW, Moore B, Goucke R, Irwin M. Chronic opioid therapy for chronic non-cancer pain: a review and comparison of treatment guidelines. Pain Physician 2014;17:401–14.
22. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. JAMA 2016;315:2415–23.
23. Boudreau DM, Chen L, Yu O, Bowles EJA, Chubak J. Risk of second breast cancer events with chronic opioid use in breast cancer survivors. Pharmacoepidemiol Drug Saf 2019;28:740–53.
24. Cronin-Fenton DP, Heide-Jorgensen U, Ahern TP, Lash TL, Christiansen PM, Ejlertsen B, et al. Opioids and breast cancer recurrence: a Danish population-based cohort study. Cancer 2015;121:3507–14.
25. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: the National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. Int J Epidemiol 2017;46:e15.
26. Jiang X, Orton M, Feng R, Hossain E, Malhotra NR, Zager EL, et al. Chronic opioid usage in surgical patients in a large academic center. Ann Surg 2017;265:722–7.
27. Pereira J, Lawlor P, Vigano A, Dorgan M, Bruera E. Equianalgesic dose ratios for opioids. A critical review and proposals for long-term dosing. J Pain Symptom Manage 2001;22:672–87.
28. Le-Wendling L, Nin O, Capdevila X. Cancer recurrence and regional anesthesia: the theories, the data, and the future in outcomes. Pain Med 2016;17:756–75.
29. Tedore T. Regional anaesthesia and analgesia: relationship to cancer recurrence and survival. Br J Anaesth 2015;115:ii34–45.
30. Wigmore T, Farquhar-Smith P. Opioids and cancer: friend or foe? Curr Opin Support Palliat Care 2016;10:109–18.
31. Mathew B, Lennon FE, Siegler J, Mirzapoiazova T, Mambetsariev N, Sammani S, et al. The novel role of the mu opioid receptor in lung cancer progression: a laboratory investigation. Anesth Analg 2011;112:558–67.
32. Bandieri E, Romero M, Ripamonti CI, Artioli F, Sichetti D, Fanizza C, et al. Randomized trial of low-dose morphine versus weak opioids in moderate cancer pain. J Clin Oncol 2016;34:436–42.
33. Brattwall M, Turan I, Jakobsson J. Musculoskeletal pain: prescription of NSAID and weak opioid by primary health care physicians in Sweden 2004–2008 - a retrospective patient record review. J Pain Res 2010;3:131–5.
34. Vijayan R, Afshan G, Bashir K, Cardosa M, Chadha M, Chaudakshetrin P, et al. Tramadol: a valuable treatment for pain in Southeast Asian countries. J Pain Res 2018;11:2567–75.
35. Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. Br J Anaesth 2018;120:1335–44.
36. Pischon T, Nimptsch K. Obesity and risk of cancer: an introductory overview. Recent Results Cancer Res 2016;208:1–15.
37. Okifuji A, Hare BD. The association between chronic pain and obesity. J Pain Res 2015;8:399–408.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

T.K. Oh: Conceptualization, data curation, formal analysis, methodology, writing–original draft. **I.-A. Song:** Conceptualization, supervision, methodology, writing–review and editing.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received February 8, 2020; revised March 22, 2020; accepted July 15, 2020; published first July 22, 2020.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Chronic Opioid Use and Risk of Cancer in Patients with Chronic Noncancer Pain: A Nationwide Historical Cohort Study

Tak Kyu Oh and In-Ae Song

Cancer Epidemiol Biomarkers Prev 2020;29:1962-1967. Published OnlineFirst July 22, 2020.