

1 **Chronic opioid use and risk of cancer in patients with chronic non-cancer pain: A nationwide**
2 **historical cohort study**

3

4 **Running head:** Chronic opioid therapy and cancer risk

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18 **Word and Element Counts:** Total: 2,597 (Abstract: 247)

19 **Number of figures/tables:** 3/3

20 **Supplementary tables/figures:** 2/0

21 **Prior Presentation:** None

22

23 **Conflict of Interest:** The authors declare no potential conflicts of interest

1 **Funding:** None

2

3 **Keywords:** Neoplasms; Population; Analgesics, Opioid

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5

1 **Abstract**

2 *Background:* To investigate whether chronic opioid therapy is associated with a higher risk of cancer
3 among non-cancer patients with chronic pain.

4
5 *Methods:* A population-based historical cohort study of the South Korean adult population was
6 conducted using data from the National Health Insurance Service. We included patients registered
7 with a diagnostic code of M00–M99 (musculoskeletal system and connective tissue diseases)
8 according to the International Classification of Diseases, 10th revision, in 2010. Patients prescribed a
9 continuous supply of any opioid drug for ≥ 90 days were defined as chronic opioid users.

10

11 *Results:* A total of 351,701 patients were analyzed. Among them, 25,153 (7.2%) were chronic opioid
12 users. Using a multivariable time-dependent Cox regression model, the risk of cancer in chronic
13 opioid users was 1.20-fold higher than that in controls (hazard ratio [HR], 1.20; 95% confidence
14 interval [CI], 1.15–1.25; $P < 0.001$). On subgroup analysis according to opioid potency, the cancer risk
15 in chronic weak and strong opioid users was 1.18-fold (HR, 1.18; 95% CI, 1.13–1.23; $P < 0.001$) and
16 1.32-fold (HR, 1.32; 95% CI, 1.10–1.59; $P = 0.003$) higher than that in controls, respectively.

17

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

22

23 *Impact:* Chronic opioid therapy was associated with an increased risk of cancer among non-cancer
24 patients.

1 **Introduction**

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

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

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

24 Therefore, this study aimed to investigate whether chronic opioid therapy is associated with a higher
25 risk of cancer in non-cancer patients with chronic pain from musculoskeletal and connective tissue

1 diseases. In addition, we assessed whether this association may differ according to the potency of the
2 opioid agent or the type of cancer.

3

1 **Materials and Methods**

2 *Data source*

3 The “historical cohort database” of the National Health Insurance Service (NHIS) was used to obtain
4 data for this study, which includes health and medical surveys of the Korean population. The database
5 comprised a stratified random sample of approximately one million people registered with the NHIS
6 since 2002, and was designed to be representative of the national population in terms of demographic
7 and socioeconomic variables. To maintain the demographic and socioeconomic integrity of the cohort,
8 people were added to the cohort each year to replace individuals who had died or emigrated in the
9 preceding year, using stratified extraction methods to ensure that the cohort remained representative
10 of the national population in terms of demographic and socioeconomic information (25). For instance,
11 if a 65-year-old individual who lived in the capital city at the lowest income level died in the
12 preceding year, the cohort was supplemented with a new 65-year-old individual who lived in the
13 capital city at the lowest income level in the following year, using a stratified extraction method.
14 Through this process, the cohort remained balanced at one million individuals until 2015.

15

16 *Ethical statement*

17 The protocol of this study was approved by the Institutional Review Board of Seoul National
18 University Bundang Hospital (no. X-1808-489-904) and the Health Insurance Review and Assessment
19 Service (NHIS-2018-2-256).

20

21 *Study population*

22 We included all adult patients (age ≥ 18 years) registered with a diagnostic code of M00–M99
23 (diseases of the musculoskeletal system and connective tissue) according to the International
24 Classification of Diseases, 10th revision (ICD-10), in 2010. We then excluded individuals who died in

1 2010 and those who had emigrated between 2011 and 2015, as opioid prescription information was no
2 longer available after emigration. In addition, individuals with a history of cancer in 2010 were
3 excluded, as our study focused on new cancer diagnoses between 2011 and 2015.

4 5 *Long-term opioid prescription as an exposure variable*

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

14 15 *Study endpoint*

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

18 19 *Development of cancer as the dependent variable*

20 In this study, the development of cancer was defined as newly registered diagnoses of any malignancy
21 (C00–C96) between 2011 and 2015 in the 2010 NHIS cohort in South Korea. In detail, the cancers
22 were categorized as follows: gastric cancer (C16), esophageal cancer (C15), colorectal cancer (C18–
23 C20), gall bladder and biliary tract cancer (C23–C24), head and neck cancer (C00–C14), brain cancer
24 (C71), liver cancer (C22), pancreatic cancer (C25), lung cancer (C34), bone and articular cartilage

1 cancer (C40–C41), neoplasms of the breast and genital organs (C50–C63), urinary tract cancer (C64–
2 C68), thyroid cancer (C73), and lymphoma or leukemia (C81–C96). The time to cancer diagnosis was
3 calculated from January 1, 2011 to the date of cancer diagnosis, as registered officially in the NHIS
4 database. In South Korea, all patients diagnosed with cancer of any C-code should be registered in the
5 NHIS database to receive special financial coverage; the NHIS covers 95% of the total cost of cancer
6 treatment. Therefore, all patients in South Korea who received a diagnosis of cancer were registered
7 in the NHIS database.

8

9 *Confounding variables*

10 Data on the following variables as confounders were collected in this study: (1) demographic
11 information (age and sex); (2) socioeconomic information (income level in deciles and place of
12 residence in 2010 [Seoul, metropolitan cities, or others]); (3) Charlson’s comorbidity index, which
13 was calculated using the registered ICD-10 diagnostic codes between 2009 and 2010 in the NHIS
14 database (Supplementary Table 1); (4) surgical history in 2010; and (5) chronic use of other analgesics
15 for ≥ 90 days (nonsteroidal anti-inflammatory drugs, paracetamol, gabapentin, and pregabalin). Data
16 on obesity and physical activity, as well as lifestyle-related risk factors for cancer, such as smoking
17 and alcohol consumption, were not included in this study because they were not included in the NHIS
18 database.

19

20 *Statistical analysis*

21 The baseline characteristics of the chronic opioid users and controls were compared using the *t*-test
22 for continuous variables and the chi-square test for categorical variables. The results of the tests are
23 presented as means with standard deviations for continuous variables and numbers with percentages
24 for categorical variables. First, as our study focused on time-dependent exposure to chronic opioid
25 therapy in the 2010 cohort between 2011 and 2015, we investigated the proportion of chronic opioid

1 users who discontinued opioid therapy or commenced it during the evaluation period, that is, 2011–
2 2015. Exposure to chronic opioid therapy among both the chronic opioid users and controls in 2010
3 varied throughout the evaluation period (Supplementary Table 2).

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

10 During the first subgroup analysis, the chronic opioid users were categorized into two groups (chronic
11 strong opioid users and chronic weak opioid users), and the association of chronic strong and weak
12 opioid use with the development of cancer was assessed using a time-dependent Cox regression
13 model. We then developed 14 time-dependent Cox regression models to investigate whether chronic
14 opioid use was associated with specific cancer development. Diagnoses of 14 specific cancer types
15 were used as endpoints in these models. The results of the Cox regression models are presented as
16 hazard ratios (HRs) with 95% confidence intervals (CIs). All multivariable models of the entire cohort
17 were confirmed to contain no multicollinearity (variance inflation factor <2.0).

18 All statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing,
19 Vienna, Austria). *P*-values <.05 were considered statistically significant.

20

21

1 **Results**

2 The 2010 NHIS cohort comprised 826,909 individuals. We excluded 4,487 individuals who died in
3 2010, 208 who emigrated between 2011 and 2015, and 51,334 who had a history of cancer in 2010.
4 Thus, 770,880 individuals were initially screened. Among them, 351,701 were registered with a
5 diagnosis of musculoskeletal and connective tissue disease (ICD-10 codes M00–M99) in 2010.
6 Among them, 25,153 (7.2%) were chronic opioid users, whereas 326,548 (92.8%) were controls.
7 Among the chronic opioid users, 24,415 (6.9%) and 712 (0.2%) were chronic weak and strong opioid
8 users, respectively. There were 21,788 (6.2%) cases of newly diagnosed cancer between January 2011
9 and December 2015 (Fig 1). The median duration from January 1 to the date of diagnosis of cancer
10 was 2.3 (interquartile range, 1.1–3.6) years. The results of comparison of the demographic and clinical
11 characteristics between the chronic opioid users and the control group are shown in Table 1.

12

13 *Development of cancer*

14 The results of the multivariable time-dependent Cox regression analysis for the development of cancer
15 are presented in Table 2. The risk of cancer in chronic opioid users was 1.20-fold higher than that
16 among controls (HR, 1.20; 95% CI, 1.15–1.25; $P < .001$; model 1). In the subgroup analysis according
17 to opioid potency, the cancer risk in chronic weak and strong opioid users was 1.18-fold (HR, 1.18;
18 95% CI, 1.13–1.23; $P < .001$; model 2) and 1.32-fold (HR, 1.32; 95% CI, 1.10–1.59; $P = 0.003$;
19 model 2) higher than that among controls, respectively.

20 Details of the results regarding the development of cancer during 2011–2015 are shown in Table 3.

21 Using multivariable time-dependent Cox regression models, we found that chronic opioid users had
22 HRs of 1.35 (95% CI, 1.22–1.50; $P < .001$) for liver cancer, 1.19 (95% CI, 1.04–1.36; $P = 0.009$) for
23 lung cancer, 1.36 (95% CI, 1.26–1.47; $P < .001$) for neoplasms of the breast and genital organs, and
24 1.48 (95% CI, 1.24–1.78; $P < .009$) for thyroid cancer, compared with controls.

25

1 **Discussion**

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

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

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

25 The subgroup analysis according to opioid dosage was also noteworthy. As reported in previous

1 studies (32,33), we classified tramadol as a weak opioid in this study, because oral tramadol is
2 commonly prescribed in outpatient clinics in South Korea for patients with chronic non-cancer pain
3 (34). Since long-term weak opioid therapy also causes opioid dependence or addiction similar to
4 strong opioid therapy (35), the former should also be prescribed carefully. The results of our study
5 suggest that both chronic weak and strong opioid therapy are associated with an increased risk of
6 cancer.

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

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

8

9 **Acknowledgments**

10 None

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6

7

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

Variable	Chronic opioid user (n=25,153)	Control group (n=326,548)	P-value
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)	
2 nd	1,170 (4.7)	20,247 (6.2)	
3 rd	1,347 (5.4)	24,337 (7.5)	
4 th	1,420 (5.6)	27,233 (8.3)	
5 th	1,492 (5.9)	27,927 (8.6)	
6 th	3,040 (12.1)	47,563 (14.6)	
7 th	2,457 (9.8)	34,453 (10.6)	
8 th	2,909 (11.6)	36,581 (11.2)	
9 th	3,797 (15.1)	40,554 (12.4)	
10 th (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 analgesics 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

1 DM, diabetes mellitus; NSAIDs, Nonsteroidal anti-inflammatory drugs

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

Variable	Multivariable model	
	HR (95% CI)	P-value
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 variable 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	
2 nd	1.01 (0.94, 1.08)	0.859
3 rd	1.07 (1.00, 1.15)	0.050
4 th	0.99 (0.93, 1.06)	0.819
5 th	1.05 (0.98, 1.12)	0.208
6 th	1.07 (1.01, 1.13)	0.027
7 th	0.97 (0.91, 1.04)	0.370
8 th	1.00 (0.94, 1.06)	0.913
9 th	1.02 (0.96, 1.08)	0.592
10 th (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 analgesics 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

1 HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; NSAIDs, Nonsteroidal anti-
 2 inflammatory drugs

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1 Table 3. Multivariable time-dependent Cox regression analysis for development of cancer in detail
 2 during 2011 to 2015

Type of cancer	Multivariable model	
	HR (95% CI)	P-value
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
GB 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

3 HR, hazard ratio; CI, confidence interval

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1 **Figure legend**

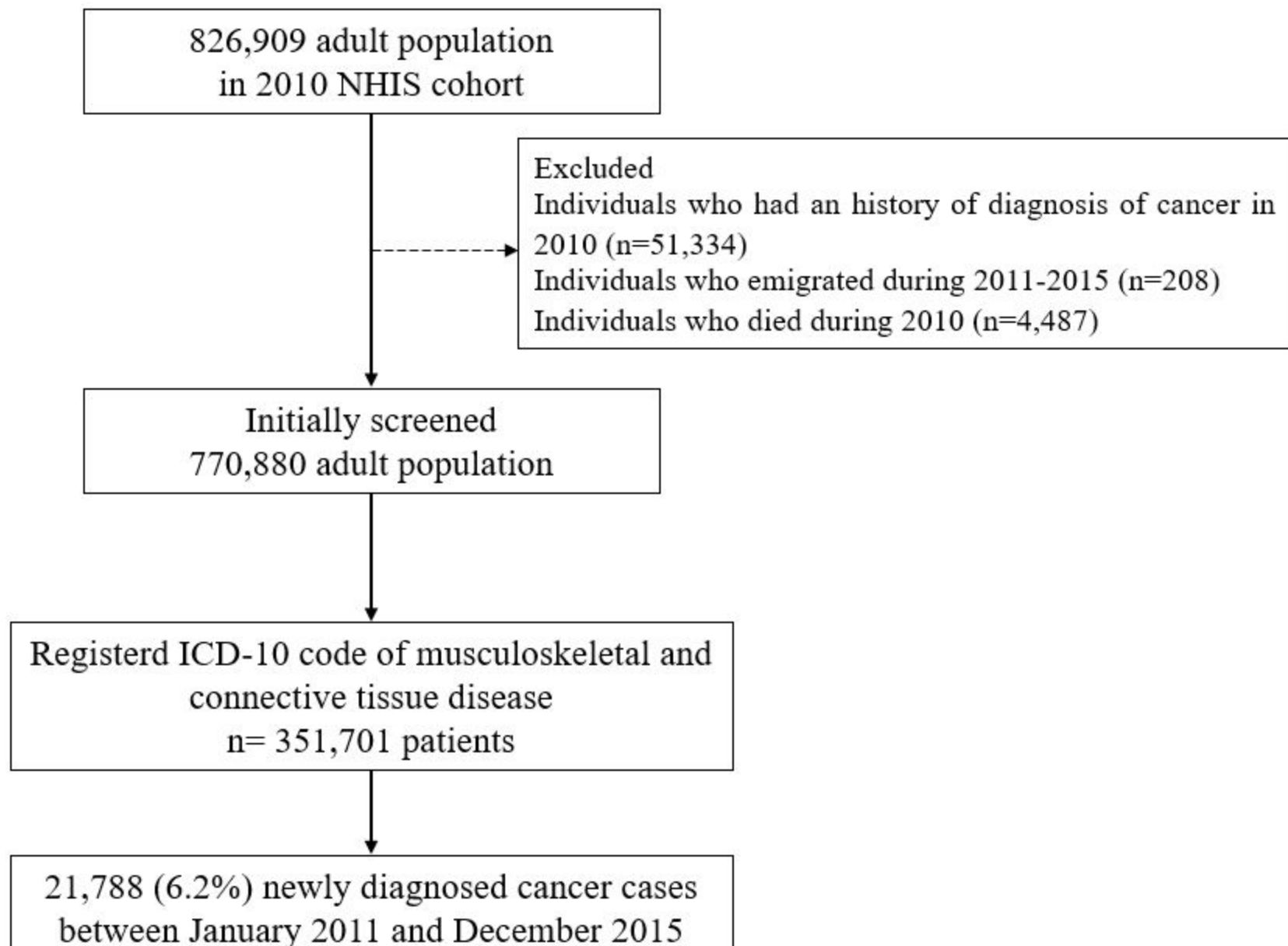
2 Fig. 1. Flow chart of patient selection in this study

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Figure 1



Cancer Epidemiology, Biomarkers & Prevention

AACR American Association
for Cancer Research

Chronic opioid use and risk of cancer in patients with chronic non-cancer pain: A nationwide historical cohort study

Tak Kyu Oh and In-Ae Song

Cancer Epidemiol Biomarkers Prev Published OnlineFirst July 22, 2020.

Updated version	Access the most recent version of this article at: doi: 10.1158/1055-9965.EPI-20-0206
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